Duke University School of Medicine

TRANSPORT2 Study on the StrokeNet

Science and Beyond Science

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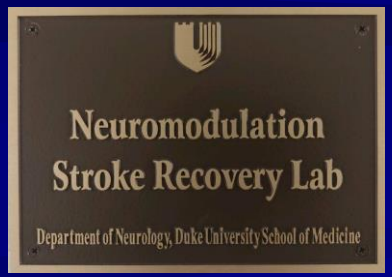


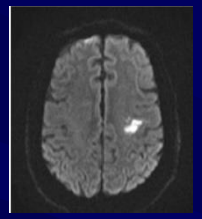
TRANSPORT2

Disclosure

- **National Institute of Health**
  - "Optimizing Transcranial Direct Current Stimulation Current and Electrode Montage for Stroke Patients, 1P20 GM109040
  - “TRANScranial direct current stimulation for POst-stroke motor Recovery – a phase II sTudy (TRANSPROT2)” 1U01NS102353-01A1
- American Heart/Stroke Association
  - Prediction and Imaging Biomarker for Post-Stroke Motor Recovery, 14SDG18290003
  - Optimizing parameters of Low Intensity Focused Ultrasound for Cortical Modulation in stroke patients. 20IPA35360039
- Ipsen Inc and Huamed Inc
  - Consultant prn
- Transponder Inc
  - Site PI

Stroke Recovery
Use the Brain Plasticity to Recover the Brain

Mild Stroke

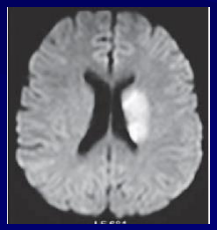


Increase dose of rehabilitation therapy. reduce time to full recovery

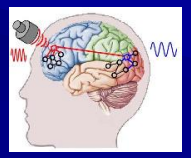
Dosage Matters

Live Normal

Moderate stroke, still has neural substrate



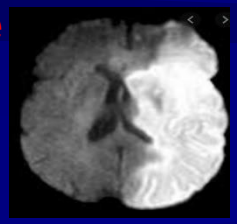
Brain Stimulation + intensive therapy



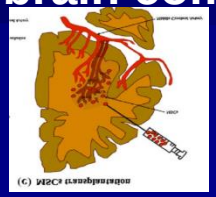
Electrical
Ultrasonic
Magnetic
Light

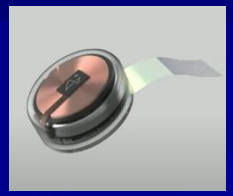
Live near normal

Severe stroke, Minimal or no neural substrate



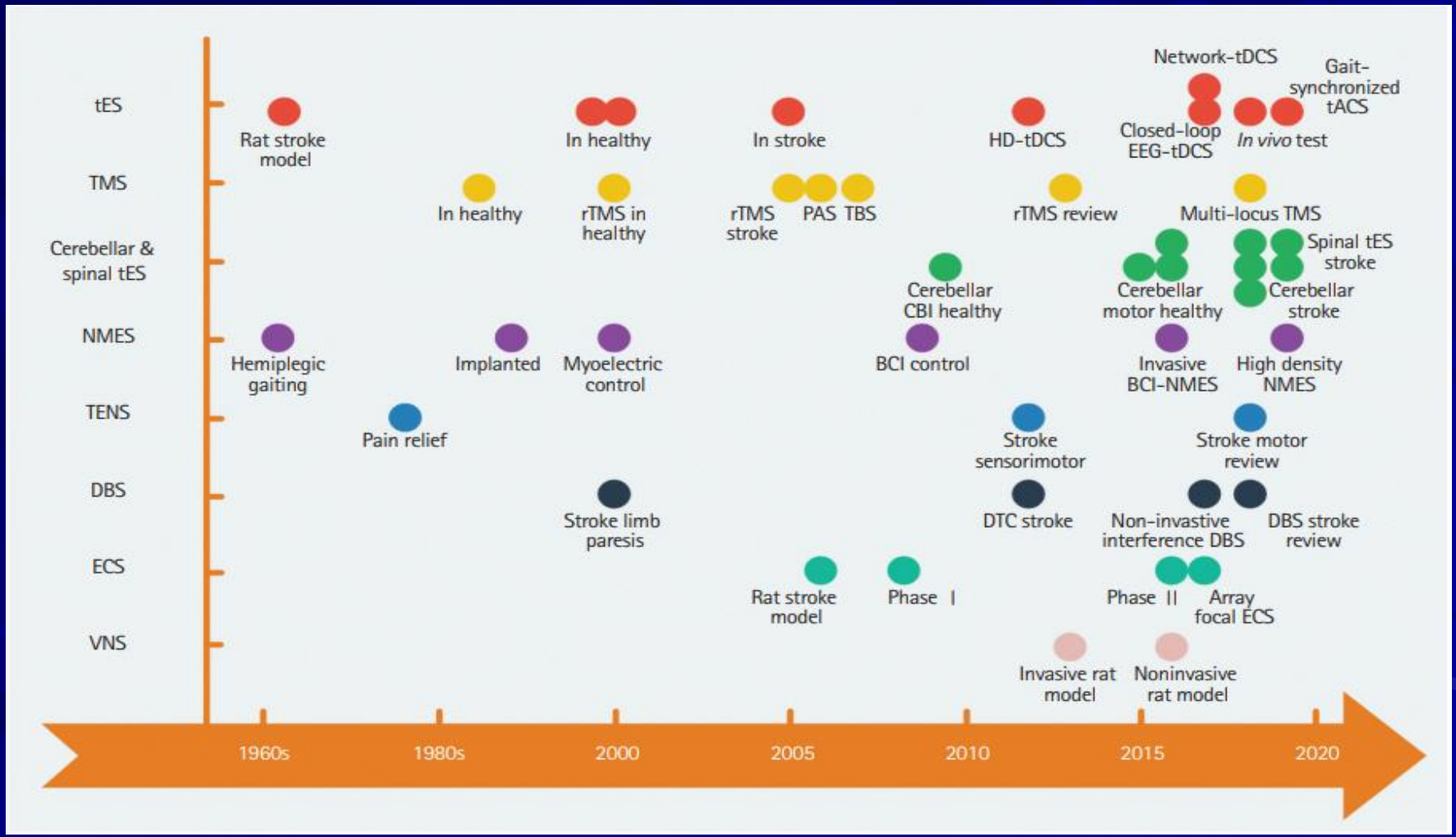
Cell based therapy, exoskeleton and brain computer interface



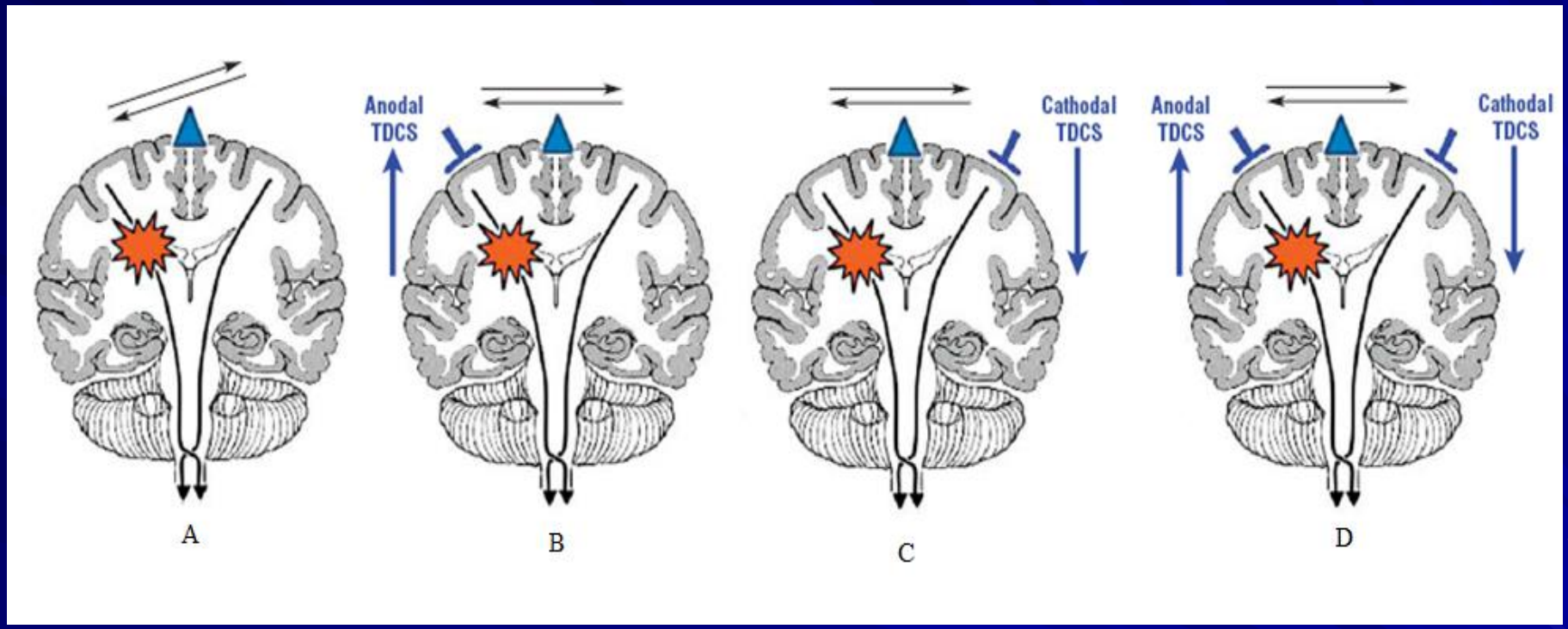


Find a different way to live

Brain Stimulation for Stroke Recovery

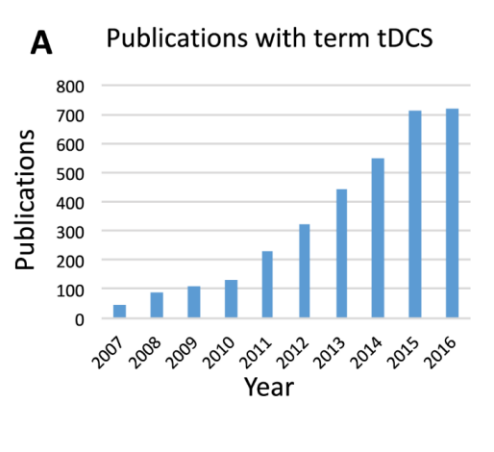


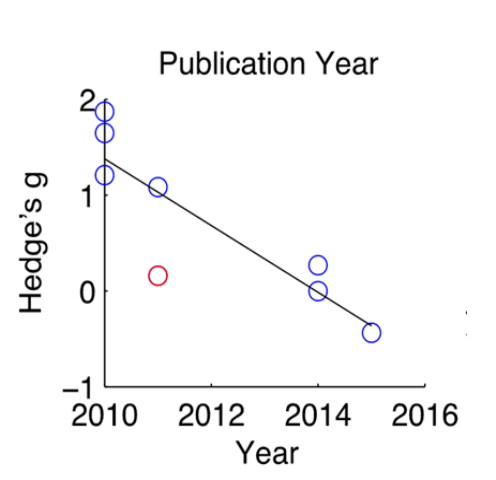
Interhemispheric Inhibition & Modality of Brain Stimulation



Transcranial Direct Current Stimulation for Poststroke Motor Recovery: Challenges and Opportunities

Wuwei Feng, MD, MS, Steven A. Kautz, PhD, Gottfried Schlaug, MD, PhD, Caitlyn Meinzer, PhD, Mark S. George, MD, Pratik Y. Chhatbar, MD, PhD





- Dosage
- Montage
- Blinding
- Time of intervention
- Patient selection
- Outcome measure(s)
- Peripheral Rehab Therapy
- power issue in small study

Define Dosage FIRST

Described Stimulation Parameters

- Current (mA) [1-2mA]
- Pad Size (cm^2) [3*5; 5*5; 5*7]
- Duration (min) [10 -40]
- Number of Sessions [5-30]

Derived Stimulation Parameters

- Current (mA)
- Current Density (A/m^2) = Current ÷ pad Size
- Charge (C) = Current × Duration
- Charge Density (C/m^2) = Current Density × Duration
- Total Charge (C) = Charge × Sessions
- Total Charge Density (C/m^2) = Charge Density × Sessions

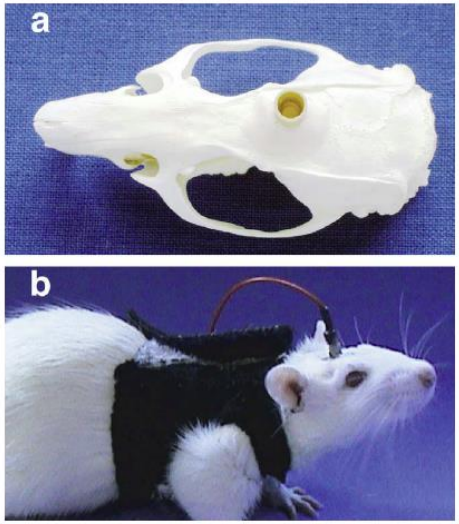
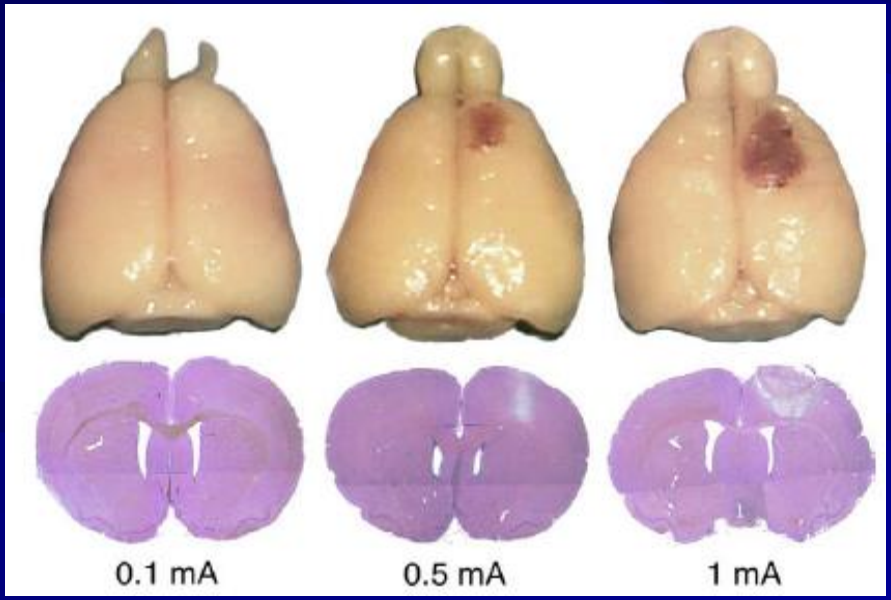


Fig. 1. Electrode montage used for transcranial DC stimulation in the rat. (a) The epicranial electrode (contact area = 3.5 mm²) is fixed onto the skull unilaterally above the frontal cortex (1.5 mm right and 2 mm anterior to bregma) using dental cement. (b) Before DC stimulation the epicranial electrode is filled with saline solution. A large rubber plate mounted on the chest serves as the counter electrode (b).

Table 1
Summary of stimulation parameter of single and repetitive tDCS.

Animals(n)	Currents (μA)	Current density (A/m²)	Time (min)	Charge (C)	Charge density (C/m²)	Lesion size (mm³)
2	1	0.286	1 × 30	0.0018	514	
2	1	0.286	1 × 90	0.0054	1543	
2	1	0.286	1 × 270	0.0162	4629	
3	10	2.86	1 × 10	0.006	1714	
2	10	2.86	1 × 30	0.018	5143	
2	10	2.86	1 × 90	0.054	15429	
2	10	2.86	1 × 270	0.162	46286	
2	50	14.3	1 × 10	0.03	8571	
3	50	14.3	1 × 30	0.09	25714	
3	50	14.3	1 × 90	0.27	77143	
3	50	14.3	1 × 270	0.81	231429	
4	100	28.6	1 × 10	0.06	17143	
2	100	28.6	1 × 30	0.18	51429	
6	100	28.6	1 × 90	0.54	154286	
4	100	28.6	1 × 270	1.62	462857	
3	500	142.9	1 × 3.33	0.1	28571	
1	500	142.9	1 × 10	0.3	85714	0.11
1	500	142.9	1 × 30	0.9	257143	1.82
1	500	142.9	1 × 90	2.7	771429	6.70
1	500	142.9	1 × 270	8.1	2314287	23.49
3	1000	285.7	1 × 3.33	0.2	57143	0.025
4	1000	285.7	1 × 10	0.6	171429	0.47
2	1000	285.7	1 × 30	1.8	514286	6.94
1	1000	285.7	1 × 90	5.4	1542857	13.44
4	400	114.3	5 × 10	5 × 0.24	5 × 68571	



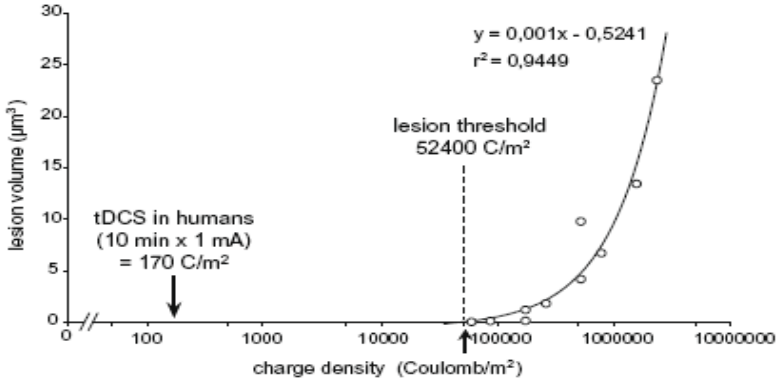
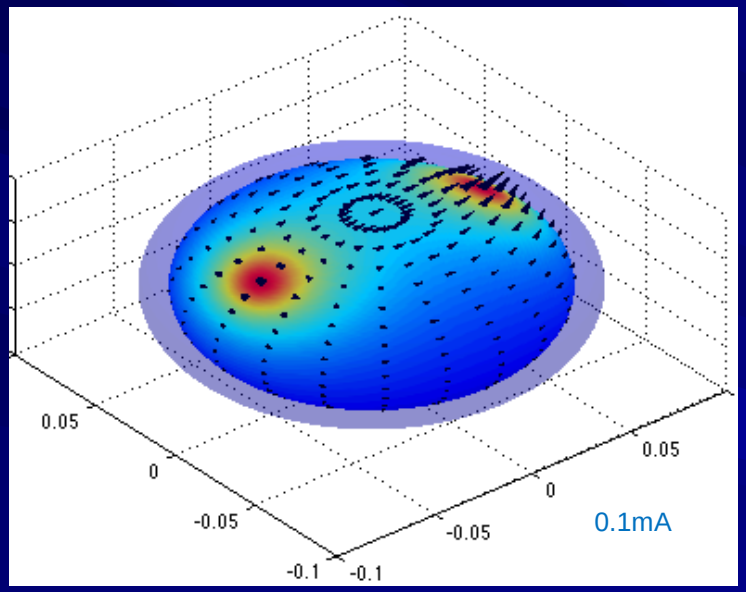


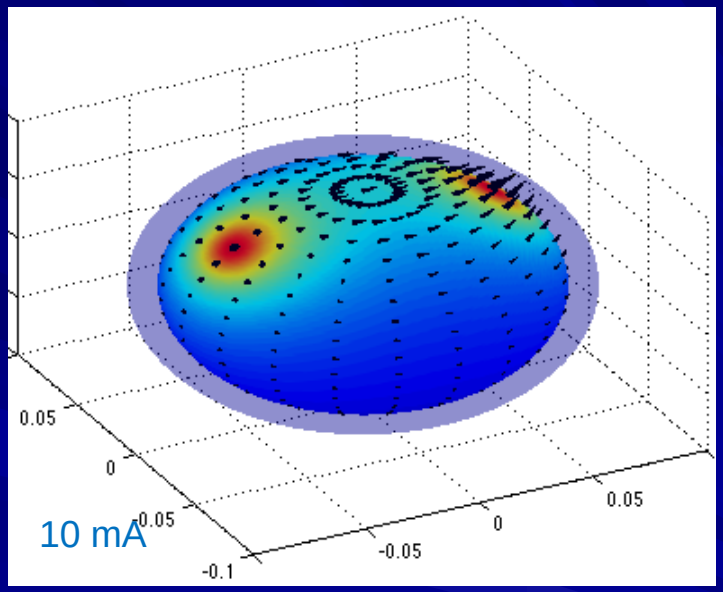
Fig. 4. Threshold estimation from the relation of charge density and lesion size at current intensities of 500–1000 μA. The results of all above-threshold experiments (n = 12) are depicted with respect to the charge density (C/m²) and the size of the DC-induced brain lesion (μm³). For better overview, the charge density is scaled logarithmically. The regression analysis indicates a linear relation of charge density and lesion size (r^2 = 0.945, F = 171.33, P < 0.001). The intercept point, at which the lesion size is theoretically zero, corresponds to 52400 C/m². The upwards-directed arrow indicates the daily charge density of the group that received repetitive tDCS over 5 days without inducing tissue damage.

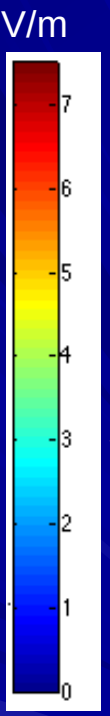
Electric Field Spherical Model

RAT (0.8 cm radius)

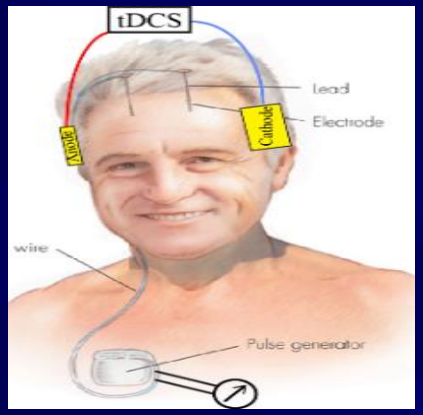


Human (8cm radius)





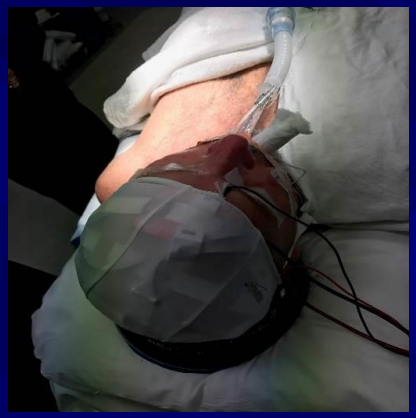
Spheres-tDCS Modeling Interface; http://neuralengr.com/spheres/



Evidence of transcranial direct current stimulation-generated electric fields at subthalamic level in human brain *in vivo*

Pratik Y. Chhatbar [a], Steven A. Kautz [b, c], Istvan Takacs [d], Nathan C. Rowland [d], Gonzalo J. Revuelta [a], Mark S. George [c, e], Marom Bikson [f], Wuwei Feng [a, b, *]

The crude estimate of generated electric field with 4 mA bitemporal tDCS at the level of subthalamic nuclei was 0.19-0.26 mV/mm



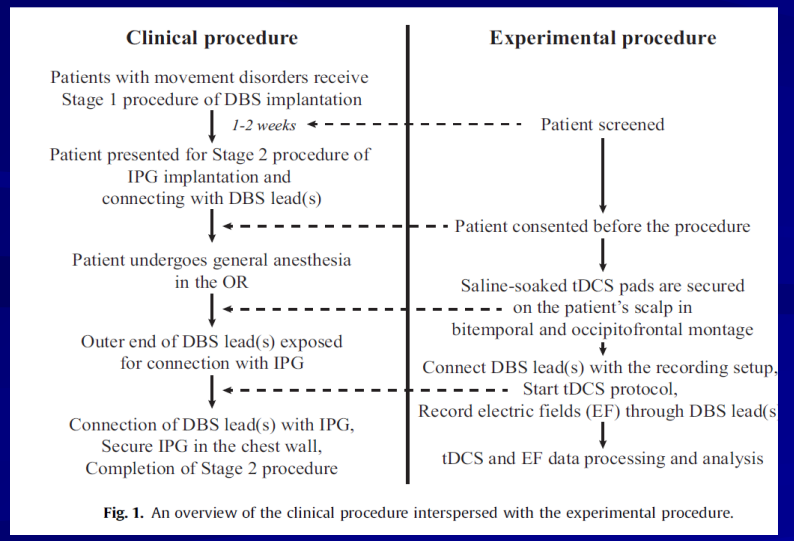
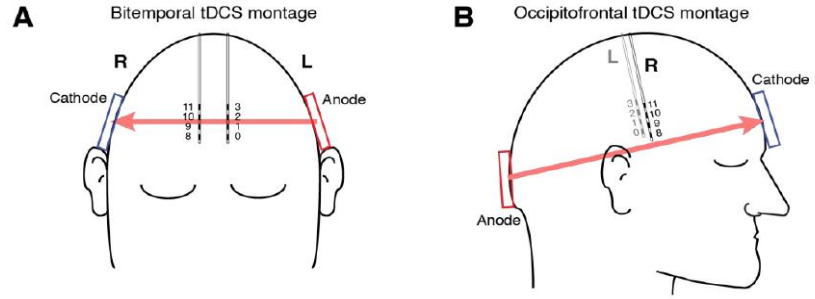
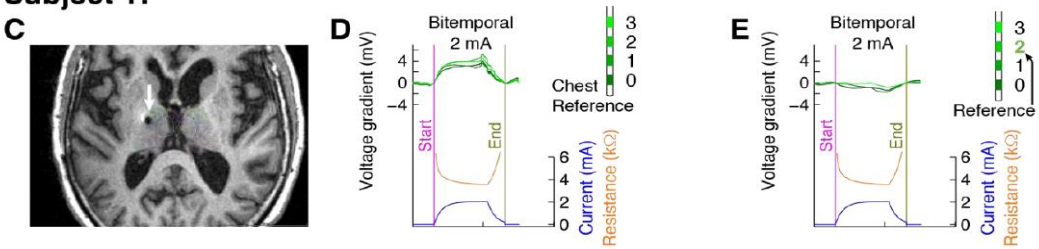


Fig. 1. An overview of the clinical procedure interspersed with the experimental procedure.

Schematics:



Subject 1:



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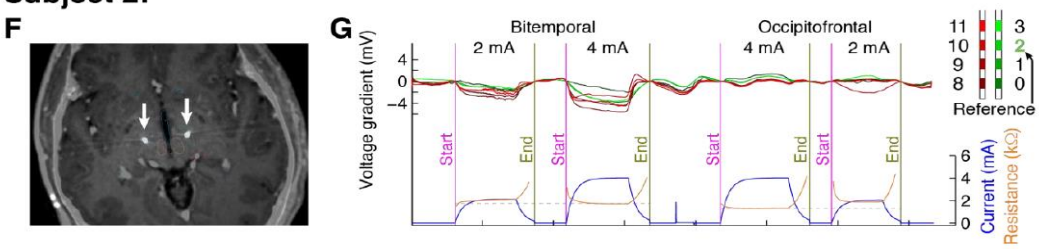

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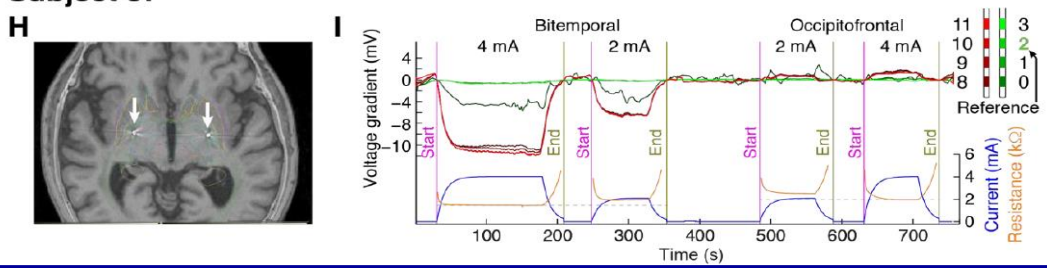

Transcranial Direct Current Stimulation Post-Stroke Upper Extremity Motor Recovery Studies Exhibit a Dose–Response Relationship

Pratik Y. Chhatbar [a], Viswanathan Ramakrishnan [b], Steven Kautz [c,d], Mark S. George [d,e], Robert J. Adams [a], Wuwei Feng [a,c,*]

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BRAIN STIMULATION

Basic, Translational, and Clinical Research in Neuromodulation

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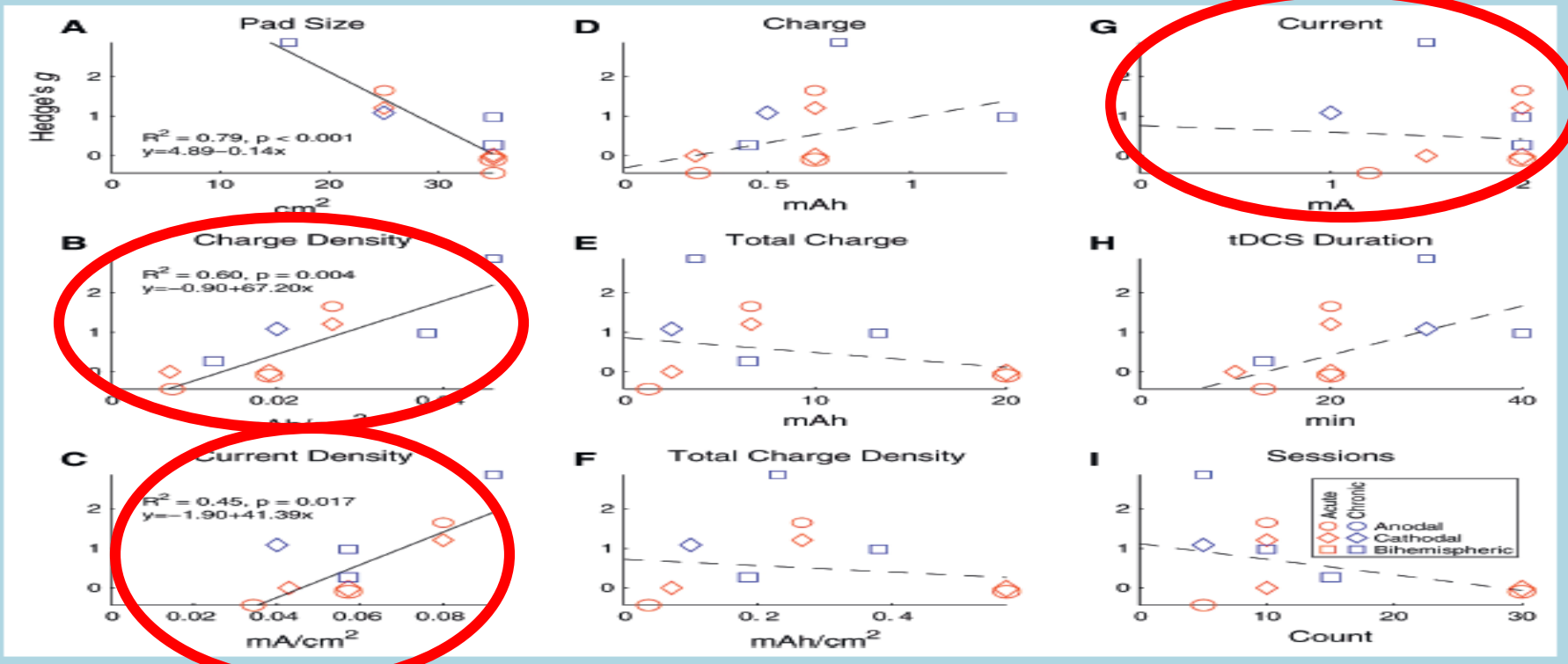


Safety and tolerability of transcranial direct current stimulation to stroke patients – A phase I current escalation study

Pratik Y. Chhatbar, MD, PhD [a], Rong Chen, MD, PhD [a], Rachael Deardorff, MS [b], Blair Dellenbach, OT [c], Steven A. Kautz, PhD [c, d], Mark S. George, MD [d, e], Wuwei Feng, MD, MS [a, c, *]

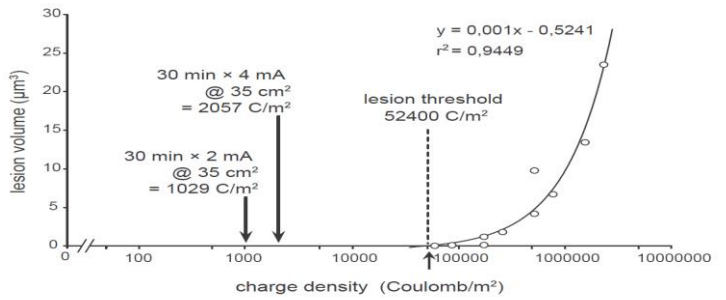


Fig. 1. Established brain lesion threshold from an animal study is more than 50-times higher than typical (≤2 mA) human tDCS setup. tDCS current of 2 mA delivered for 30 min using 35 cm² is much smaller than the charge that was reported to incur brain damage (1029 vs 52400 C/m²). Tested safety limit of 4 mA proposed in this study is still about 25× smaller (2057 vs 52400 C/m²). Adapted from Ref. [19], note that charge density on azimuth is projected on a logarithmic scale.

Pre-specified major responses or stopping rules:

- Second degree scalp burn at the site of electrode pad; or
- Clinical Seizure; or
- New lesion(s) on DWI sequence of MRI scan and the lesion(s) not explained by any other cause(s) or decreased ADC under the electrode pad; or
- Patient discontinues from the study due to any reasons above.

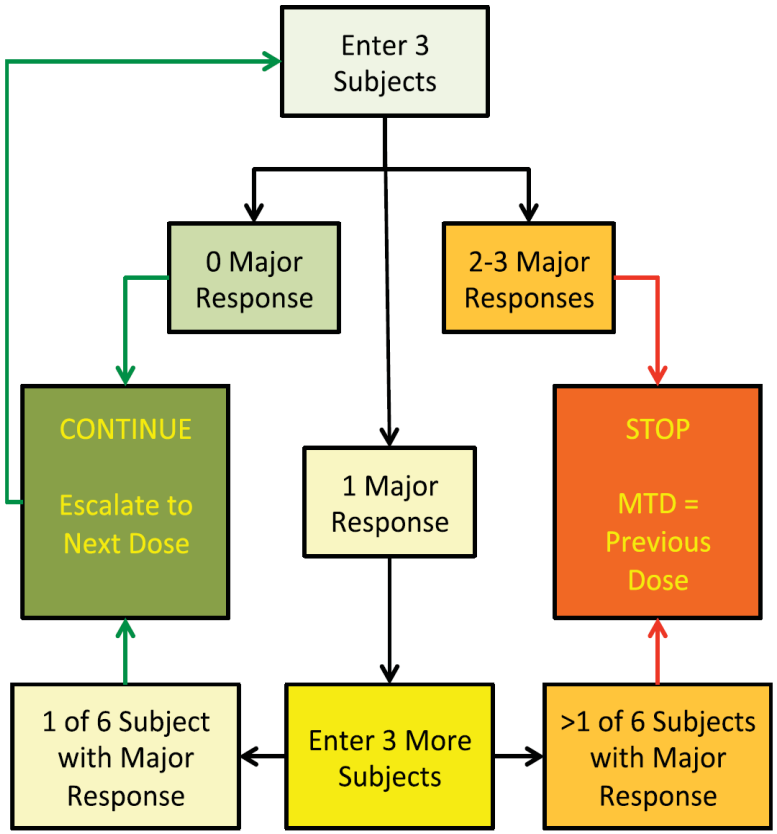
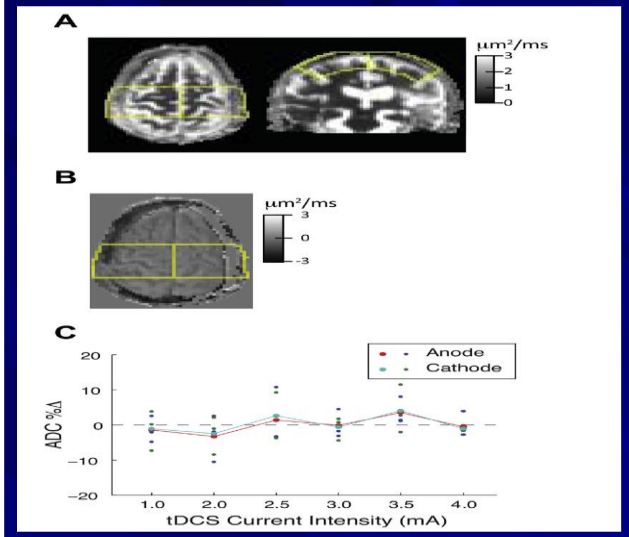


Fig. 2. 3 + 3 dose escalation trial design. Subjects were tested at incremental dose/current levels of 1.0, 2.0, 2.5, 3.0, 3.5 and 4.0 mA, making six dose/current levels with minimum three subjects at each dose/current level.

Table 1
Safety and tolerability profiles at each dose level.

	tDCS current					
	1.0 mA	2.0 mA	2.5 mA	3.0 mA	3.5 mA	4.0 mA
Baseline characteristics						
Subjects (n)	3	3	3	3	3	3
Females (n)	1	0	2	2	1	1
Age (years, Mean)	50	57	53	62	58	52
FM-UE (affected side, Mean)	40	51.3	38	54.7	47	42.7
rMT (affected side, Mean)	42.7	45.3	69.3	36.7	48	39.3
rMT (non-affected side, Mean)	40.3	35.3	36.7	32.7	44.3	44.7
Safety profile						
Second degree skin burn (n)	0	0	0	0	0	0
Clinical seizure (n)	0	0	0	0	0	0
New DWI lesion (n)	0	0	0	0	0	0
Subject discontinuation (n)	0	0	0	0	0	0
Tolerability profile						
Headache (n)	0	0	0	0	0	0
Neck pain (n)	0	0	0	0	0	0
Scalp pain (n)	0	0	0	0	0	0
Tingling (n)	0	0	0	0	0	0
Itching (n)	0	0	0	0	0	0
Burning (n)	0	0	0	0	0	0
Electric shock sensation (n)	0	0	0	0	0	0
Sleepiness (n)	0	0	0	0	0	0
Trouble concentrating (n)	0	0	0	0	0	0
Mood change (n)	0	0	0	0	0	0
Other issues (n)	0	0	0	0	0	0
Skin redness at Anode (n)	2	2	1	0	2	2
Skin redness at Cathode (n)	0	0	0	0	1	2

FM-UE: Fugl Meyer Upper Extremity Scale; **rMT**: Resting Motor Threshold; **DWI**: Diffusion Weighted Imaging.



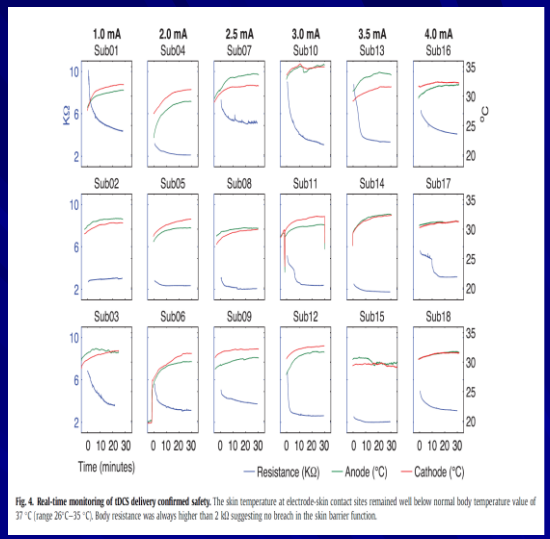


Fig. 4. Real-time monitoring of tDCS delivery confirmed safety. The skin temperature at electrode-skin contact sites remained well below normal body temperature value of 37 °C (range 26°C–35 °C). Body resistance was always higher than 2 kΩ suggesting no breach in the skin barrier function.

Extending the parameter range for tDCS: Safety and tolerability of 4 mA stimulation

Non-invasive brain stimulation with direct currents (tDCS) is increasingly applied to modulate brain physiology, psychological and motor processes, and behavior in humans. The efficacy of tDCS, similar to other non-invasive brain stimulation (NIBS) protocols, is currently limited, including significant variability in individual response. The potential of tDCS to modify respective physiological and psychological processes safely and to a maximum extent, which is of critical importance for clinical application, has so far not been explored systematically for many potentially important parameters. These include electrode positioning, stimulation duration, intensity, timing in relation to task performance, individualization of stimulation protocols, amongst others. Taking into account non-linear features of neuroplasticity, such as the switch from long term depression to potentiation, depending on intraneuronal calcium concentration [1], and brain state-dependency of tDCS, optimization of stimulation effects is not trivial. Previous studies have shown that prolongation of stimulation duration can lead to a switch of directionality of effects [2], and a similar switch from long-term depression to potentiation-like plasticity has been demonstrated for higher stimulation intensity [3]. Moreover, dependent on baseline excitability, different stimulation intensities seem to have maximum efficacy [4]. Thus systematic exploration of safety and effects of extended tDCS protocols is critical for identification of maximally efficient stimulation approaches.

One approach to potentially boost efficacy is increasing stimulation intensity from the conventional limit of 2 mA, but the assumption that higher current boost clinical outcome has not been systematically explored. While animal models suggest a relatively large intensity range of tDCS to enhance neuromodulation at high current densities [5] with no evidence of tissue damage [6], human neurophysiology shows potential non-monotonic effects [3]. Thus, systematic studies to probe extension of tDCS protocol intensity are important. A report in this issue [7] provides initial evidence for the safety of tDCS intensities up to 4 mA.

The authors adapted a 3+3 study design derived mainly from animal studies to probe safety and tolerability of stimulation intensities between 1 and 4 mA for a stimulation duration of 30 min in patients after ischemic stroke, and combined the intervention with occupational therapy. Safety and tolerability of respective protocols were determined via stopping rules in case of serious side effects, tolerability questionnaires, body resistance and skin temperature. The results of this study are in accordance with safety and good tolerability of these extended protocols. No major adverse events did occur, body resistance and skin temperature did not change. The most frequent side effect was a transient skin redness in 50% of all patients, which was however not associated with skin damage.

The results of this study are important, because they deliver first evidence about the safety profile and tolerability of tDCS intensity relevantly higher than that used thus far in most clinical trials. Studies of this type are required to extend the parameter space to optimize efficacy of tDCS, which is of evidently important for optimized clinical studies. However, some relevant caveats have to be taken into consideration. This pilot clinical trial allows no statement about non-deterministic/infrequent side effects, because an inherent design aspect of the study is that only a very limited number of subjects were tested for each stimulation intensity. While this design is sufficient to identify deterministic side effects, it is not well suited to identify infrequent or rare adverse events. Moreover, the obtained tolerability and safety parameters are not suited to rule out subtle tissue alterations, which may not be associated to clinical side effects or the imaging sequences selected for this study, but might be detectable by other imaging techniques or laboratory tests (e.g. MRI, NSE etc.). Though conversely, there is no scientific basis to expect injury based on totality of evidence from animal and human trials [6]. In animal studies, much higher current density was required to induce tissue damage [6,8].

It is important to emphasize that the safety and tolerability of tDCS, as with any NIBS protocol, can be specific to the equipment and accessories used, including electrode size and distance, which are relevant for resulting current density at skin and brain levels, all details of the respective trial protocol including inclusion/exclusion criteria, operator training, and monitoring plan [9]. Thus, the report in this issue is an important step in expanding the range of dose available to researchers. As noted by the authors, prospective physiological and clinical test are required to test usefulness – including potentially individualized dose - within the new range. This is relevant because of the above-mentioned non-linearity of stimulation effects, because stronger stimulation might also involve deeper structures not modulated by "conventional" protocols, which might result in qualitatively different effects, and presumably non-linear effects on task performance, which are well known for other neuromodulatory agents, such as pharmacological interventions. Thus this study represents an important first step to broaden the applicable parameter space for tDCS. Especially for therapeutic applications, more of these studies are required to evaluate the therapeutic usefulness of this intervention. Follow up studies to explore

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"The results of this study are important, because they deliver first evidence about the safety profile and tolerability of tDCS intensity relevantly higher than that used thus far in most clinical trials. Studies of this type are required to extend the parameter space for optimized clinical studies."

ARTICLE
DOI: 10.1038/s41467-018-02928-3 OPEN

Direct effects of transcranial electric stimulation on brain circuits in rats and humans

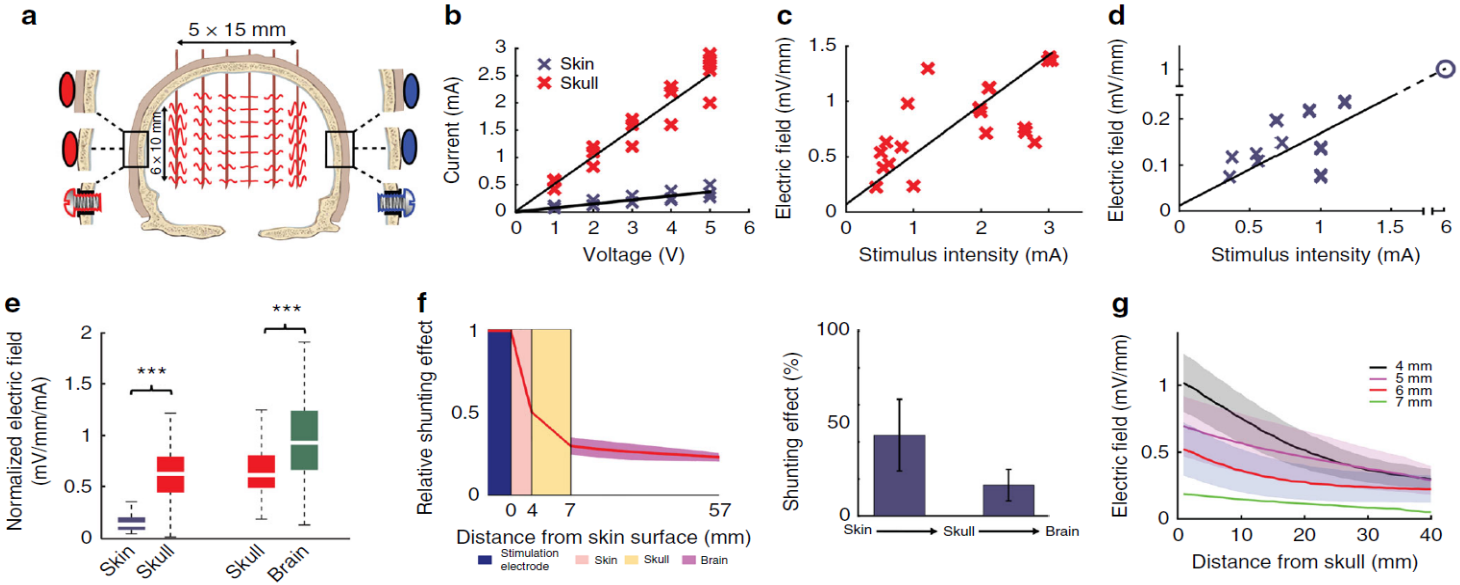


Fig. 5 Skin and subcutaneous soft tissue diffuses scalp-applied current in cadaver brains. **a** Schematic of the experimental arrangement for transcutaneous, subcutaneous, and epidural stimulation. Example signal traces recorded in a coronal plane. Note the phase reversal of sinusoid voltage traces between the two sides. **b** Both transcutaneous and subcutaenous stimulation show intensity-independent linear (ohmic) properties ($n = 81$ in four different arrangements in 10 cadavers, $R = 0.92$, $P < 0.001$ for subcutaneous, and $n = 14$ in 6 cadavers, $R = 0.86$, $P < 0.001$ for transcutaneous stimulation; raw data and fitted line are shown), which allows the calculation of voltage–current relationship. **c**, **d** Subcutaneous stimulation (**c**, $R = 0.56$, $P < 0.001$, $n = 29$ in 10 cadavers) elicited several-fold larger intracerebral gradients compared to transcutaneous stimulation (**d**, $R = 0.8$, $P < 0.001$, $n = 16$ in 6 cadavers). Extrapolation from the measured data indicates that approximately 6 mA transcutaneous current can induce 1 mV/mm intracerebral electric field (circle). Raw data and fitted lines are shown. **e** Ratios of induced intracerebral fields and stimulus amplitude in trancutaneous vs. subcutaneous ($P < 0.001$, $n = 36$ in two different arrangements in 6 cadavers), and subcutaneous vs. epidural stimulation ($P < 0.001$, $n = 60$ in 3 cadavers). **f** 58 ± 7% of the applied current is shunted by skin and soft tissue and a further 16 ± 8% is attenuated by the serial resistance of the skull. **g** Effect of skull thickness on induced fields ($n = 64$ in 8 cadavers)

In support of the estimated voltage gradients from the cadaver experiments and the 'minimum' fields (~1 mV/mm) in rodents to affect network activity, we found that >4.5 mA currents were required to reliably bias the amplitude of occipital alpha waves.

CURRENT OPINION

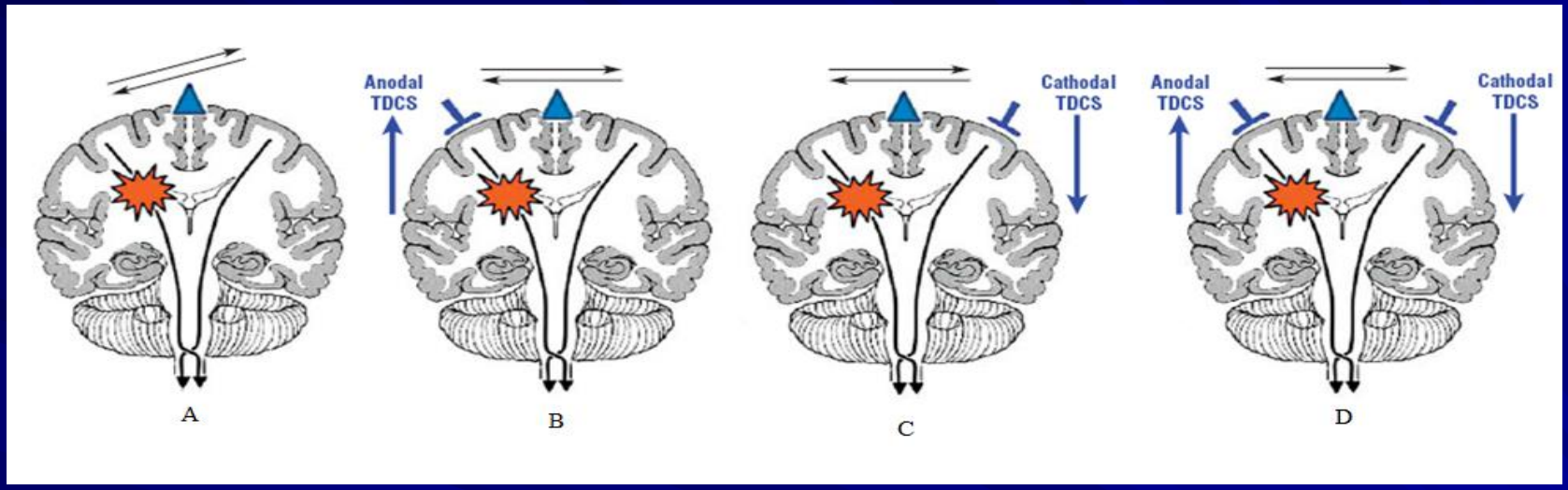
Noninvasive brain stimulation after stroke: it is time for large randomized controlled trials!

Christian Grefkes[a,b] *and Gereon R. Fink*[a,b]

- Meta-analysis suggests there is a dose-response relationship between current density and motor impairment reduction
- High current level up to 4mA is likely safe and tolerable in ischemic stroke patients
- Direct current can penetrate inside of human brain and can be detected.
- Majority of prior tDCS studies are small sample and likely all under powered

- Dosage
- Montage
- Blinding issue
- Patient selection
- Outcome measure(s)
- Peripheral Rehab Therapy
- power issue in small study

Bihemispheric Montage is likely Better



A

Study or Subgroup	tDCS (Change Scores) Mean	SD	Total	Sham (Change Scores) Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Anodal								
Hesse 2011 Anodal	10.75	11.77	32	11.91	11.43	32	13.8%	−0.10 [−0.59, 0.39]
Kim 2010 Anodal	25.67	12.32	6	2.29	13.86	7	7.9%	1.65 [0.32, 2.98]
Sattler 2015 Anodal	6.6	4.2	10	9	6.2	10	10.8%	−0.43 [−1.32, 0.46]
Subtotal (95% CI)			**48**			**49**	**32.5%**	**0.21 [−0.72, 1.14]**
Heterogeneity: Tau² = 0.47; Chi² = 6.99, df = 2 (P = 0.03); I² = 71%								
Test for overall effect: Z = 0.45 (P = 0.65)								
Cathodal								
Fusco 2014 Cathodal	4	5	5	4	7	6	8.7%	0.00 [−1.19, 1.19]
Hesse 2011 Cathodal	11.72	8.39	32	11.91	11.43	32	13.8%	−0.02 [−0.51, 0.47]
Kim 2010 Cathodal	21.8	16.39	5	2.29	13.86	7	8.1%	1.21 [−0.08, 2.50]
Nair 2011 Cathodal	4.14	2.7	7	1.61	1.5	7	9.0%	1.08 [−0.07, 2.23]
Subtotal (95% CI)			**49**			**52**	**39.6%**	**0.43 [−0.23, 1.08]**
Heterogeneity: Tau² = 0.20; Chi² = 5.46, df = 3 (P = 0.14); I² = 45%								
Test for overall effect: Z = 1.28 (P = 0.20)								
Bihemispheric								
Bolognini 2011 Bihemi	5.9	5.06	7	1.4	3.41	7	9.1%	0.98 [−0.15, 2.11]
Lindenberg 2010 Bihemi	5.6	1.92	10	1.15	0.85	10	7.9%	2.87 [1.55, 4.19]
Viana 2014 Bihemi	9.3	5.7	10	7.5	7.1	10	10.9%	0.27 [−0.61, 1.15]
Subtotal (95% CI)			**27**			**27**	**27.9%**	**1.30 [−0.14, 2.75]**
Heterogeneity: Tau² = 1.30; Chi² = 10.30, df = 2 (P = 0.006); I² = 81%								
Test for overall effect: Z = 1.77 (P = 0.08)								
Total (95% CI)			**124**			**128**	**100.0%**	**0.61 [0.08, 1.13]**
Heterogeneity: Tau² = 0.46; Chi² = 30.51, df = 9 (P = 0.0004); I² = 71%								
Test for overall effect: Z = 2.25 (P = 0.02)								
Test for subgroup differences: Chi² = 1.60, df = 2 (P = 0.45), I² = 0%								

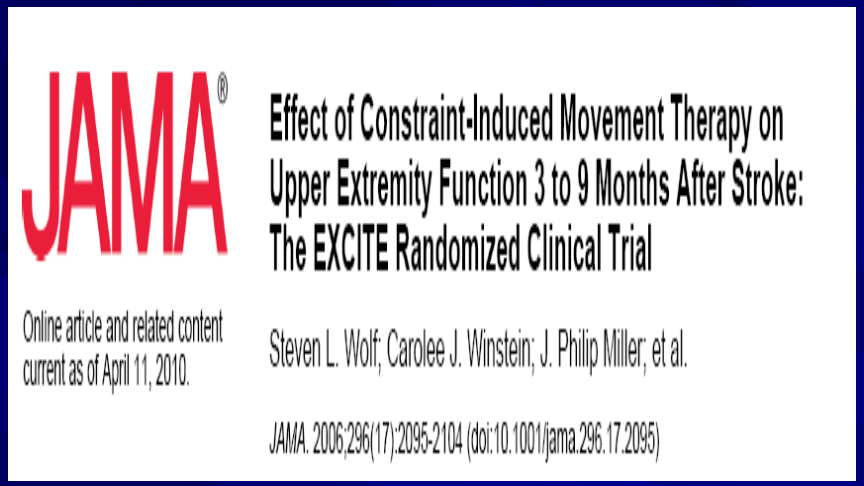
Std. Mean Difference
IV, Random, 95% CI

−4 −2 0 2 4

Favors Sham Favors tDCS

Selection of Rehabilitation Therapy

Mean difference = (tDCS + RT) – (sham stimulation + RT)



Key Features of Constraint-Induced Movement Therapy (CIMT)

- Effective
- Standardized
- Quantifiable
- Available

Timing of Intervention
critical period after stroke

Acute phase

- Challenging medical issues
- Lack of validated patient selection tool
- Robust natural stroke recovery

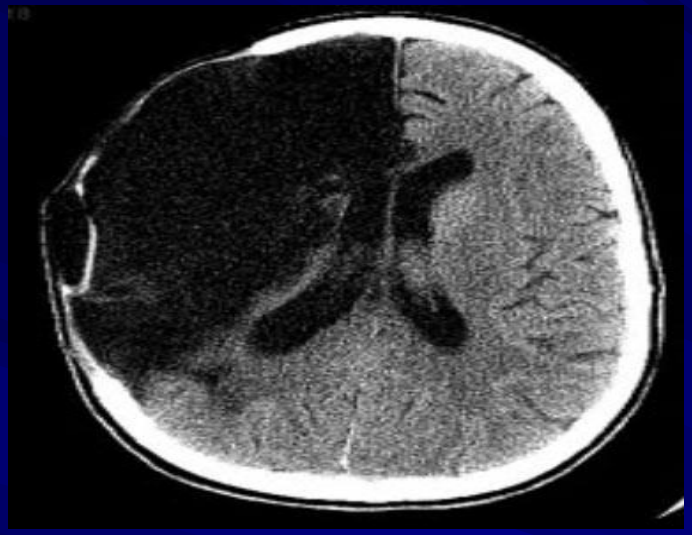
Chronic phase

- Stable deficit
- Easy to detect treatment effect
- Few confounders
- Odds of success is a little higher

We choose the subacute phase: 1-6 months from the stroke

Now CPASS study support this subacute phase is likely the critical period after stroke

Patient Selection



- >10° of active wrist extension, >10° of thumb abduction/extension, and > 10° of extension in at least 2 additional digits; and
- Unilateral limb weakness with a Fugl-Meyer Upper Extremity score of ≤ 54 (out of 66) to avoid ceiling effects; and
- An absolute difference of FM-UE scores between the two baseline assessments that is ≤ 2 points indicating stable motor impairment; if subject is not stable, then he/she will be invited for a reassessment after 1-2 weeks (but no more than 3 reassessments); and

Epidural Electrical Stimulation for Stroke Rehabilitation: Results of the Prospective, Multicenter, Randomized, Single-Blinded *Everest* Trial

Abstract

Background. This prospective, single-blinded, multicenter study assessed the safety and efficacy of electrical epidural motor cortex stimulation (EECS) in improving upper limb motor function of ischemic stroke patients with moderate to moderately severe hemiparesis. *Methods*. Patients ≥4 months poststroke were randomized 2:1 to an investigational (n = 104) or control (n = 60) group, respectively. Investigational patients were implanted (n = 94) with an epidural 6-contact lead perpendicular to the primary motor cortex and a pulse generator. Both groups underwent 6 weeks of rehabilitation, but EECS was delivered to investigational patients during rehabilitation. The primary efficacy endpoint (PE) was defined as attaining a minimum improvement of 4.5 points in the upper extremity Fugl-Meyer (UEFM) scale as well as 0.21 points in the Arm Motor Ability Test (AMAT) 4 weeks postrehabilitation. Follow-up assessments were performed 1, 4, 12, and 24 weeks postrehabilitation. Safety was evaluated by monitoring adverse events (AEs) that occurred between enrollment and the end of rehabilitation. *Results*. Primary intent-to-treat analysis showed no group differences at 4 weeks, with PE being met by 32% and 29% of investigational and control patients, respectively ($P = .36$). Repeated-measures secondary analyses revealed no significant treatment group differences in mean UEFM or AMAT scores. However, post hoc comparisons showed that a greater proportion of investigational (39%) than control (15%) patients maintained or achieved PE ($P = .003$) at 24 weeks postrehabilitation. Investigational group mean AMAT scores also improved significantly ($P < .05$) when compared to the control group at 24 weeks postrehabilitation. Post hoc analyses also showed that 69% (n = 9/13) of the investigational patients who elicited movement thresholds during stimulation testing met PE at 4 weeks, and mean UEFM and AMAT scores was also significantly higher ($P < .05$) in this subgroup at the 4-, 12-, and 24-week assessments when compared to the control group. Headache (19%), pain (13%), swelling (7%), and infection (7%) were the most commonly observed implant procedure-related AEs. Overall, there were 11 serious AEs in 9 investigational group patients (7 procedure related, 4 anesthesia related). *Conclusions*. The primary analysis pertaining to efficacy of EECS during upper limb motor rehabilitation in chronic stroke patients was negative at 4 weeks postrehabilitation. A better treatment response was observed in a subset of patients eliciting stimulation induced upper limb movements during motor threshold assessments performed prior to each rehabilitation session. Post hoc comparisons indicated treatment effect differences at 24 weeks, with the control group showing significant decline in the combined primary outcome measure relative to the investigational group. These results have the potential to inform future chronic stroke rehabilitation trial design.

Clinical Research Articles

Combined Transcranial Direct Current Stimulation and Robot-Assisted Arm Training in Subacute Stroke Patients: An Exploratory, Randomized Multicenter Trial

Stefan Hesse, MD[1], Andreas Waldner, MD[2], Jan Mehrholz, PhD[3], Christopher Tomelleri, PhD[2], Michael Pohl, MD[3], and Cordula Werner, MA[1]

Neurorehabilitation and Neural Repair
25(9) 838–846

DOI: 10.1177/1545968311413906
http://nnr.sagepub.com
SAGE

Blinding & Randomization

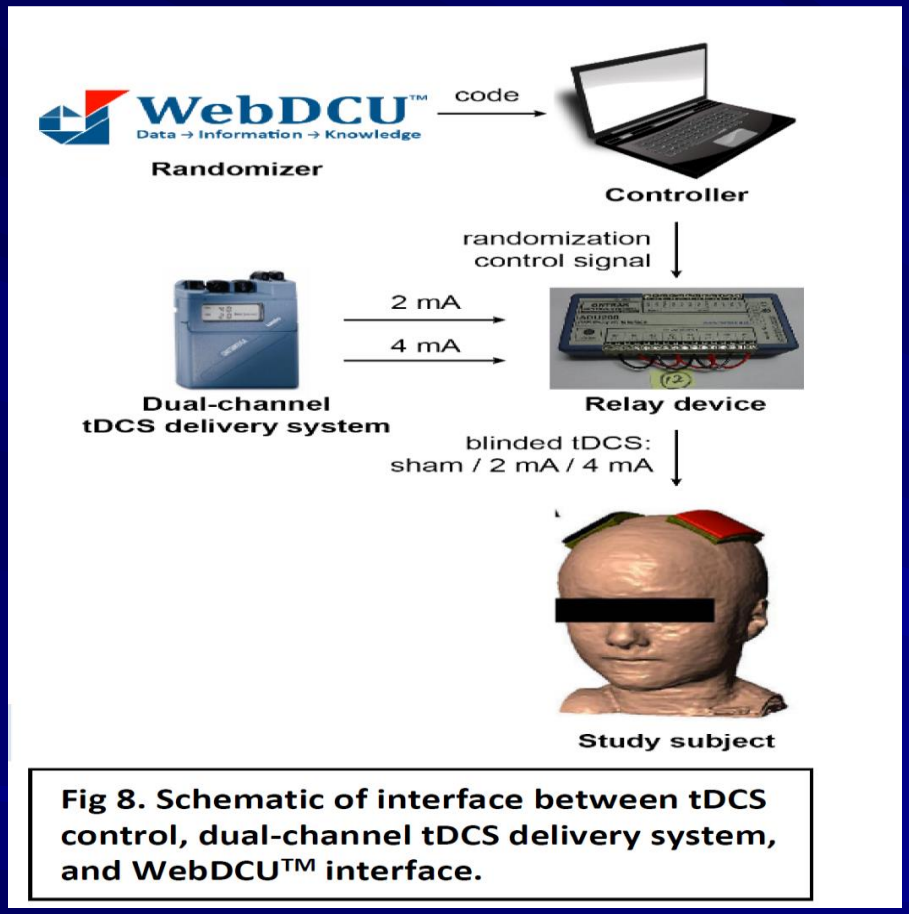


Fig 8. Schematic of interface between tDCS control, dual-channel tDCS delivery system, and WebDCU™ interface.

- Centrally controlled automated randomization process
- Participant, therapist, PI and tDCS technician are all blinded.
- Therapist is not allowed to do tDCS and outcome assessment to minimize bias

Choices of Outcomes

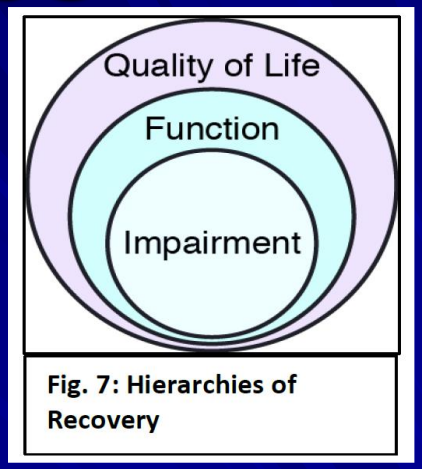
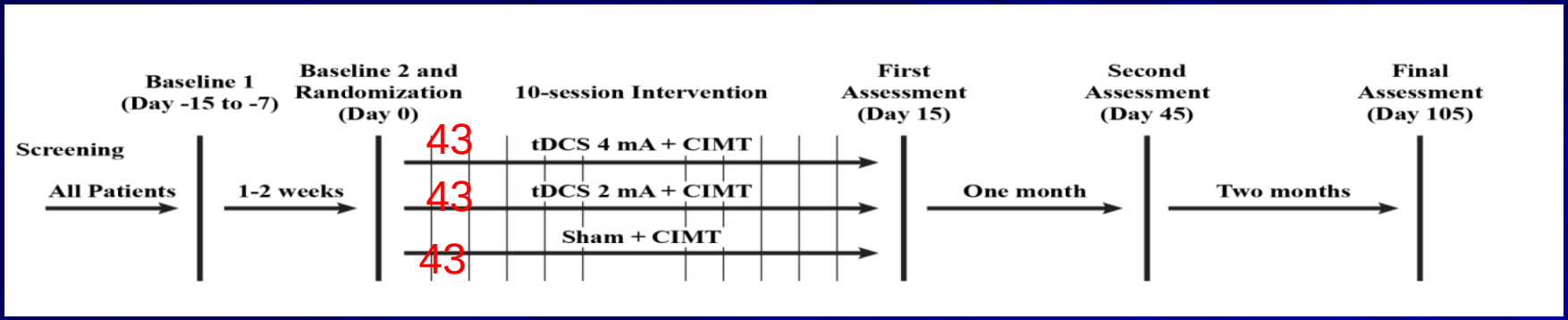


Fig. 7: Hierarchies of Recovery

- **Primary Outcome**
  - Fugl-Meyer Upper Extremity scale: Motor Impairment
- **Secondary Outcomes**
  - Wolf Motor Function Test: Motor Function
  - Stroke Impact Scale (Hand Subscale): Quality of Life
  - Secondary outcomes should have the same trend or consistent with the primary outcome
- Good psychometric property: ***reliability, validity and responsiveness***

TRANSPORT2 Study Design

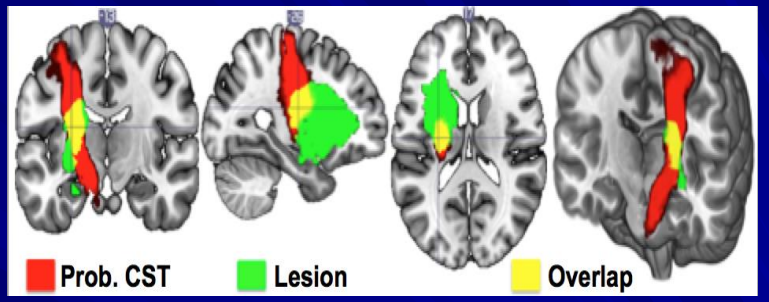


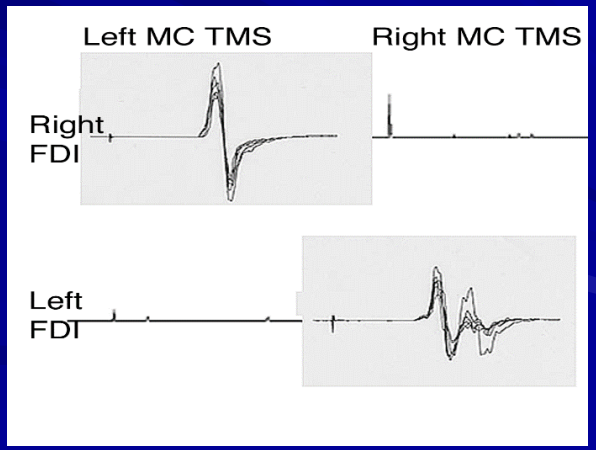
- **Primary Aim**: To determine whether there is an initial overall treatment effect (FM-UE) among 3 dosing groups: (sham + mCIMT vs. 2 mA + mCIMT vs. 4 mA + mCIMT)
  - Efficacy (FM-UE change) is measured at day 15 after the initiation of the 10-day intervention.
- **Secondary Aims**: To confirm that the proposed intervention is **safe**, **tolerable**, and **feasible** to administer in a multi-site trial setting.
  - Safety: Rate of Adverse Events
  - Tolerability: Visual Analog Scale
  - Feasibility: Treatment Completion Rate

Exploratory Aims

PATIENT SELECTION

- To examine whether ***wCST-LL (structural assessment of integrity of descending motor tract)*** or ***MEPs (functional assessment of integrity of descending motor tract)*** or ***combination of both*** are correlated with changes in FM-UE scale, and evaluate the utility of these measures as biomarkers for subject selection criteria in the future confirmatory Phase III study
- To examine whether functional or structural changes in motor tracts correlates with changes in impairment and functional motor activity induced by the intervention.





Go or No-Go Decision for Phase II >> Phase III

	Feasible	95% CI			Primary P-Value	Safe	Tolerable	Secondary Endpoints	Conclusion
		Sham	2mA	4mA					
A	N								*No-Go: The trial was terminated early due to lack of feasibility*
B	Y	4.4 (2.4, 6.3)	4.4 (1.5, 7.2)	3.3 (0.7, 5.8)	**0.52**	Y	Y		*No-Go: The study will not proceed to Phase III, because the confidence interval includes the hypothesized null treatment effect, 4.5, for both active doses and the p-value is not significant. Therefore, the study results do not support the additional investigation.*
C	Y	**4.1 (1.3, 6.8)**	**2.8 (0.3, 5.2)**	**0.1 (-2.9, 3.2)**	0.04	Y	Y		*No-Go: Although we reject the null hypothesis of no-difference, the difference is in the wrong direction as evidenced by the confidence intervals.*
D	Y	4.3 (1.9, 6.7)	9.7 (6.9, 12.6)	12.1 (9.6, 14.6)	<0.001	Y	Y	Consistent	*Go: We will reject the primary null hypothesis and conclude that at least one treatment arms is different. Both arms are safe, tolerable, and demonstrate a signal of improvement at day 15. We would consider proceeding with the 4mA arm because there is modest evidence that it is better than 2mA*
E	Y	4.3 (1.9, 6.7)	9.7 (6.9, 12.6)	12.1 (9.6, 14.6)	<0.001	Y	**N (4mA)**	Consistent	*Go: The evidence for efficacy is the same as above, however since the 4mA was not tolerable to patients, a Phase III comparing 2mA vs. sham would be proposed.*
F	Y	4.3 (1.9, 6.7)	9.7 (6.9, 12.6)	12.1 (9.6, 14.6)	<0.001	Y	Y	**Inconsistent**	*No-Go: Although we reject the primary null hypothesis and conclude that at least one treatment arm is different, neither WMFT nor SIS show any indications of efficacy. Ad Hoc exploratory analysis would be required to explain this discrepancy before proceeding.*
G	Y	4.5 (2.3, 6.6)	9.1 (7.1, 11.2)	10.3 (7.7, 13.0)	<0.001	Y	Y	**Consistent**	*Go: There is sufficient evidence that tDCS active arm is better than sham. However, there is not a strong difference between the two doses in the primary outcome (FM-UE). In this case, we will proceed with 2mA*
H	Y	4.5 (2.3, 6.6)	9.1 (7.1, 11.2)	10.3 (7.7, 13.0)	<0.001	Y	Y	**Inconsistent**	*Go: The evidence for efficacy is the same as above, however the WMFT and SIS clearly indicate that 4mA has additional benefits in functional and QOL improvement. In this case, we will proceed with 4mA*

Eligibility

Inclusion

- 1) 18-80 years old; and
- 2) First-ever unihemispheric ischemic stroke radiologically verified and occurred within the past 30-180 days; and
- 3) >10° of active wrist extension, >10° of thumb abduction/extension, and > 10° of extension in at least 2 additional digits; and
- 4) Unilateral limb weakness with a Fugl-Meyer Upper Extremity score of ≤ 54 (out of 66) to avoid ceiling effects; and
- 5) An absolute difference of FM-UE scores between the two baseline assessments that is ≤ 2 points indicating stable motor impairment; if subject is not stable, then he/she will be invited for a reassessment after 1-2 weeks (but no more than 3 reassessments); and
- 6) Pre-stroke mRS ≤2; and
- 7) Signed informed consent by the subject or Legally Authorized Representative (LAR)

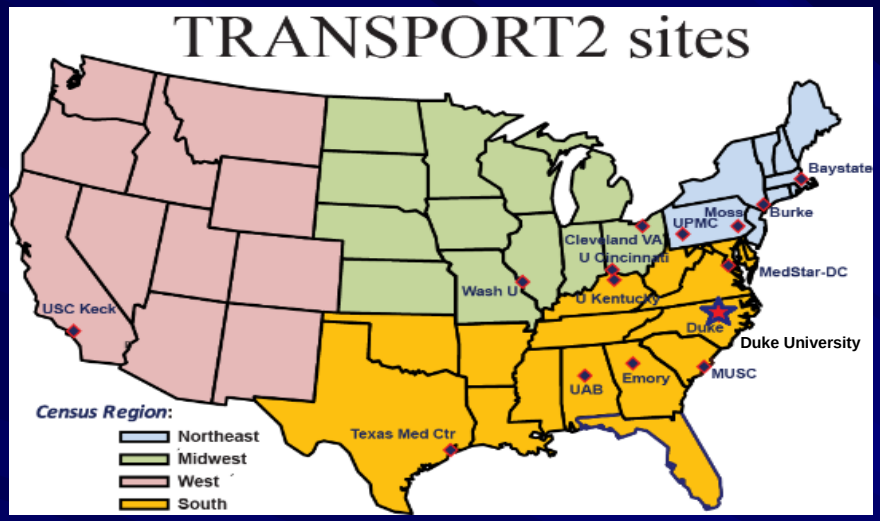
Exclusion

- **1) Primary intracerebral hematoma, subarachnoid hemorrhage or bi-hemispheric or bilateral brainstem ischemic strokes;**
- **.....**
- **5) Moderate to severe cognitive impairment defined as Montreal Cognitive Assessment (MOCA) score < 18/30;**
- **....**
- 8) **Presence of any MRI/tDCS/TMS risk factors including but not limited to:**
  - **8a) an electrically, magnetically or mechanically activated metallic or nonmetallic implant including cardiac pacemaker, intracerebral vascular clips or any other electrically sensitive support system;**
  - **8b) a non-fixed metallic part in any part of the body, including a previous metallic injury to eye;**
  - **8c) pregnancy (effects of MRI, TMS, and tDCS on the fetus are unknown);**
  - **8d) history of seizure disorder or post-stroke seizure;**
  - **8e) preexisting scalp lesion under the intended electrode placement or a bone defect or hemicraniectomy;**
- **.....**
- **11) Has received Botulinum toxin injection to the affected upper extremity in the past 3 months prior to randomization or expectation that Botulinum will be given to the Upper Extremity prior to the completion of the last follow-up visit;**
- **13) Doesn't speak sufficient English to comply with study procedures;**
- **14) Expectation that subject cannot comply with study procedures and visits.**

TRANSPORT2 MAJOR TIME LINES

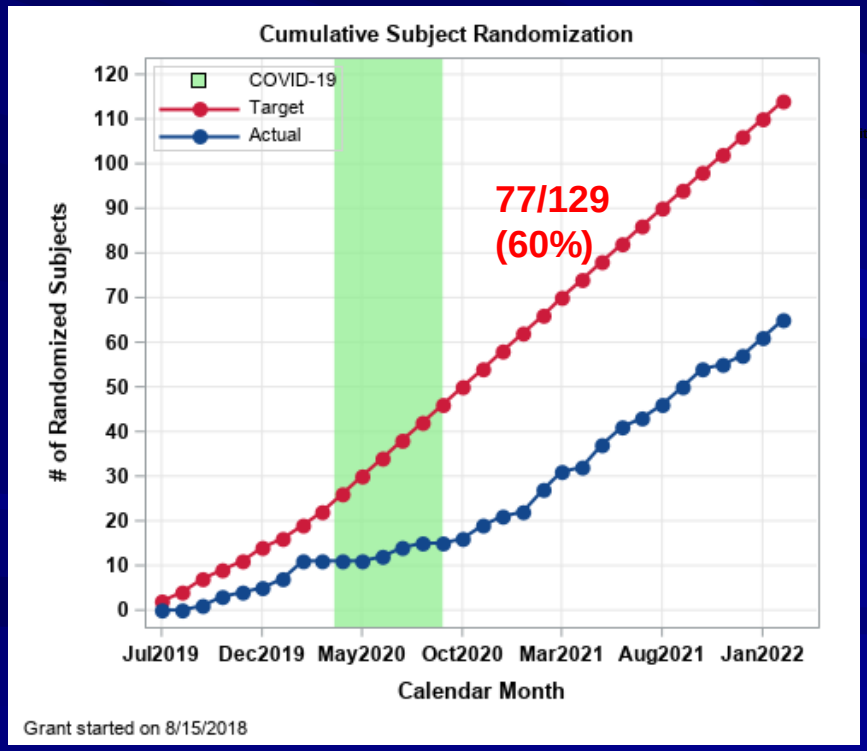
- First presentation with recovery working group (03/10/16)
- Budget approval by NIH Executive Scientific Committee (07/25/16)
- First grant submission (10/05/16)
- Study section meeting (04/18/2017, delayed from 02/25/17) Impact score: 51
- Revised submission (07/10/2017)
- Study section meeting (11/02/2017) Impact score: 29
- NINDs advisory council met and approved (02/01/2018)
- Transport2 weekly meeting started (03/14/2018)
- NOA released (08/15/2018 and start grant on 09/01/2018)
- cIRB approved (10/29/2018)
- First investigator meeting/training workshop (02/25-02/26/2019)
- Expected first participant enrollment (04/30/2019) but the first participant was enrolled in 09/01/2019
- Strokenet shutdown trial enrollment due to covid19 on 03/2020
- Strokenet resume trial enrollment on 08/2020
- Trial reach 50% enrollment on 03/2022

Almost 2 years



NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY
Funded by a Grant from the National Institutes of Health

RACE_CAT	Frequency	Percent	Cumulative Frequency	Cumulative Percent
ASIAN	2	2.99	2	2.99
BLACK	28	41.79	30	44.78
UNKNOWN	2	2.99	32	47.76
WHITE	35	52.24	67	100.00



	N (%) MISSING VISITS OVER EXPECTED VISITS
15 Day Follow-Up	1/62 (1.6%)
45 Day Follow-Up	6/59 (10.2%)
105 Day Follow-Up	2/54 (3.7%)

1 patient suffered covid19, had to be discontinued from study (3 visits), 4 patients could not be Followed due to strokenet shut down for nearly 5 months (5 visits) and only 1 patients missed one visit.
With regard to the primary endpoint = 98.4%

Lessons Learned - Part I

- Things are easy in one site may not be easy on multi-center trial setting
  - Manual of operation has to be crystal clear
  - List of frequently asked question is useful
- The first enrollment is always tough
  - Implement training protocol
  - Protocol warm-up site call on the Friday before the first enrollment
- You need to learn to compromise which can be not-easy for scientist
  - Set up small meeting to reach overall consensus and get nod from the big meeting
- You need to be positive and find opportunity to recognize/praise your team

Lessons Learned – Part II

- Sometimes you have to be hands-on certain things
  - We provide detailed information – nailed down on days to enroll or not to enroll during the holiday season
- Build a fast respond team
  - Everyone has project manager's and my cellphone number
- Be a good listener to the study coordinators
  - Monthly study coordinators only meeting to specifically hear their needs and concerns
- Communication, communication, communication
  - Weekly operation committee meeting
  - Biweekly PIs and project managers meeting
  - Bimonthly site-wide call meeting
  - Monthly study coordinators only meeting

TRANSPORT2 ORGANIZATION

NINDS

- Sponsor
- Grant management

National Coordination Center (NCC)

- *Contracting*
- *Site initiation & Payment*
- *Regulatory*

TRANSPORT2 Sites

- *Patient recruitment*
- *Study protocol execution*
- *Data collection*

National Data Management Center (NDMC)

- Data management
- Site monitoring
- Statistical Analysis

TRANSPORT2 Central Team

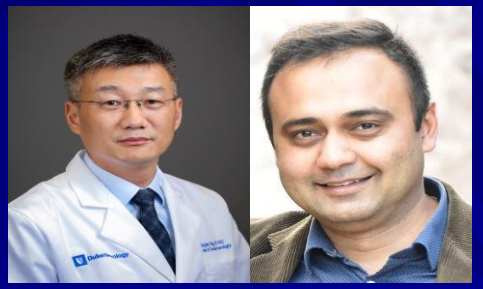
- Protocol development
- MOP development & Training
- Imaging and TMS Data analysis
- Grant Management

Assemble team and appoint the right person

CIMT core

Outcome assessment core

tDCS core



Imaging core

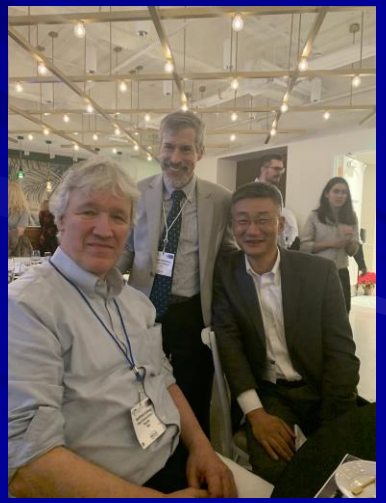
TMS core

Project manager

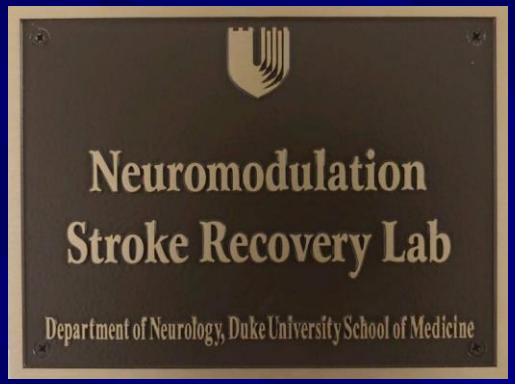
Standardization & Quality Control

- TMS protocol
- tDCS protocol
- MRI protocol
- Outcome assessment certification process
  - Fugl-Meyer Upper Extremity scale
    - Online certificate, one-day workshop, training subject with self & central assessment, central adjudication, recertification process
  - Wolf motor function test
  - Stroke impact scale
- Constraint-induced movement therapy protocol & certification process

Team Engagement and Connection



TRANSPORT2 Family Picture

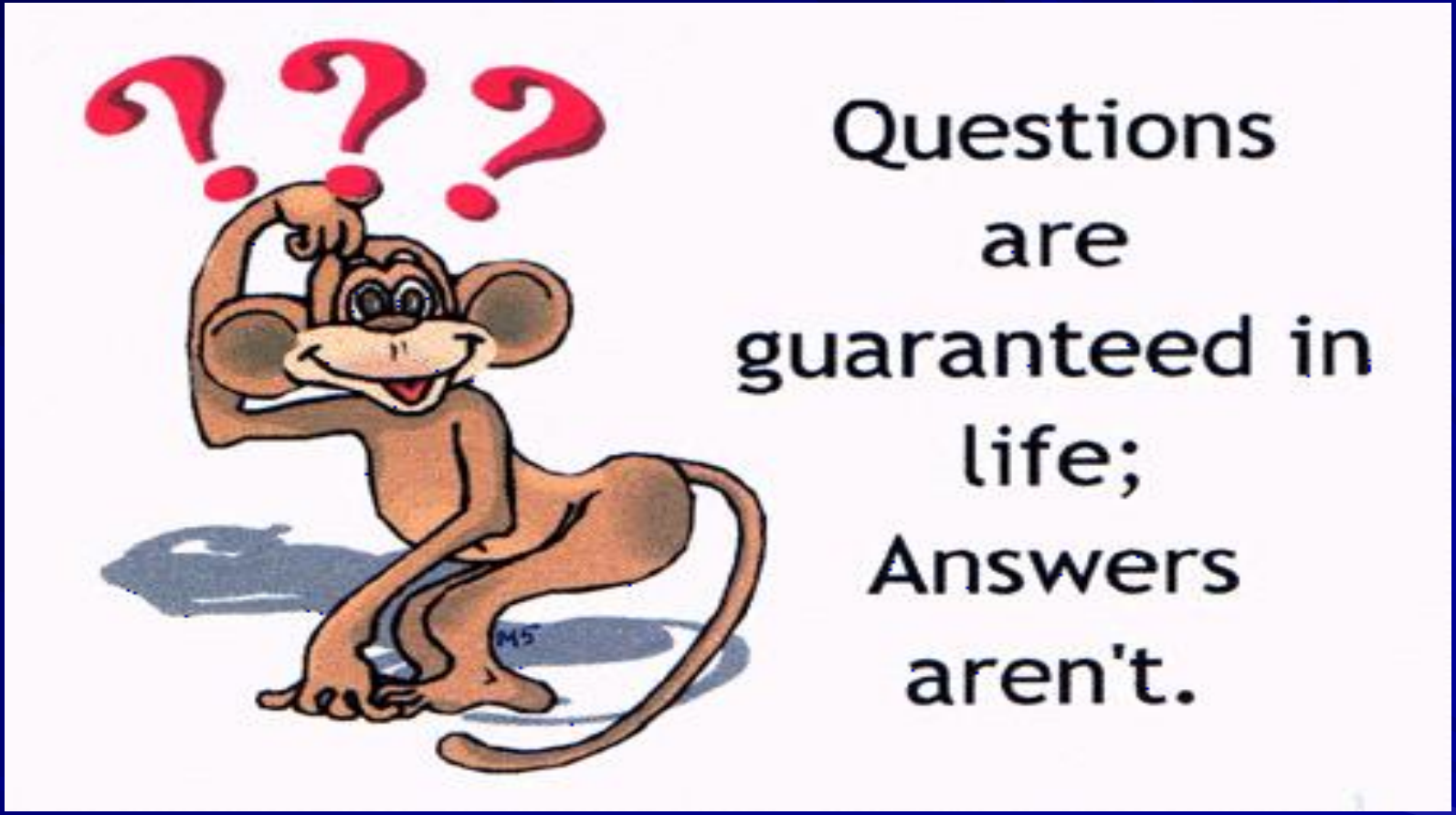


Transcranial direct current stimulation
Multi-center Phase II study

Motor imagery driven Brain-Computer Rehab system
Phase I/IIa study

Low intensity focused transcranial ultrasonic stimulation Phase I parameter optimization study

Questions?



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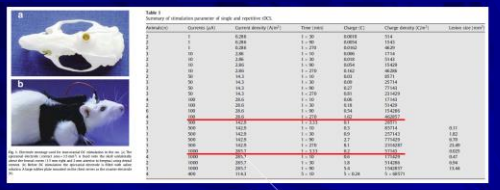
Transcranial Direct Current Stimulation for Poststroke Motor Recovery: Challenges and Opportunities

Wuwei Feng, MD, MS, Steven A. Kautz, PhD, Gottfried Schlaug, MD, PhD, Caitlyn Meinzer, PhD, Mark S. George, MD, Pratik Y. Chhatbar, MD, PhD

- Animal study suggest our dosing regimen is only about 1/100 of safety threshold dose in animal.
- Simulation data suggest there is likely under dosing issue in human tDCS study.
- Meta-analysis suggests there is a dose-response relationship between current density and motor impairment reduction
- Direct current can penetrate inside of human brain in a cohort of patients with Parkinson disease and can be detected.
- High current level up to 4mA is likely safe and tolerable in ischemic stroke patients



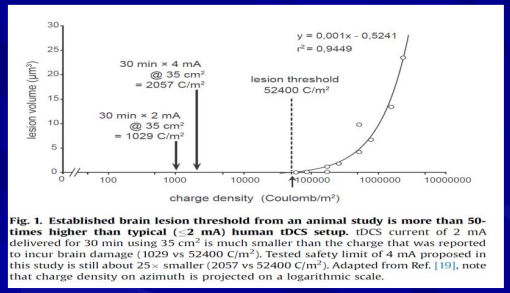
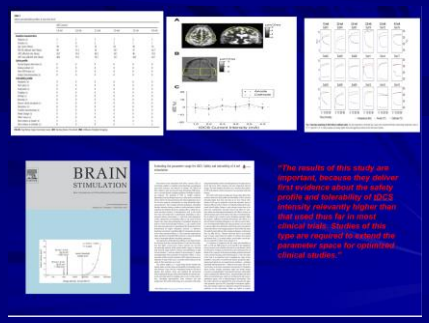
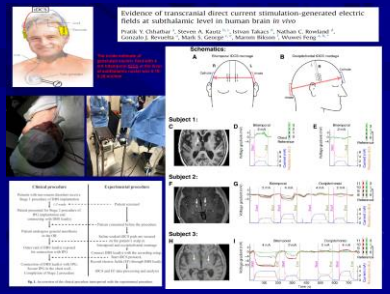
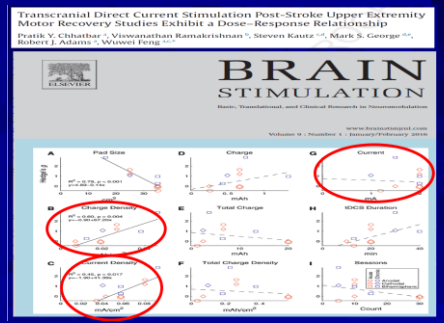
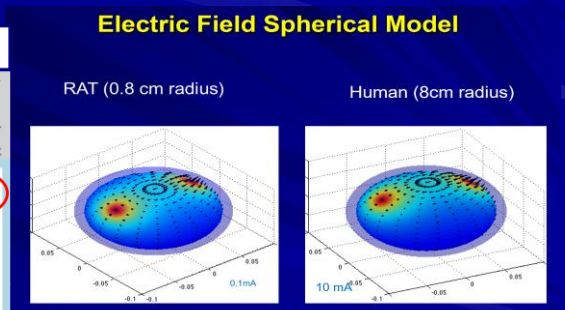


Fig. 1. Established brain lesion threshold from an animal study is more than 50-times higher than typical (≤2 mA) human tDCS setup. tDCS current of 2 mA delivered for 30 min using 35 cm² is much smaller than the charge that was reported to incur brain damage (1029 vs 52400 C/m²). Tested safety limit of 4 mA proposed in this study is still about 25× smaller (2057 vs 52400 C/m²). Adapted from Ref. [19], note that charge density on azimuth is projected on a logarithmic scale.





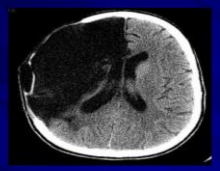




CURRENT OPINION

Noninvasive brain stimulation after stroke: it is time for large randomized controlled trials!

Christian Grefkes[a,b] *and Gereon R. Fink*[a,b]



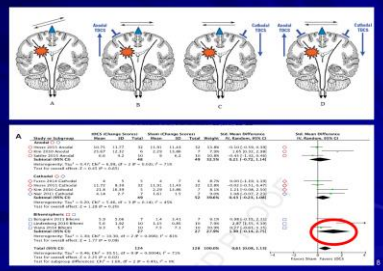
- >10° of active wrist extension, >10° of thumb abduction/extension, and > 10° of extension in at least 2 additional digits; and
- Unilateral limb weakness with a Fugl-Meyer Upper Extremity score of ≤ 54 (out of 66) to avoid ceiling effects; and
- An absolute difference of FM-UE scores between the two baseline assessments that is ≤ 2 points indicating stable motor impairment: if subject is not stable, then he/she will be invited for a reassessment after 1-2 weeks (but no more than 3 reassessments); and

Epidural Electrical Stimulation for Stroke Rehabilitation: Results of the Prospective, Multicenter, Randomized, Single-Blinded *Everest* Trial

Combined Transcranial Direct Current Stimulation and Robot-Assisted Arm Training in Subacute Stroke Patients: An Exploratory, Randomized Multicenter Trial

Stefan Hesse, MD[1], Andreas Waldner, MD[1], Jan Mehrholz, PhD[2], Christopher Tomelleri, PhD[1], Michael Pohl, MD[2], and Cordula Werner, MA[1]

Bihemispheric Montage is likely Better



Selection of Rehabilitation Therapy

Mean difference = (tDCS + RT) – (sham stimulation + RT)

Key Features of Constraint-Induced Movement Therapy (CIMT)

- Effective
- Standardized
- Quantifiable
- Available

Blinding & Randomization

Fig 8. Schematic of interface between tDCS control, dual-channel tDCS delivery system, and WebDCU™ interface.

- Centrally controlled automated randomization process
- Participant, therapist, PI and tDCS technician are all blinded.
- Therapist is not allowed to do tDCS and outcome assessment to minimize bias

Timing of Intervention

critical period after stroke

Acute phase

- Challenging medical issues
- Lack of validated patient selection tool
- Robust natural stroke recovery

Chronic phase

- Stable deficit
- Easy to detect treatment effect
- Few confounders
- Odds of success is a little higher

We choose the subacute phase: 1-6 months from the stroke

Now CPASS study support this subacute phase is likely the critical period after stroke

Dosage
Montage
Blinding
Time of intervention
Patient selection
Outcome measure(s)
Peripheral Rehab Therapy
power issue in small study

Choices of Outcomes

- **Primary Outcome**
  - Fugl-Meyer Upper Extremity scale: Motor Impairment
- **Secondary Outcomes**
  - Wolf Motor Function Test: Motor Function
  - Stroke Impact Scale (Hand Subscale): Quality of Life
  - Secondary outcomes should have the same trend or consistent with the primary outcome
- Good psychometric property: ***reliability, validity and responsiveness***

Fig. 7: Hierarchies of Recovery