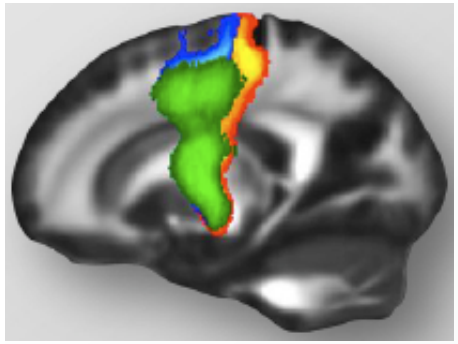
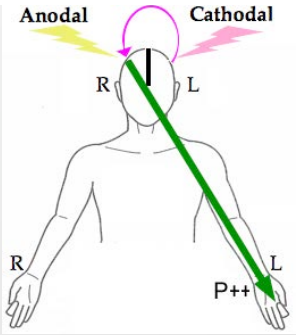




TRANScranial direct current stimulation for Post-stroke mOtor Recovery – a phase 2 sTudy (TRANSPORT2)

Gottfried Schlaug MD PhD
Beth Israel Deaconess Medical Center and Harvard Medical School
&
Wayne Feng MD MS
Medical University of South Carolina

NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

Funded by a Grant from the National Institutes of Health

Welcome

The NIH has created the NIH StrokeNet to conduct small and large clinical trials and research studies to advance acute stroke treatment, stroke prevention, and recovery and rehabilitation following a stroke. This network of 25 regional centers across the U.S., which involves more than 200 hospitals, is designed to serve as the infrastructure and pipeline for exciting new potential treatments for patients with stroke and those at risk for stroke. In addition, NIH StrokeNet will provide an educational platform for stroke physicians and clinical trial coordinators.

CLINICAL TRIALS

PREVENTION

ACUTE INTERVENTION

RECOVERY

Recovery from Stroke

- >50% with significant impairment @ 3 mo; stroke is the leading cause of lost disability-adjusted life years (Johnston et al., 2008; Saposnik, 2011)
- Most patients receive usual PT/OT/ST although the efficacy for each one of them is not clear.
- Acute to 3 months outcome can be predicted by behavioral and imaging measures; recent studies found either no or only weak effects for dose of usual PT/OT (Byblow et al., 2015; Lang et al., 2016)
- Only one randomized-controlled Phase III trial has shown efficacy (EXCITE using CIMT) (Wolf et al; JAMA, 2007)

Constraint-induced Movement Therapy (CIMT)
An Efficacy-proven Rehabilitation Therapy

JAMA®

Effect of Constraint-Induced Movement Therapy on Upper Extremity Function 3 to 9 Months After Stroke: The EXCITE Randomized Clinical Trial

Steven L. Wolf; Carolee J. Winstein; J. Philip Miller; et al.

JAMA. 2006;296(17):2095-2104 (doi:10.1001/jama.296.17.2095)

- Effective
- Standardized
- Quantifiable
- Available

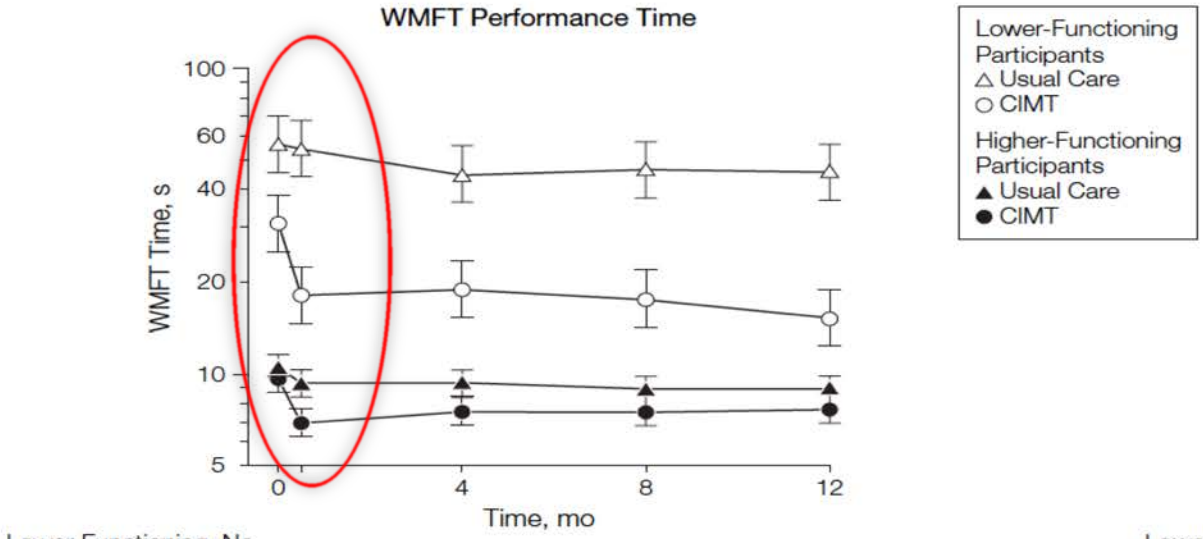
EXCITE trial was the first NIH sponsored stroke rehab trial (3-9 months after stroke; 222 pts total; 2 week intervention) and completed in 2005 with a budget of 7.5 million

Constraint-induced Movement Therapy (CIMT) An Efficacy-proven Rehabilitation Therapy

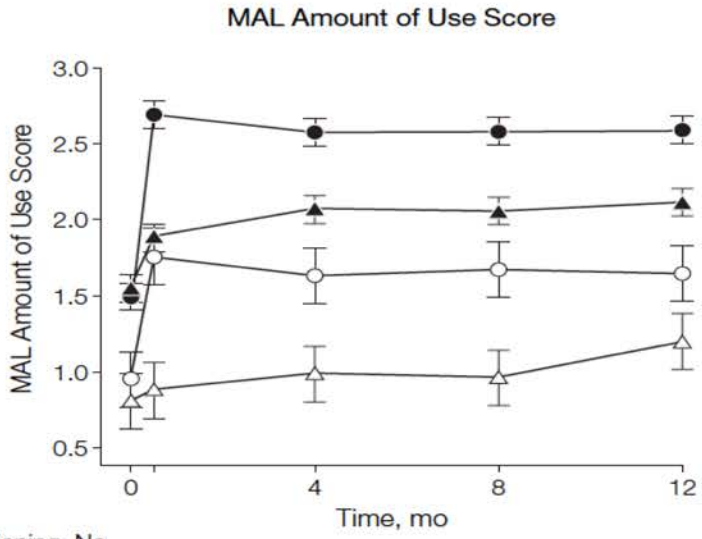
Table 1. Baseline Participant Characteristics*

Characteristics	Constraint-Induced Movement Therapy (n = 106)	Usual Care (n = 116)
Age, mean (SD), y	61.0 (13.5)	63.3 (12.6)
No. of days since stroke, mean (SD)	179.8 (66.1)	187.7 (70.8)
Fugl-Meyer Assessment Score, mean (SD)†	42.5 (11.7)	41.1 (12.9)

Figure 2. Back-Transformed Mean WMFT Performance Time and Mean MAL Amount of Use Scores

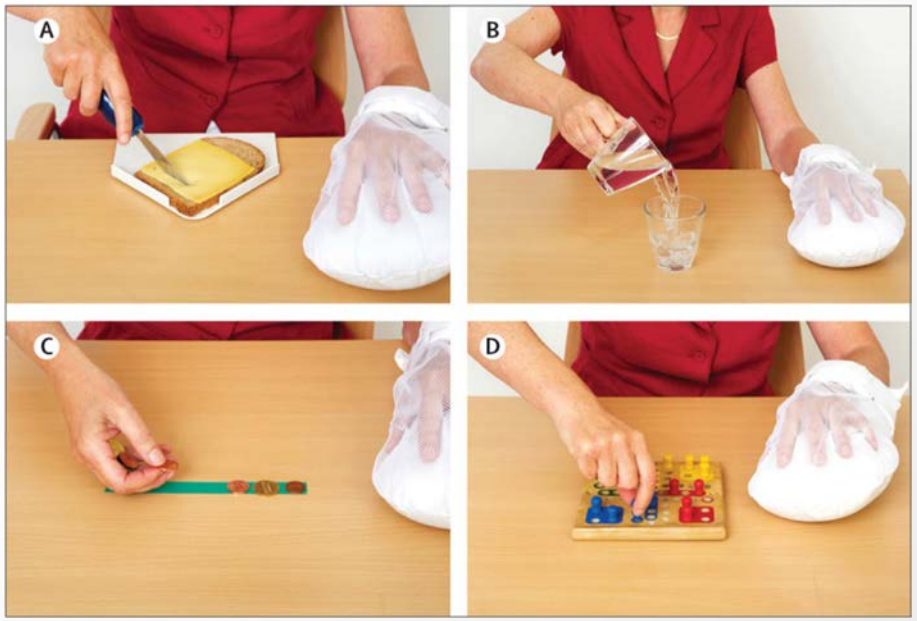


Lower Functioning, No.					
Usual Care	22	19	18	18	16
CIMT	23	20	17	17	15
Higher Functioning, No.					
Usual Care	93	85	75	74	70
CIMT	82	78	72	67	65

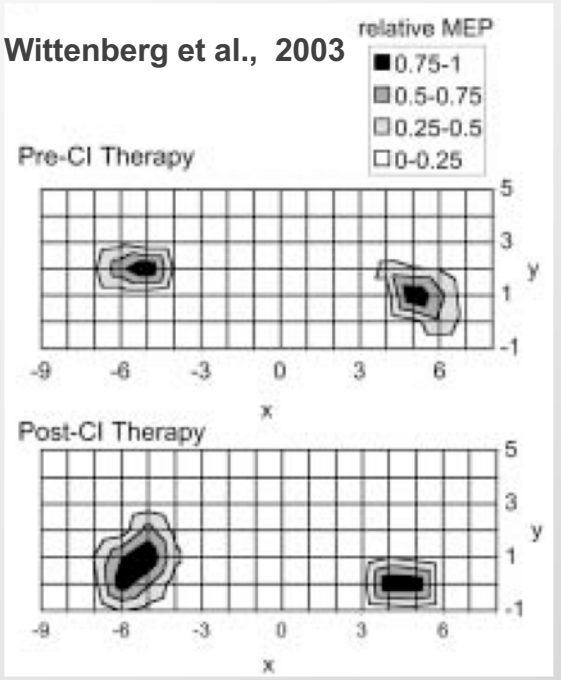


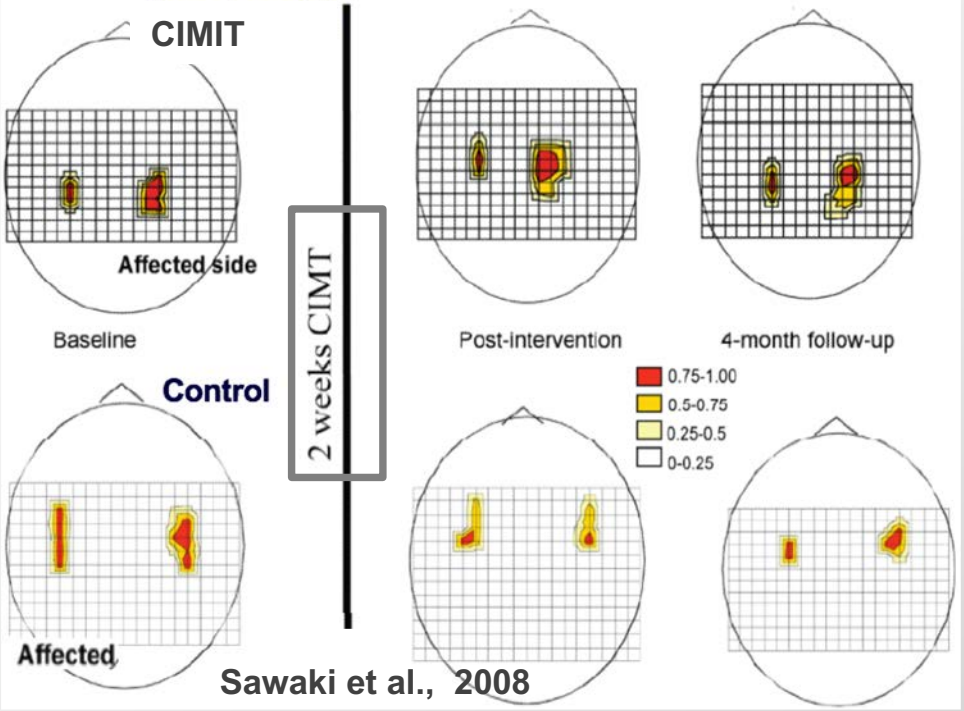
Lower Functioning, No.					
Usual Care	22	19	18	18	16
CIMT	23	20	17	17	15
Higher Functioning, No.					
Usual Care	94	84	75	74	70
CIMT	82	78	72	69	65

Cortical Changes after CIMT

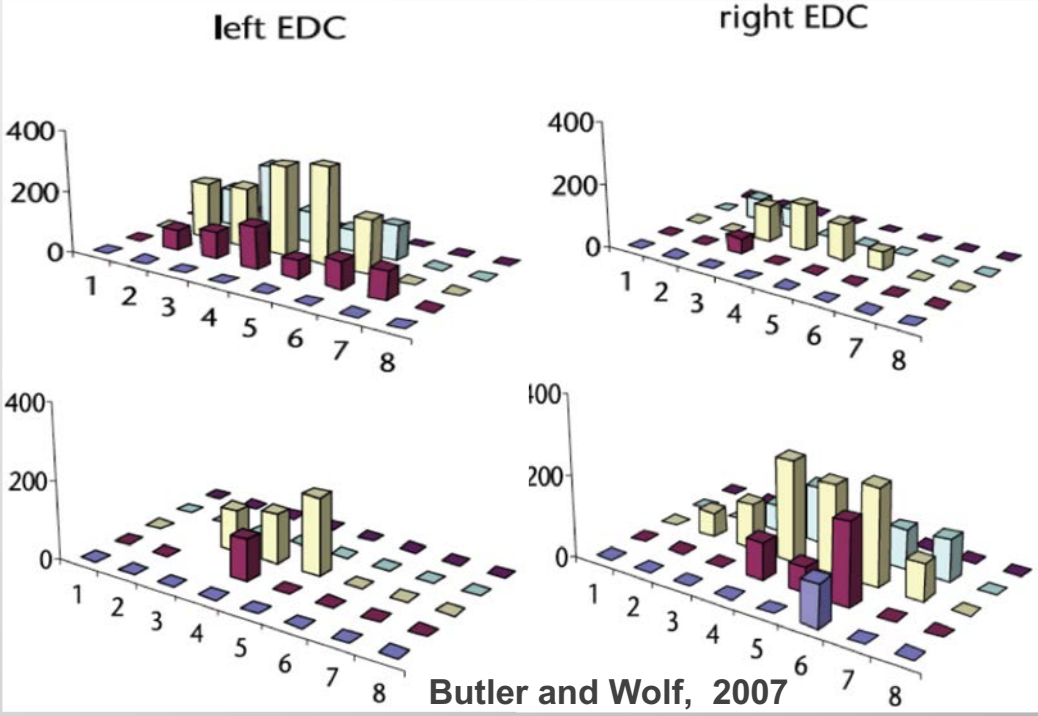


Wittenberg et al., 2003





Sawaki et al., 2008



Butler and Wolf, 2007

What affects stroke outcome or recovery?

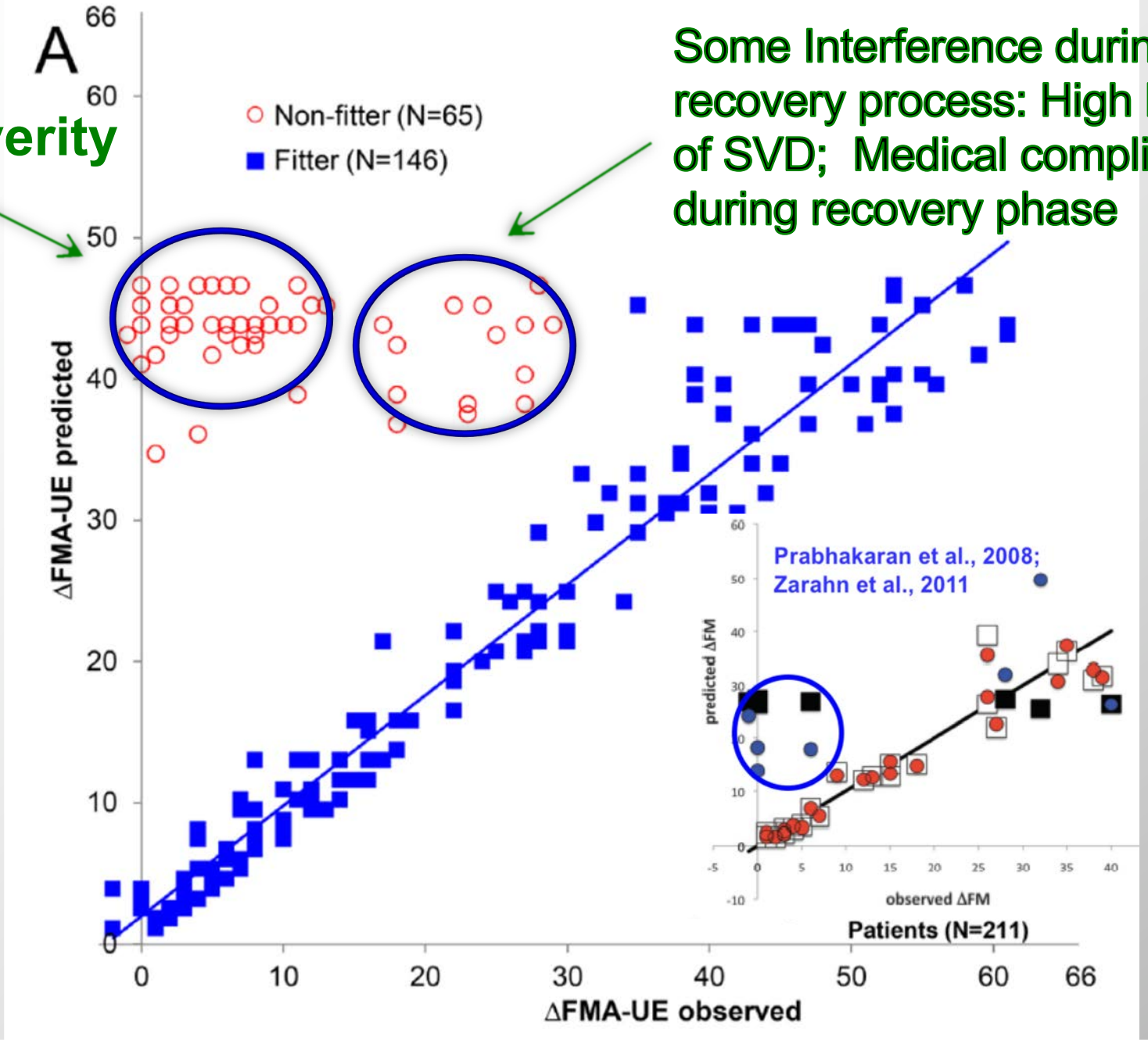
- **Brain's natural recovery ability/potential:** *seems to be dependent on the degree of initial impairments, the lesion's impact on the relevant system, and is proportional to what a patient could theoretically recover in mild to moderately impaired subjects;*

- ***Premorbid Brain Health***
- ***Medical Problems occurring during the recovery period***
- ***Age at time of stroke***
- **Appropriate time of an intervention**
- **Appropriate dose of an intervention** - *mixed results of dose/intensity studies*

- **Appropriate biological substrate:** *residual lesional substrate vs. redundant system substrates; this contributes to the discussion on recovery of function vs compensation of function;*

Predicting Behavioral (Motor) Outcome: Proportional Recovery

Stroke Severity

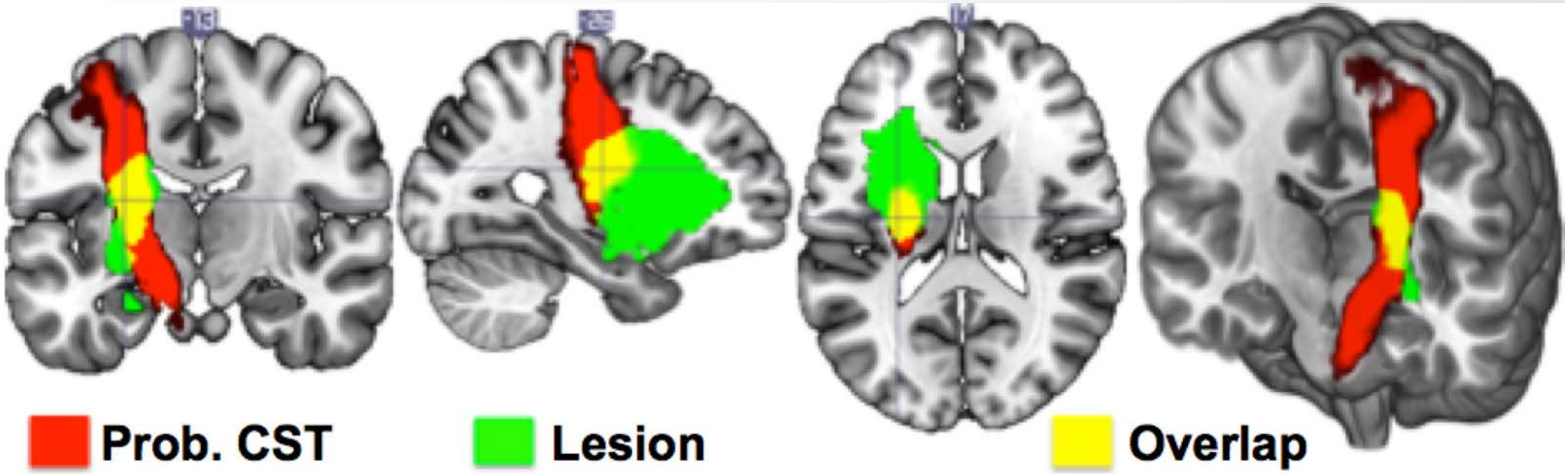


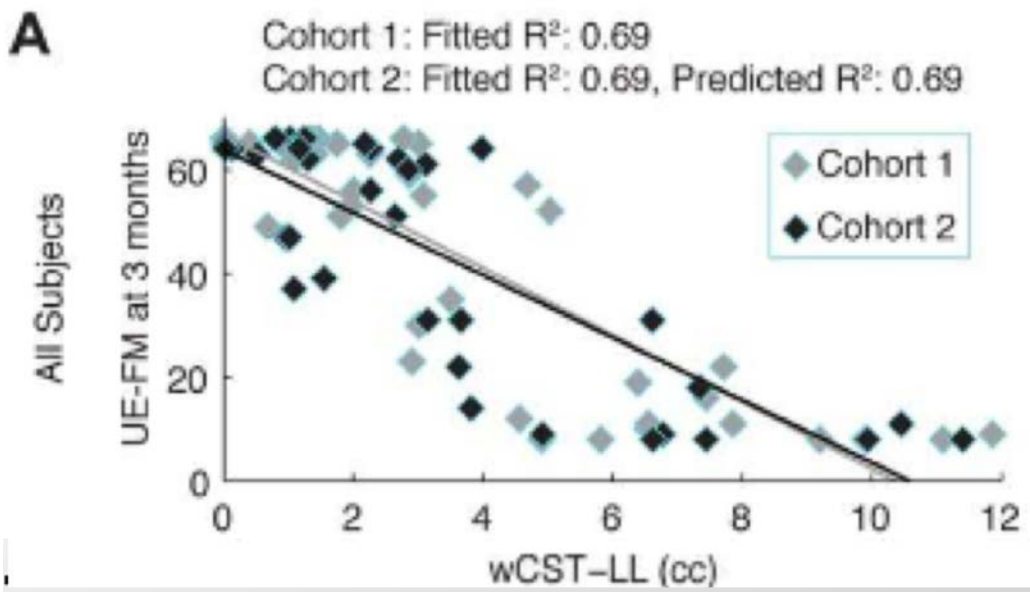
Some Interference during the recovery process: High burden of SVD; Medical complication during recovery phase

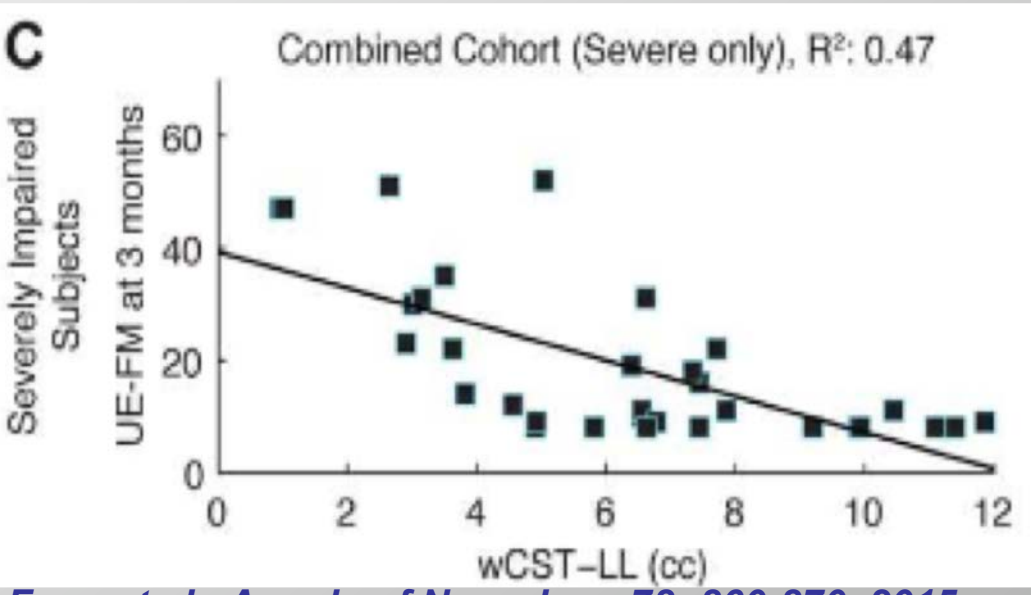
Winters et al., NNR 2015

Imaging Marker to Predict Outcome:

Combining Lesion Size and Site: wCST- Lesion-Load

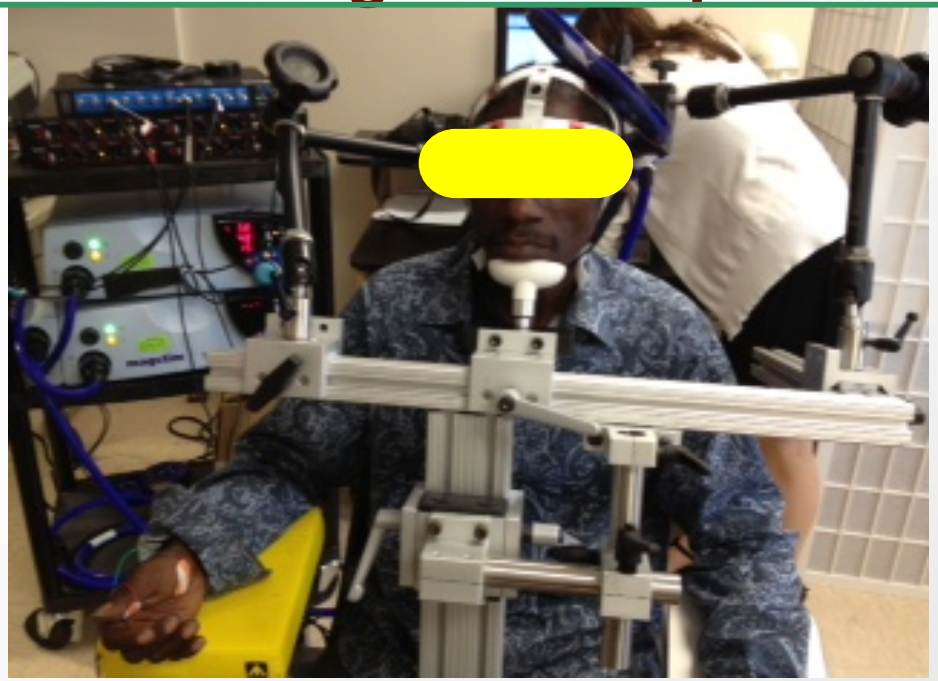


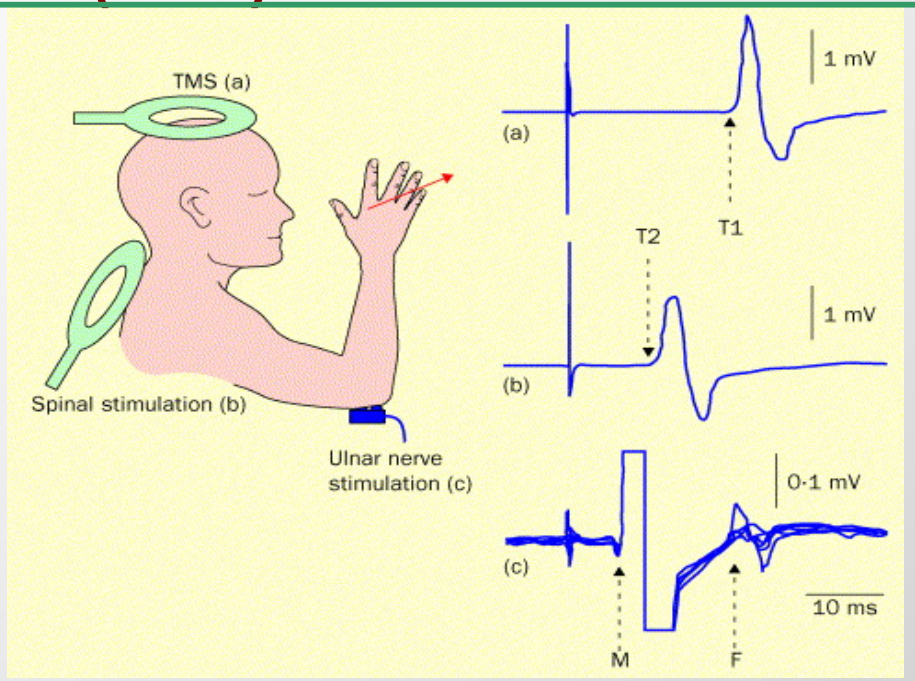




Feng et al., Annals of Neurology 78: 860-870, 2015

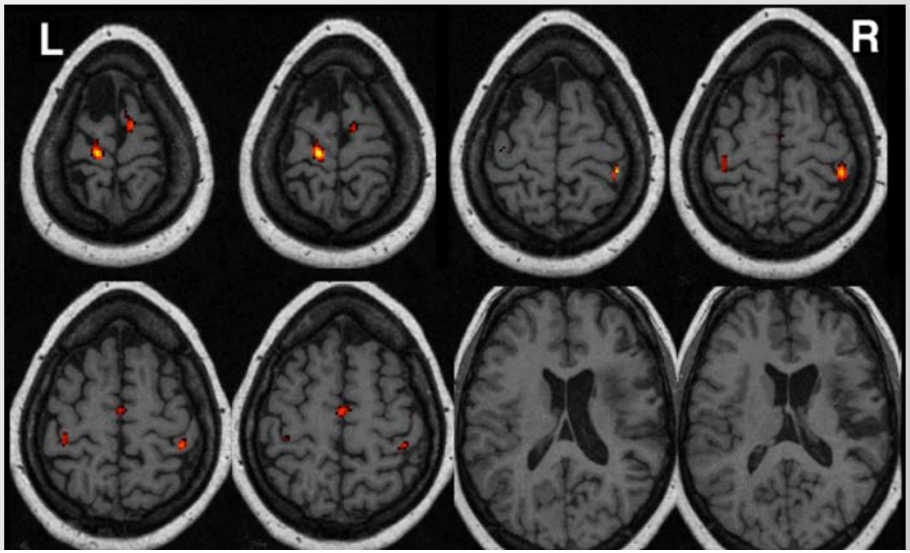
Physiological Marker to Predict Outcome:
Assessing Corticospinal Tract (CST) Function with TMS

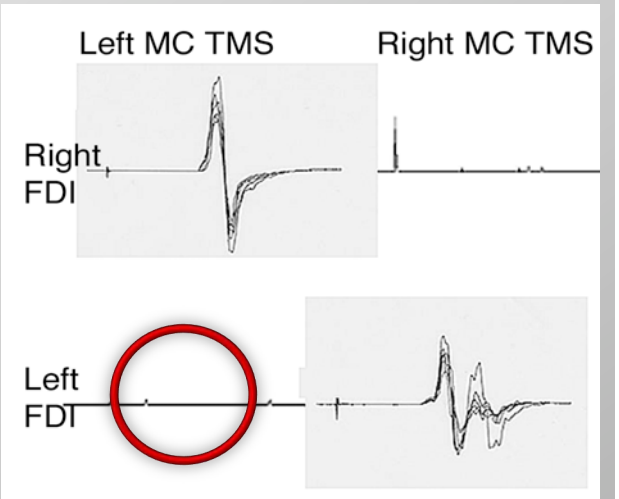




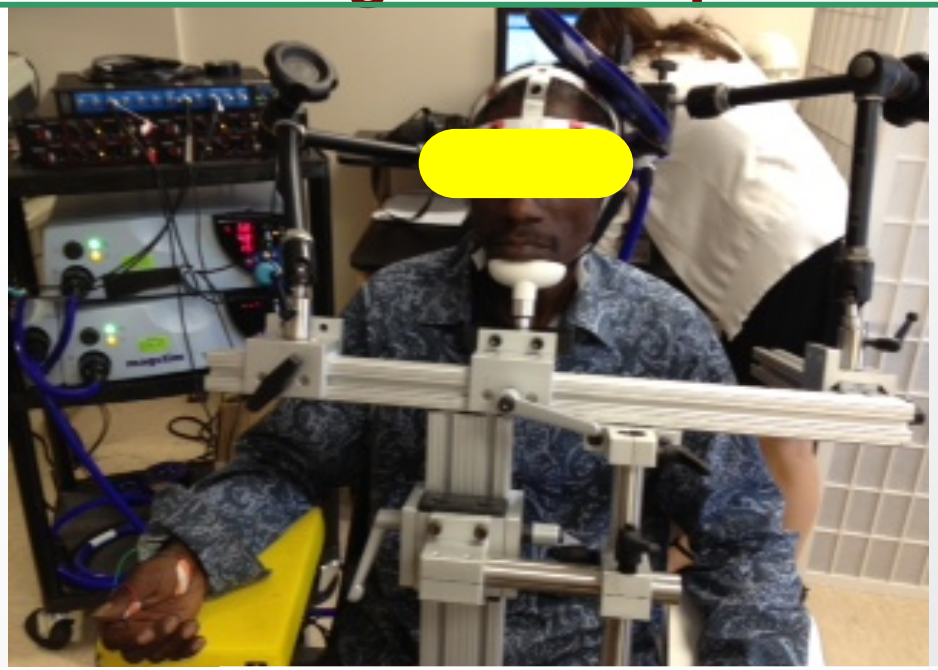
MEPs have a high sensitivity for good recovery, their specificity is relatively low, ie, absence of MEPs does not necessarily mean poor recovery. *(Arac1994; Cantano,1996)*

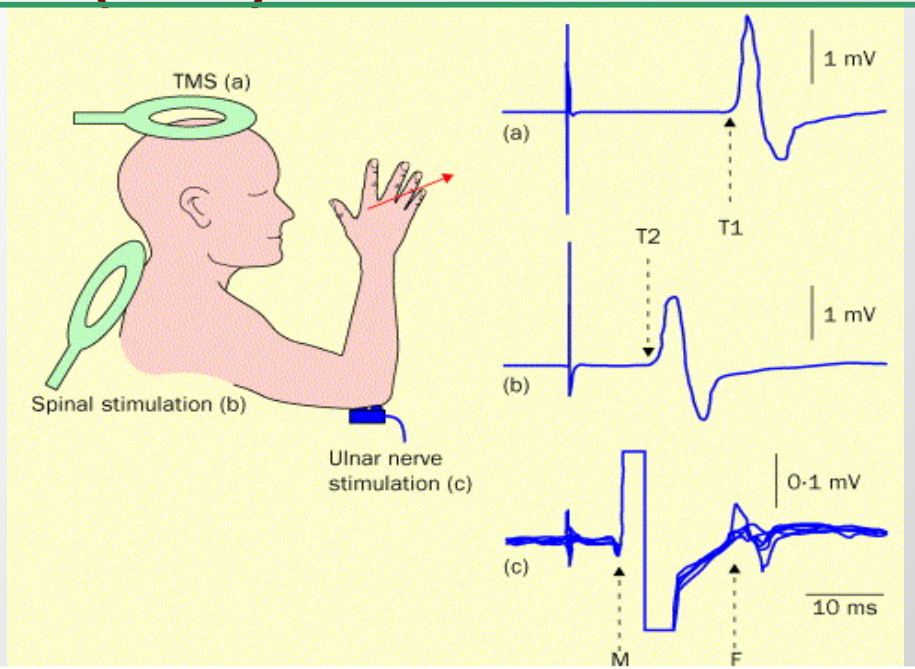
***R Hem stroke**; patient moves L Index (FDI). Contra- and ipsilateral SM1 activation.*
TMS contralateral MEPs.
No ipsilateral MEPs





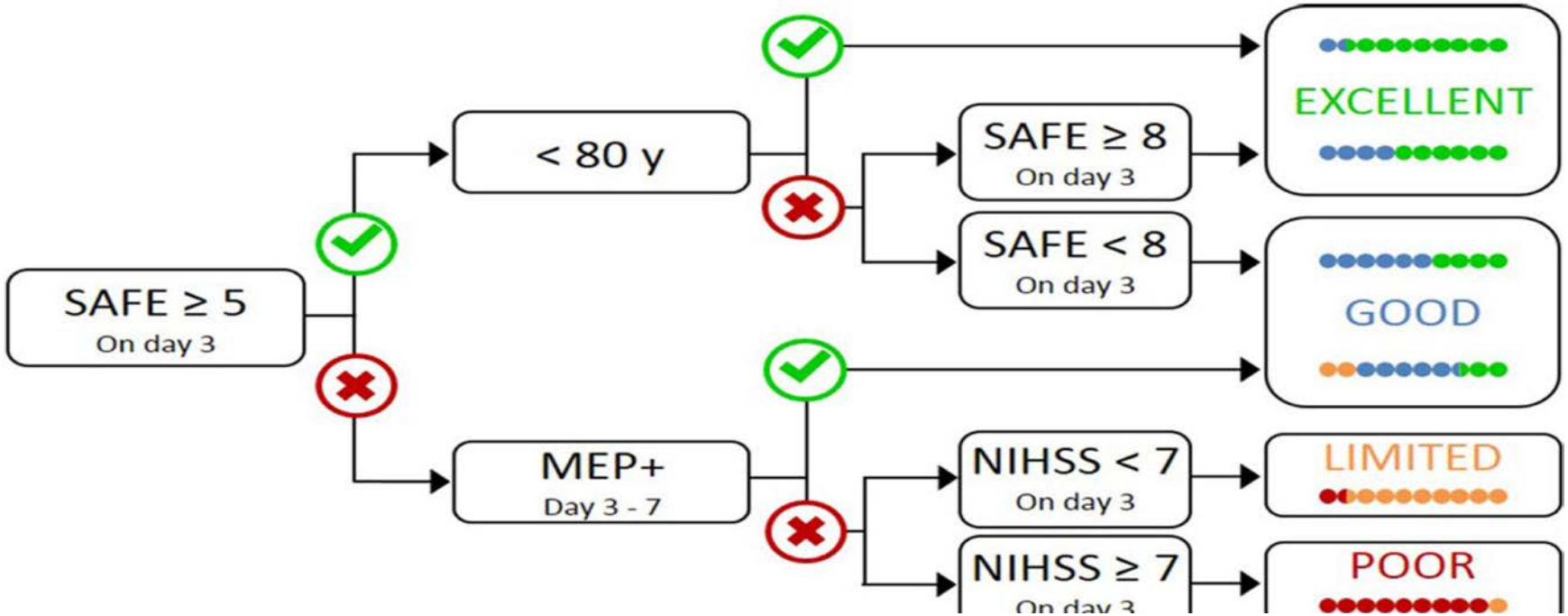
Physiological Marker to Predict Outcome:
Assessing Corticospinal Tract (CST) Function with TMS



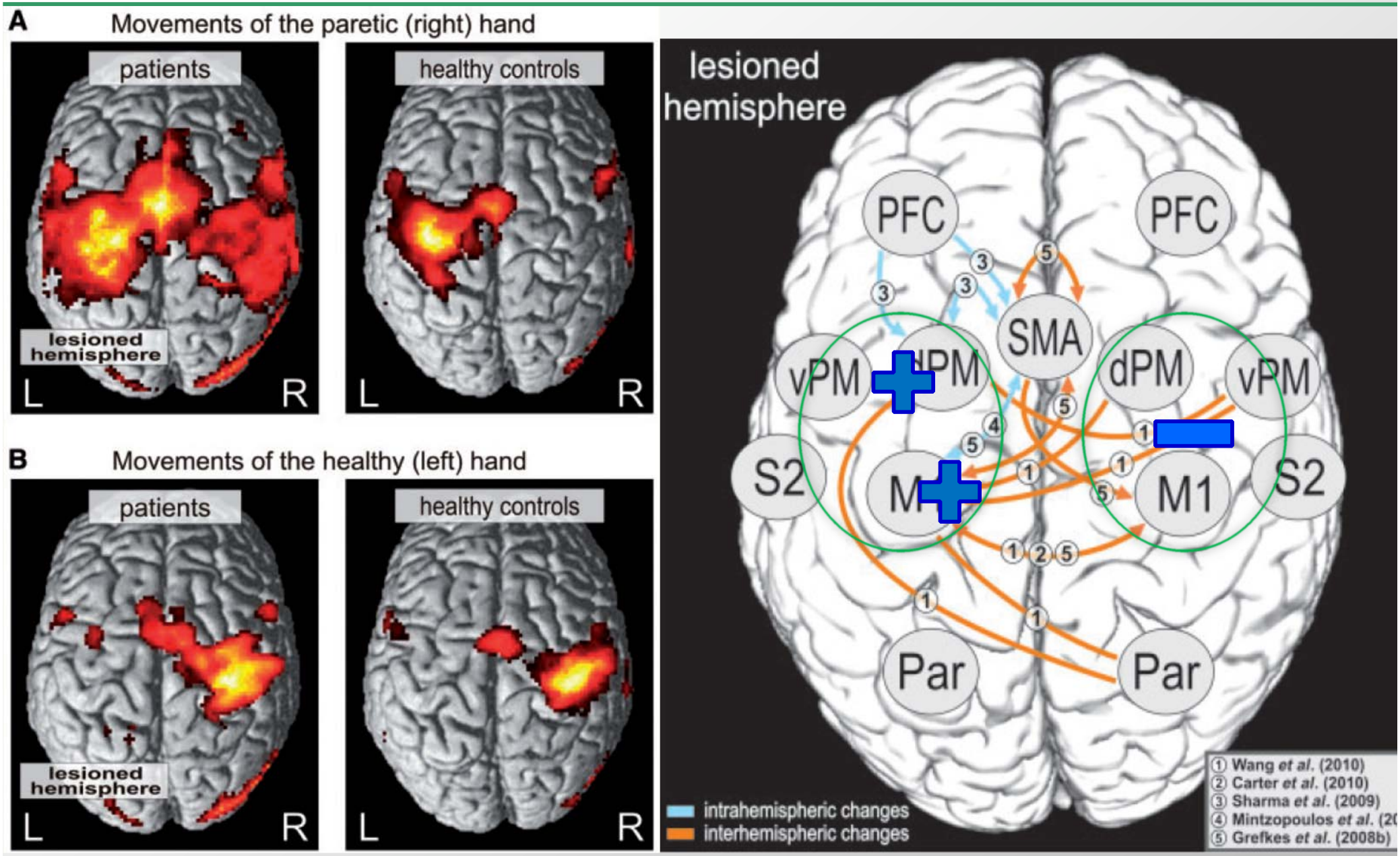


Stinear et al., ACTN 2017;

PREP-2



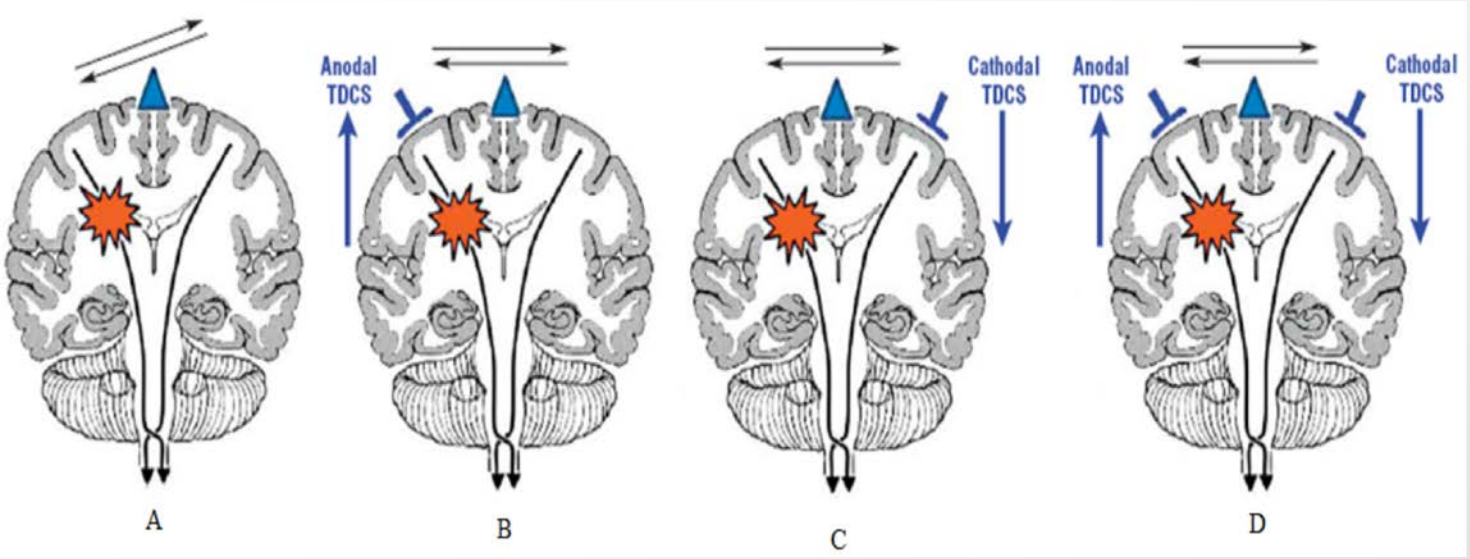
Task- and rs-fMRI reveal Targets for Interventions

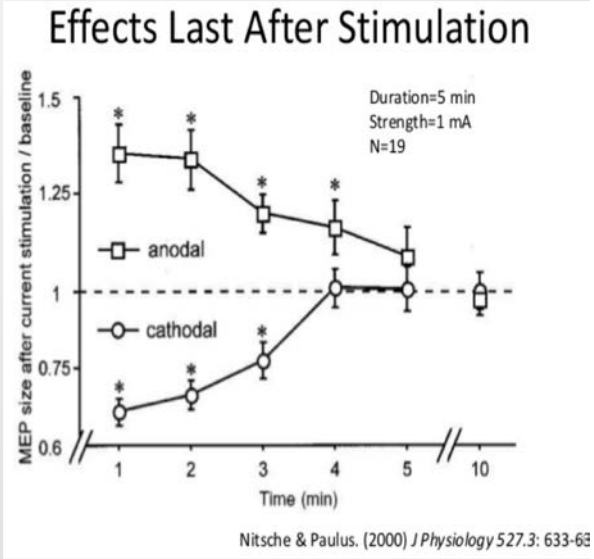


Grefkes and Fink, 2011

E-Montages and Effects of Brain-Stimulation

1. Interhemispheric interaction





Schlaug, Expert Review Medical Device, 2008; Feng, tDCS in stroke recovery, 2010

2. Increased Synaptic Plasticity in the targeted region

Cell PRESS

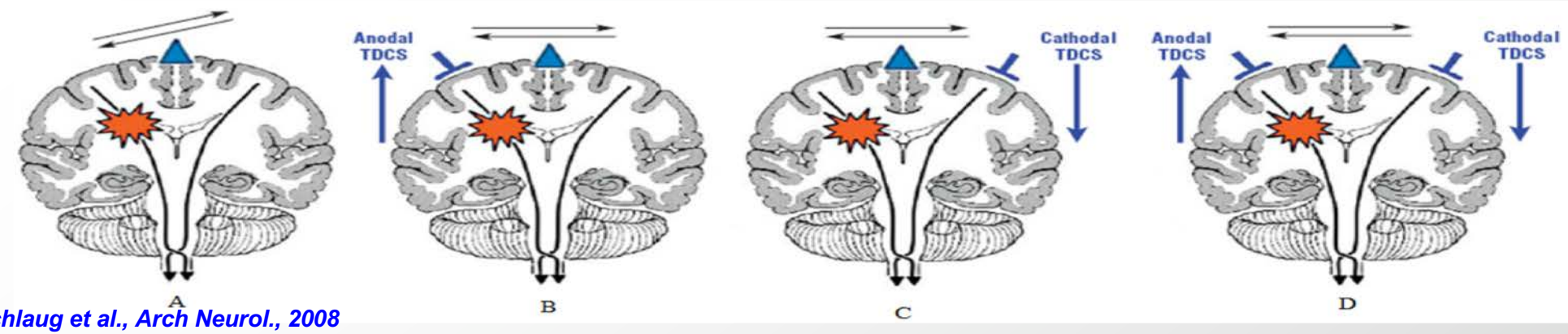
Neuron
Report

Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning

Brita Fritsch,[1,3,6] Janine Reis,[2,3,6] Keri Martinowich,[5] Heidi M. Schambra,[2] Yuanyuan Ji,[4,8] Leonardo G. Cohen,[2,7,*] and Bai Lu[4,5,7,8,*]

DCS induces a long-lasting synaptic potentiation (DCS-LTP) which is polarity specific, NMDA receptor dependent, and requires coupling of DCS with repetitive low-frequency synaptic activation (LFS)

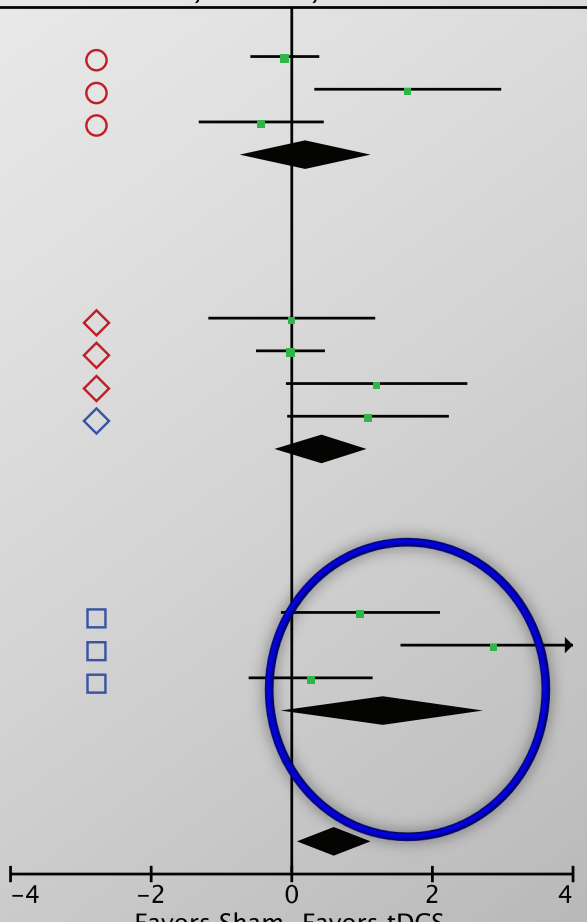
Meta-Analysis Electrode Montage (only≥5d)



Schlaug et al., Arch Neurol., 2008

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%								

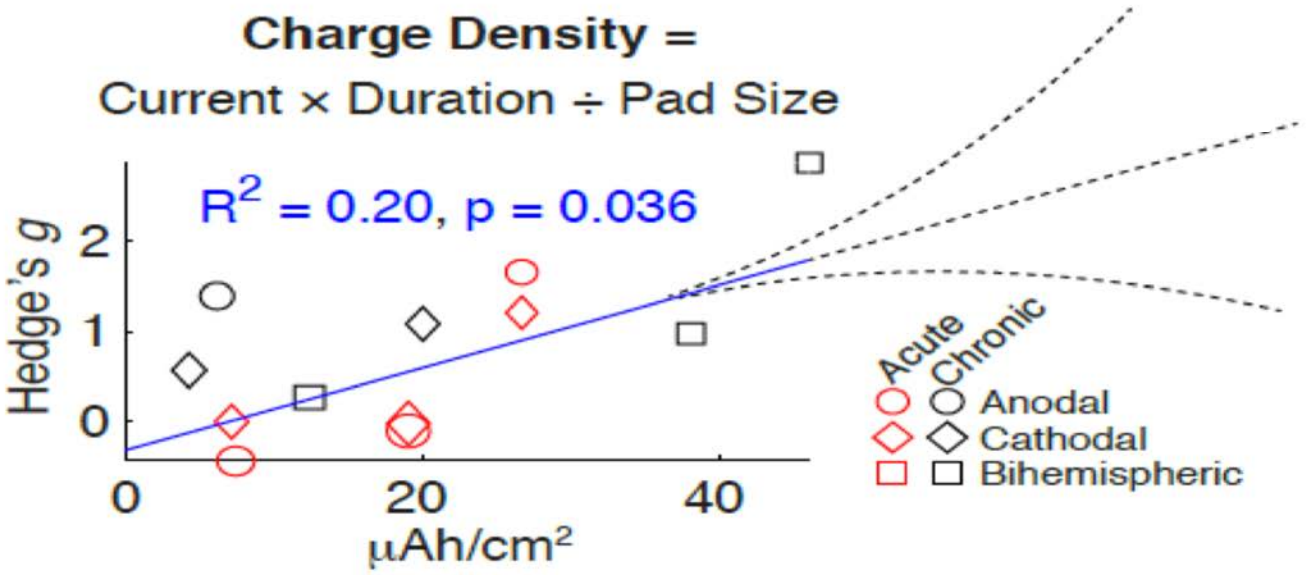
Std. Mean Difference IV, Random, 95% CI



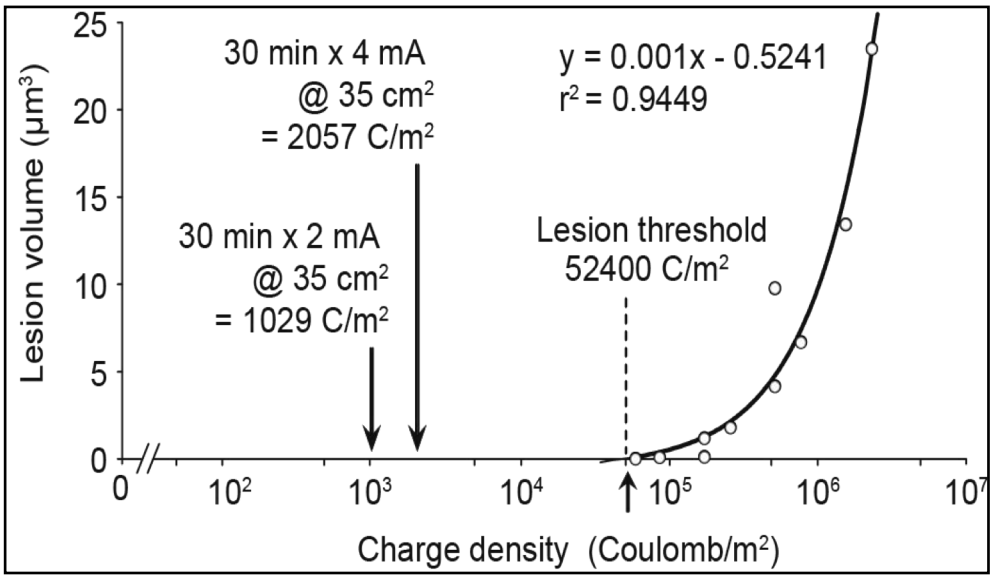
Chhatbar et al., Brain Stimulation, 2015

Dose of brain stimulation emerges as an important modulator of the effect

What is the effect of higher dose of tDCS?



What is the safety profile of high-dose of tDCS?



Safety and Tolerability of high dose tDCS

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, *]

Figure 4: 3 + 3 Design

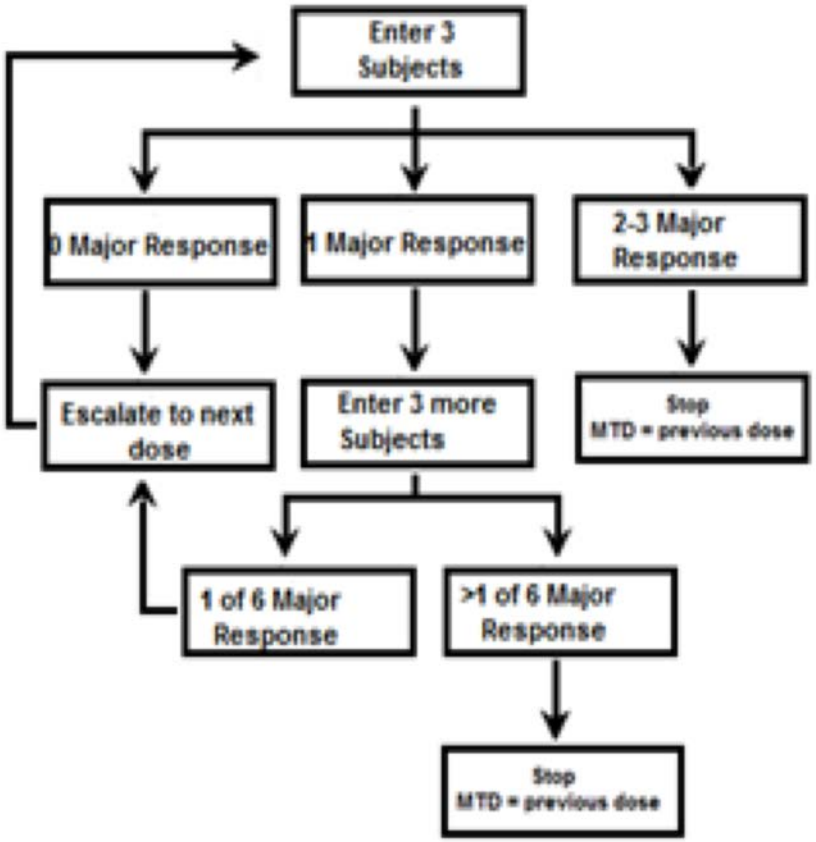


Table 1
Safety and tolerability profiles at each dose level.

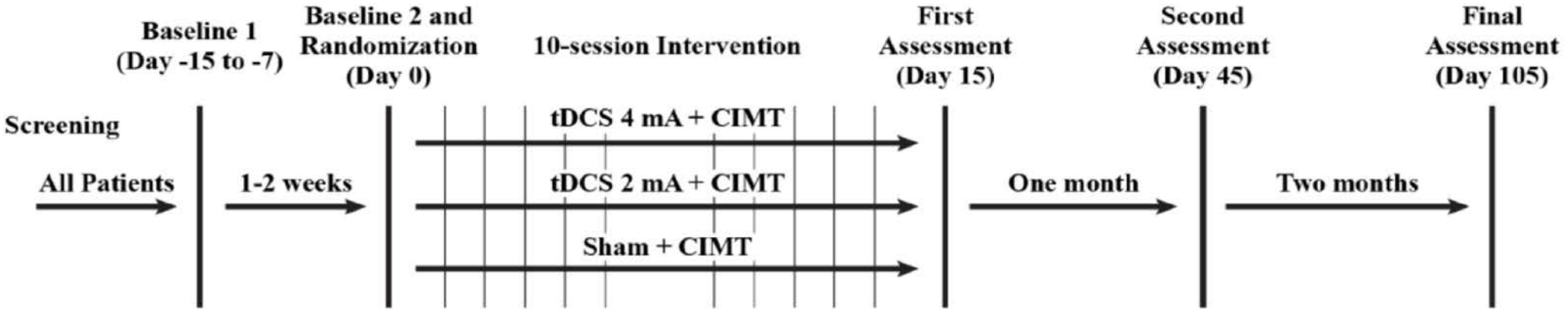
	tDCS current					
	1.0 mA	2.0 mA	2.5 mA	3.0 mA	3.5 mA	4.0 mA
Baseline characteristics						
Subjects (n)	3	3	3	3	3	3
Females (n)	1	0	2	2	1	1
Age (years, Mean)	50	57	53	62	58	52
FM-UE (affected side, Mean)	40	51.3	38	54.7	47	42.7
rMT (affected side, Mean)	42.7	45.3	69.3	36.7	48	39.3
rMT (non-affected 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.

*Funded by NIH: P20 GM109040 (Feng)

TRANSPORT2 – Design and Aims

A randomized, sham-controlled, multi-center, Phase2 dose finding study of pts (n=43/arm) after first ischemic stroke, between 1-6 months post and a UE-FM of ≤56 (max66); 30min-tDCS; 2hrs-CIMT, 6hrs of wearing a mitten



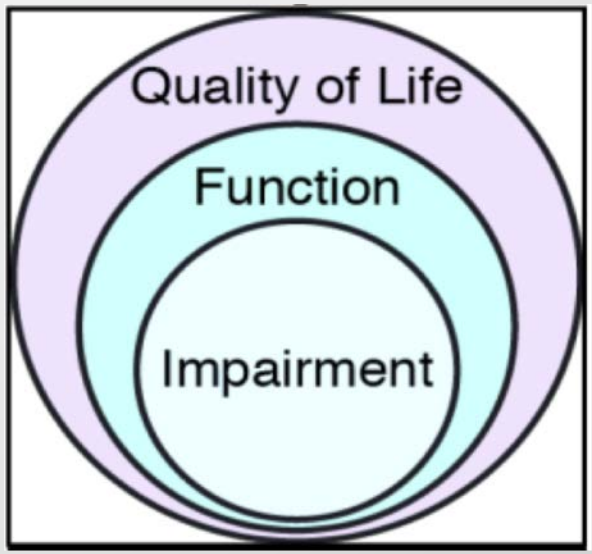
Primary Aim: To determine whether there is an **overall treatment effect among 3 dosing groups** (Sham+CIMT, 2 mA+CIMT and 4 mA+CIMT) **on day 15** after the start of the intervention and a sustained effect at 1 and 3 months in the **UE-FM (primary)**, in the **WMFT (secondary)**, and the **Stroke-Impact-Scale-Hand (secondary)**

Secondary Aims: To confirm that the proposed intervention is **safe**, t**olerable** for patients, and **feasible** to implement in a multi-sites setting in order to better plan a confirmatory phase 3 study

Exploratory Aims: To investigate whether **the wCST-LL** (**structural** integrity of descending motor tract) or **MEPs** (**functional** integrity of descending motor tract) or a combination of both are correlated with changes in FM-UE scale; to evaluate the utility of them as **biomarkers** for subject selection; to investigate a covariation in **change of rsfMRI, MEPs with change in UE-FM.**

Outcomes Measures for TRANSPORT2

- **Fugl-Meyer Upper Extremity (FM_UE) Scale**
  - Measure of motor impairment
  - Study is powered on the FM-UE

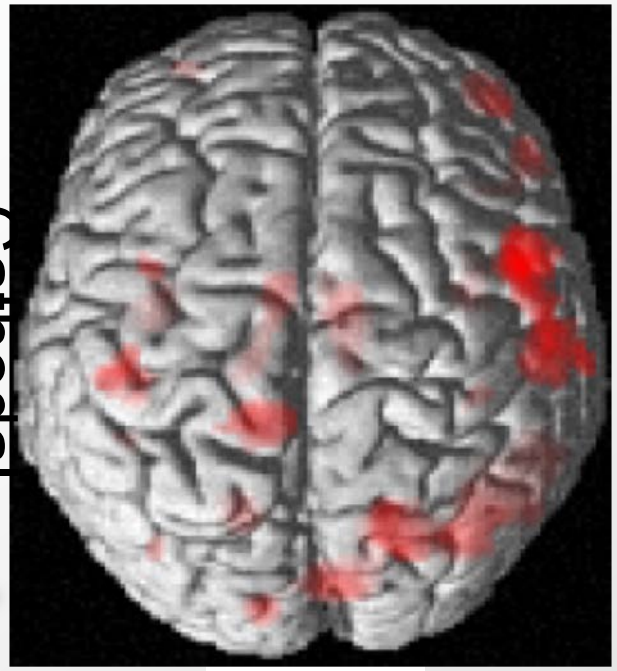


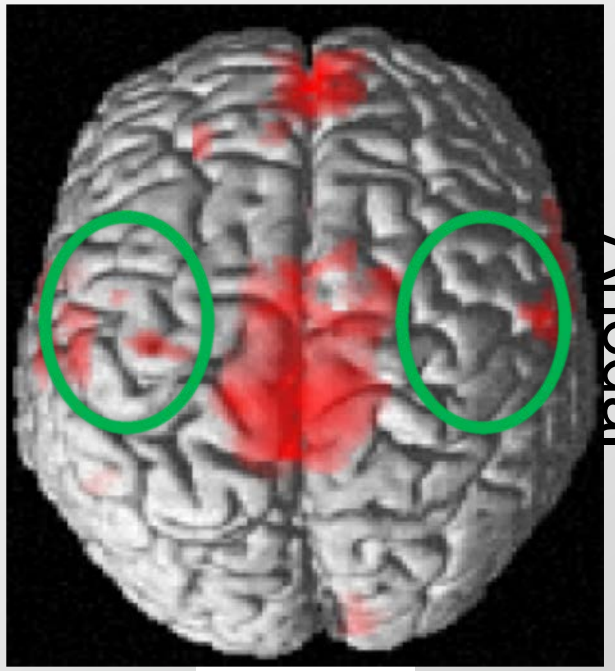
- **Wolf Motor Function Test (WMFT)**
  - Measure of motor function

- **Stroke impact scale (SIS) – hand subscale**
  - Measure of quality of life

Current Enters the Brain and Changes Function

rCBF (ASL) Changes induced by tDCS

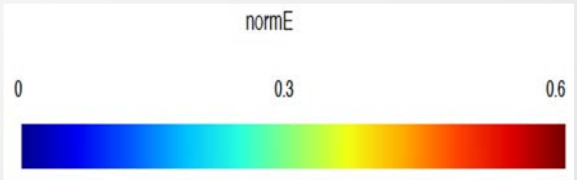


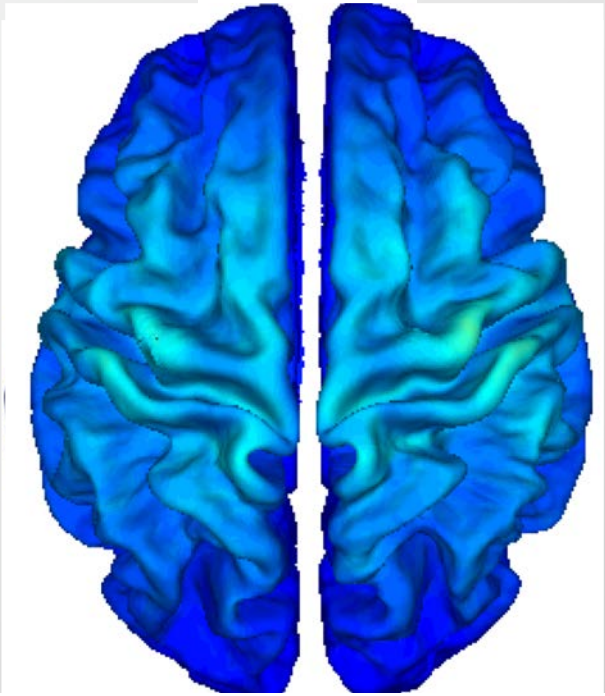


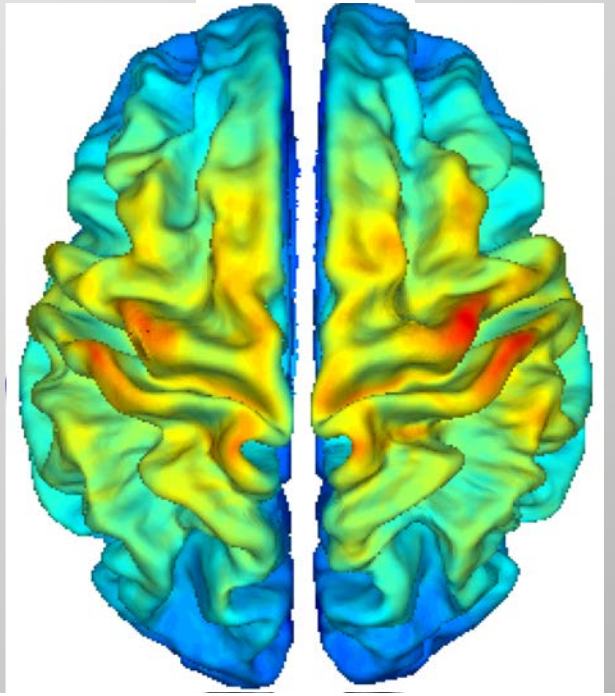
2mA

4mA

E-Field Simulation



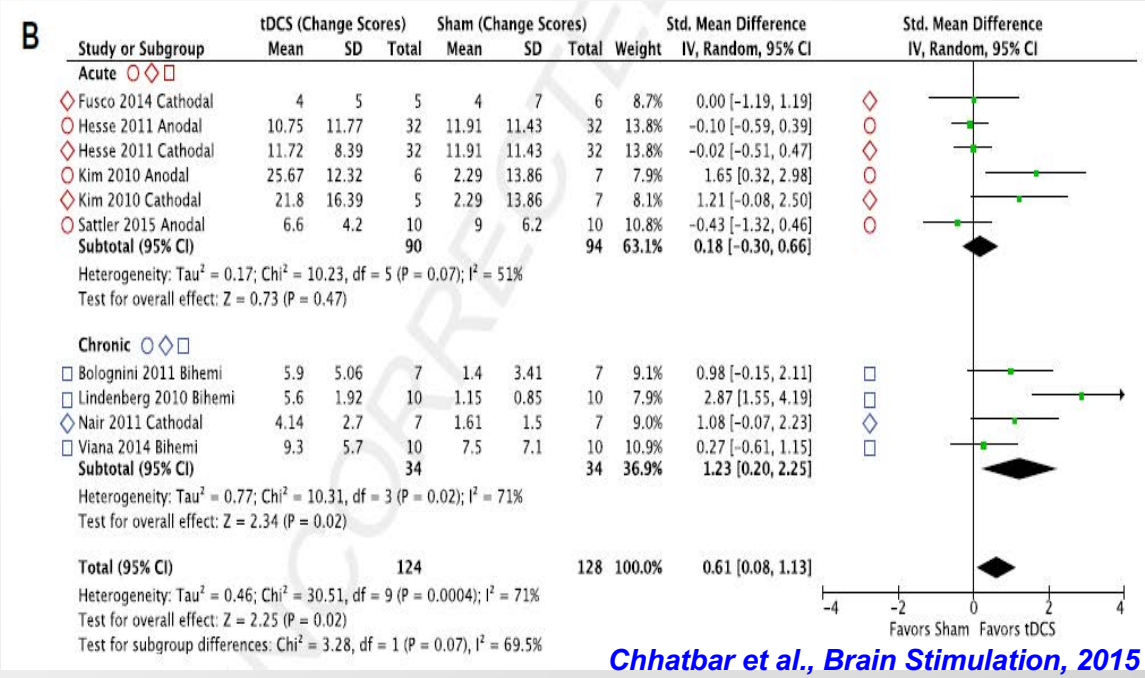




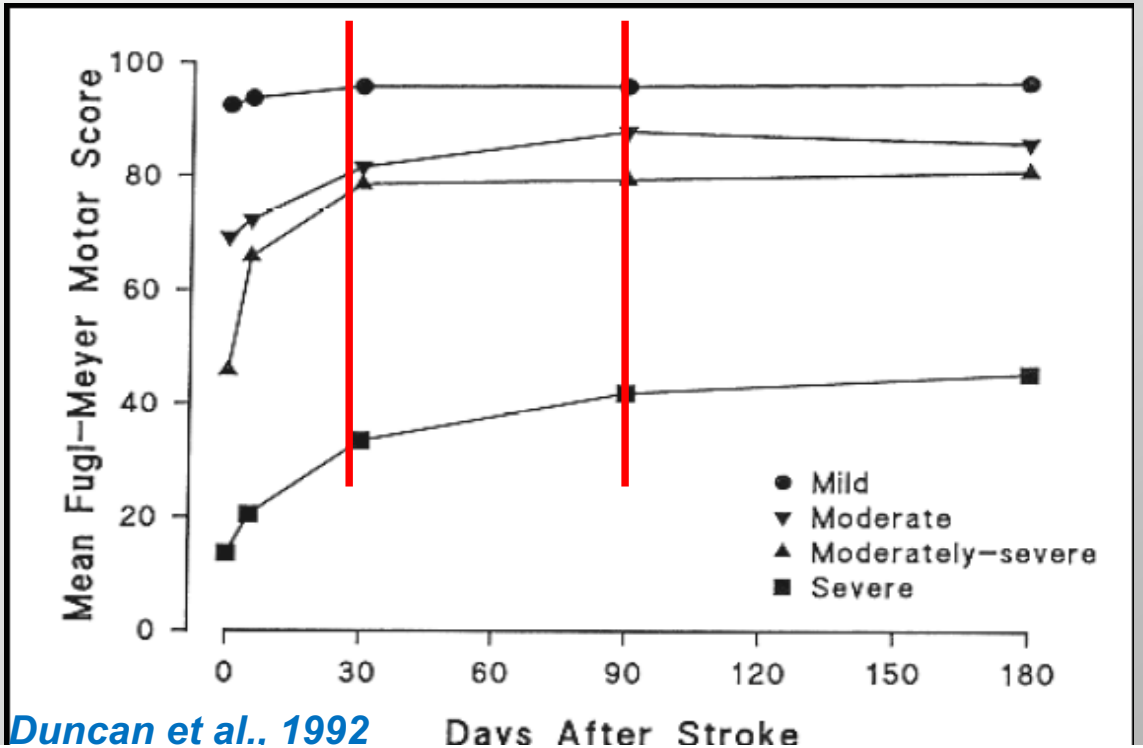
Group Avg (n=10)

Timing of Proposed Intervention

- Time after stroke interacts with the effects of an experimental intervention
- Meta-analysis of tDCS effects suggests higher signal if intervention is done in chronic stage
- Early natural recovery after stroke can be robust and has not been well harnessed by stroke rehabilitation/recovery trials.



Chhatbar et al., Brain Stimulation, 2015



Duncan et al., 1992

Innovations

- Testing a higher dose at 4mA of transcranial direct current stimulation
- Combining best practice of peripheral sensorimotor stimulation with experimental, dose modulated, central stimulation into a phase 2 clinical trial
- Investigating whether structural and/or functional biomarker can aid patient selection or predict therapeutic response

Inclusion Criteria

- Each subject must meet **all** of the following criteria to participate in this study:
  - 18-80 years old; and
  - First-ever unihemispheric ischemic stroke radiologically verified and occurred within the past 30-180 days; and
  - **>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 2 weeks (but no more than 3 reassessments); and
  - Pre-stroke mRS ≤2; and
  - Signed informed consent by the subject or Legally Authorized Representative (LAR).

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study

- Primary intracerebral hematoma, subarachnoid hemorrhage or bi-hemispheric or bilateral brainstem ischemic strokes;
- **Medication use at the time of study that may interfere with tDCS, including but not limited to carbamazepine, flunarizine, sulpiride, rivastigmine, dextromethorphan;**
- Other co-existent neuromuscular disorders (pre- or post-stroke) affecting upper extremity motor function;
- Other neurological disorders (pre- or post-stroke) affecting subject's ability to participate in the study;
- Moderate to severe cognitive impairment defined as Mini-mental Status Exam (MMSE) score<18/30;
- History of medically uncontrolled depression or other neuro-psychiatric disorders despite medications either before or after stroke that may affect subject's ability to participate in the study;
- Uncontrolled hypertension despite medical treatment(s) at the time of randomization, defined as SBP≥185 mmHg or DBP≥110 mmHg (patient can be treated, reassessed and randomized later);
- **Presence of any MRI/tDCS/TMS risk factors including but not limited to: a) an electrically, magnetically or mechanically activated metallic or nonmetallic implant including cardiac pacemaker, intracerebral vascular clips or any other electrically sensitive support system; b) a non-fixed metallic part in any part of the body, including a previous metallic injury to eye; c) pregnancy (effects of MRI, TMS, and tDCS on the fetus are unknown); d) history of seizure disorder or post-stroke seizure; e) pre-existing scalp lesion under the intended electrode placement or a bone defect or hemicraniectomy;**
- Planning to move from the local area within the next 6 months;
- Life expectancy less than 6 months;
- **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;**
- **Concurrent enrollment in another investigational stroke recovery study;**
- Doesn't speak sufficient English to comply with study procedures;
- Expectation that subject cannot comply with study procedures and visits.

Statistical Considerations

Primary Efficacy Endpoint:

generalized linear mixed effects repeated measures model with the dependent variable of change in the UE-FM scale on Day 15 after the initiation of the 2-week intervention **adjusting** for intervention arm, baseline UE-FM, time from stroke, and study site; **ITT analysis;**

Sample Size:

MCID: 4.25-7.25 in FM-UE; Assuming 4.5 with mCIMT alone, 9.0 with either 2 mA or 4 mA tDCS+mCIMT.

We have 83% power to reject the null hypothesis that the three group means are equivalent using ANOVA (assuming a two-sided type 1 error rate of 10%, SD of 7)

Considering incomplete intervention sessions and Lost to Follow-up, **43** subjects per group are needed for the ITT primary analysis

Safety: **Clinically significant adverse events:** Severe headache, Second-degree skin burn, Clinical seizure, Neurological deterioration (≥ 4-point increase in NIHSS);

Tolerability: using a Visual-Analog scale (VAS), a 10- point scale ranging from 0 (No Discomfort) to 10 (Extreme Discomfort) and a questionnaire before and after tDCS;

Feasibility: >80% of subjects complete the treatment protocol and no unexplained variability by site;

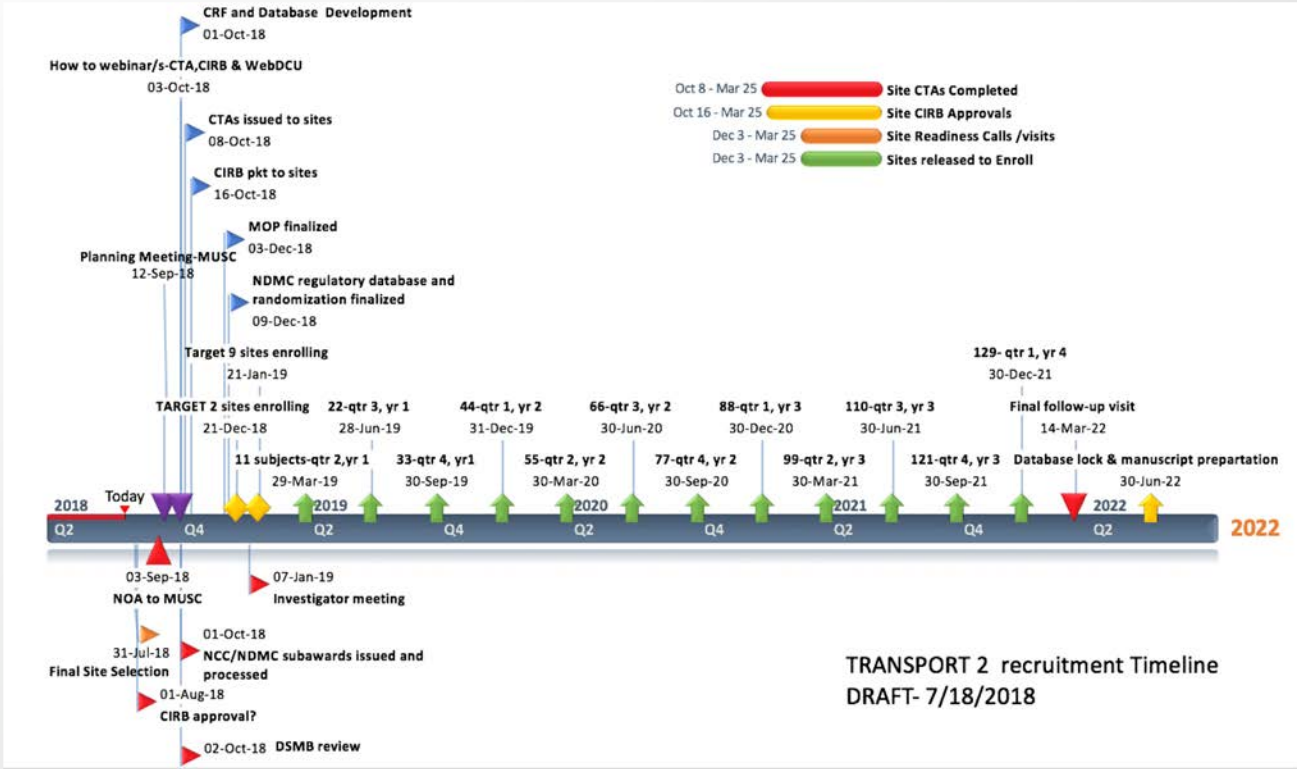
Go or No-Go Rules for Phase3

	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 are different. Both arms are safe, tolerable, and demonstrate a signal of improvement at 3 months. 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 shows 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 a 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 indicate that 4mA has additional benefits in functional and QOL improvement. In this case, we will proceed with 4mA

Table 2. Simulated trial and resulting actions under different assumed true mean changes or response rates.

Milestones

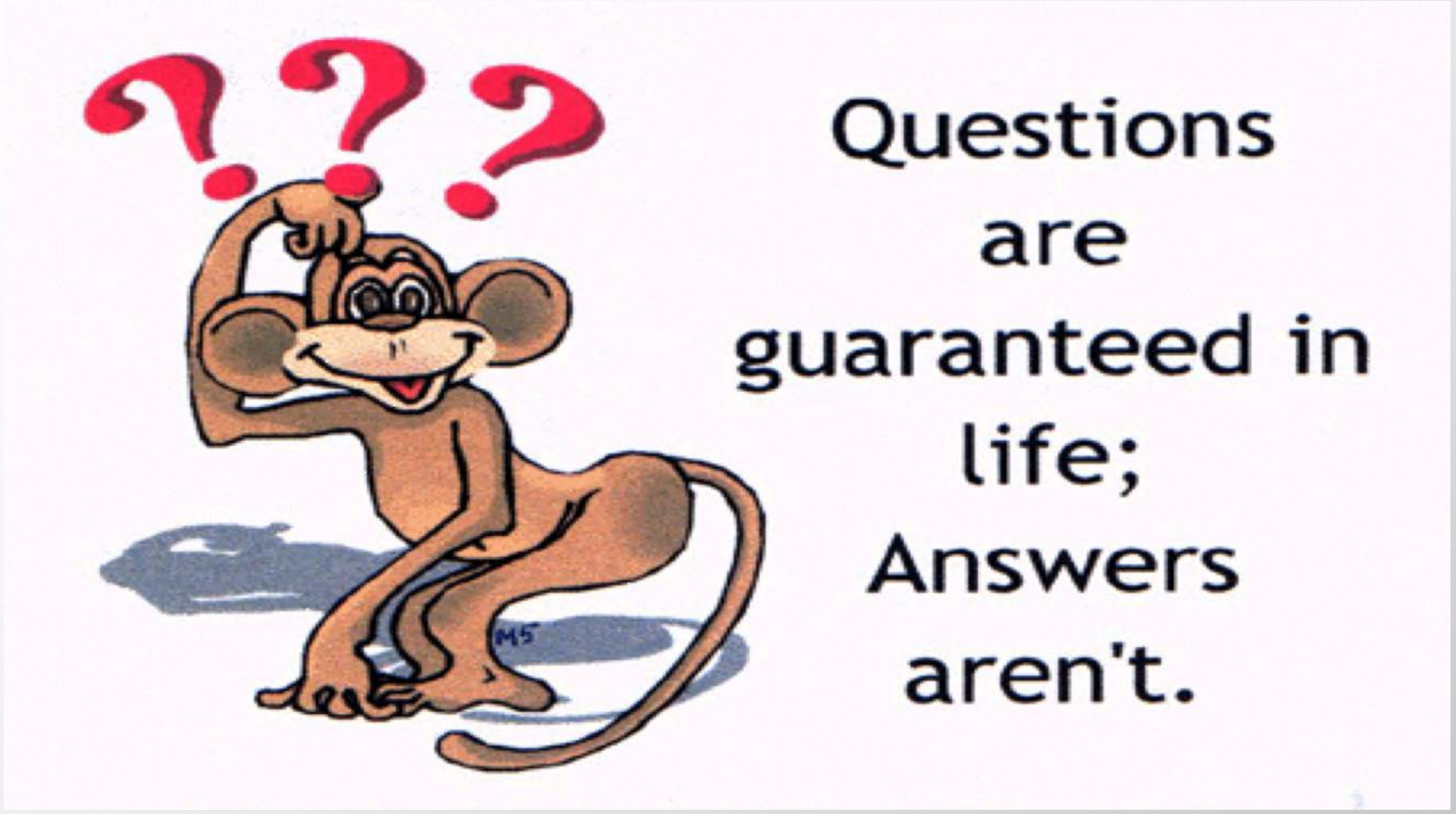
- cIRB approval as of last week
- Working on MOPs
- Sites chosen
- DSMB meeting in November
- Investigator meeting and training workshop in January
- Start recruiting at end of January 2019 (?)



Special Thanks

- **My Co-PI, Wayne Feng,** from MUSC and the **Biostatistical PI, Caitlyn Meinzer** from NDMC/MUSC.
- **StrokeNet Recovery Group** (Steve Cramer and Steve Wolf and the reviewers in that group) for their support, constructive criticism, and encouragements.
- **The StrokeNet Executive Committee** for allowing us to go forward.
- The **NIH reviewers** for their constructive criticism and for making us work harder and coming up with better justifications.
- The **NINDS council** for approving it for funding.
- **Scott Janis** and **Joanna Vivalda** at the NIH for their support and encouargement
- The **NCC in Cincinatti and Dr. Joe Broderick** for his support.
- The **NDMC at MUSC** in particular our **Yuko Palesh and her group** for their endless support in helping us design the study, holding our feet to the fire, and providing input into the design and statistical plan.

Questions?



feng@musc.edu and/or gschlaug@bidmc.harvard.edu