TRANSPORT2

Rationale & Study Design

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Brain Stimulation

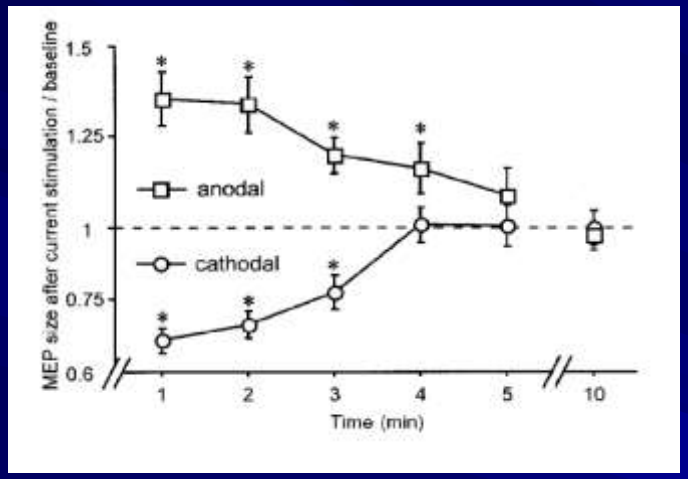
Invasive

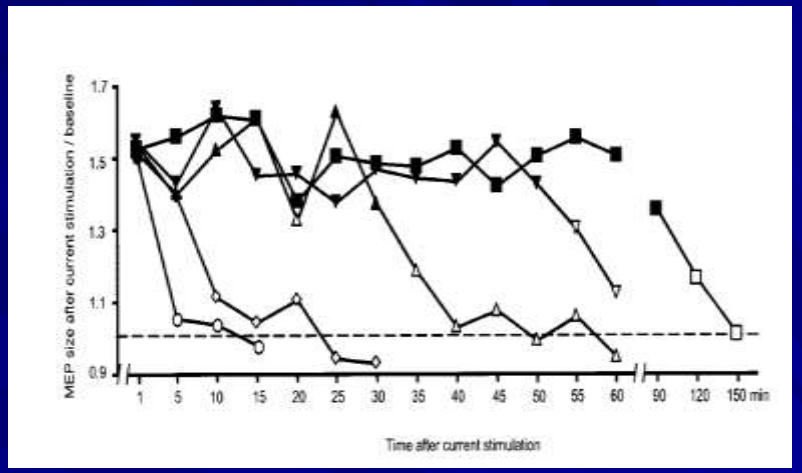
- Epidural Stimulation
- Deep brain stimulation
- Vagus nerve stimulation

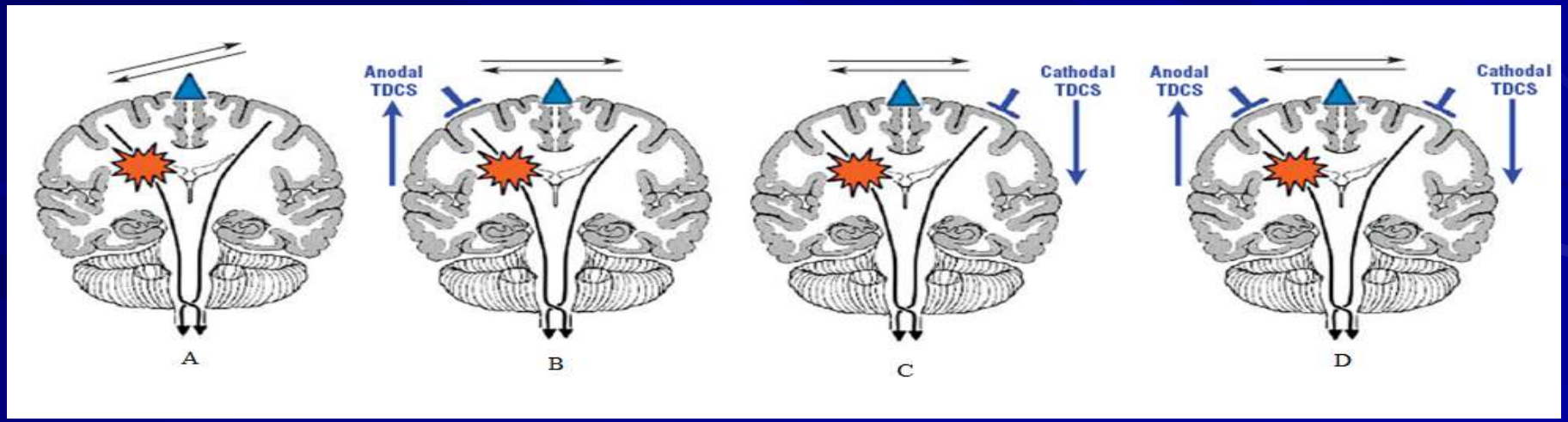
Non-invasive

- Transcranial Direct Current stimulation
- Transcranial alternating current stimulation
- Transcranial Magnetic Stimulation
- Transcranial pulsed ultrasound

Interhemispheric Inhibition & Modality of Brain Stimulation



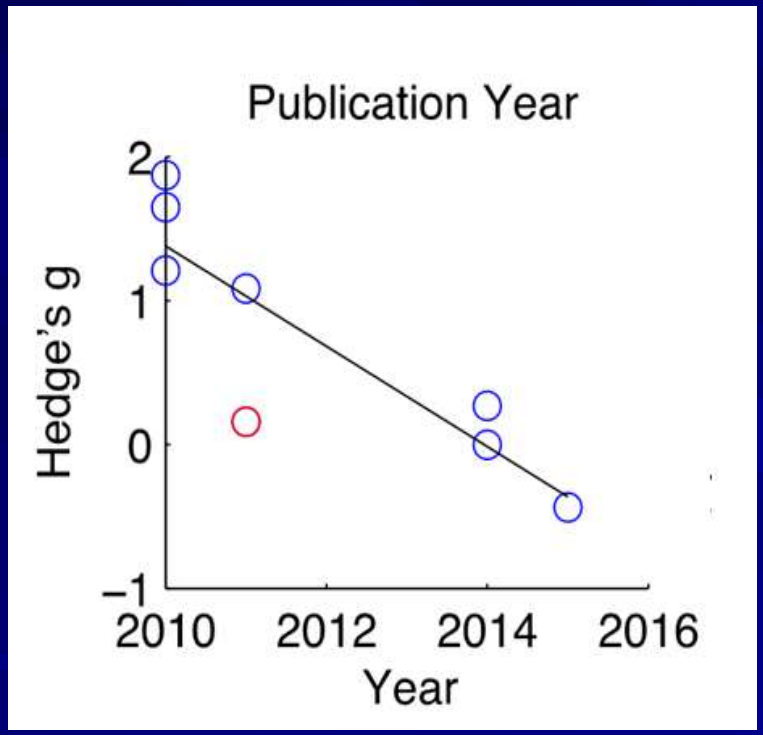




Schlaug, Expert review Medical Device, 2008 Feng, tDCS in stroke recovery, 2010

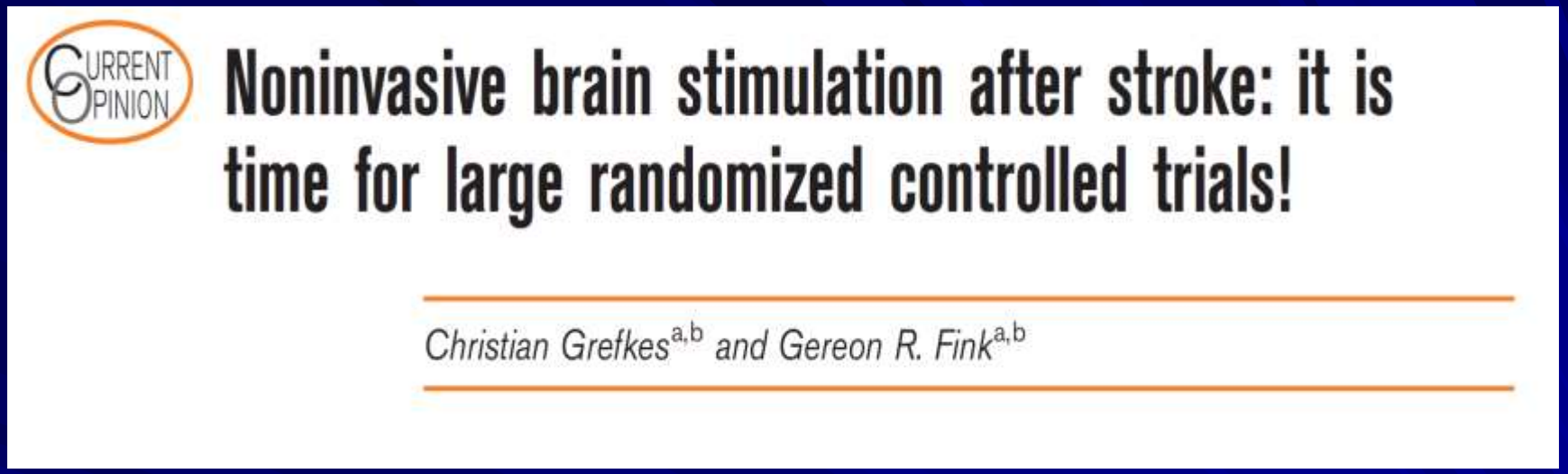
Transcranial Direct Current Stimulation for Poststroke Motor Recovery: Challenges and Opportunities

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



- tDCS has some advantages due to his portability and ease of use.
- Several small sample-size proof-concept studies suggest tDCS, along with a rehabilitation therapy, can modulate brain activity and induce behavioral changes in stroke patients
- Hurdles and opportunities co-exist for tDCS in post-stroke motor recovery

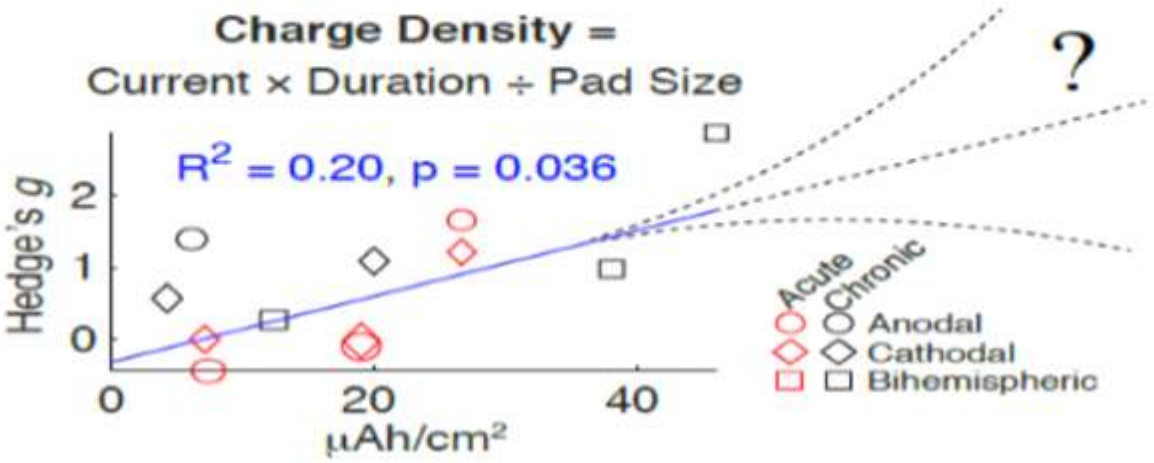
Zheng, stroke vascular neurology, 2017, feng PMR 2018



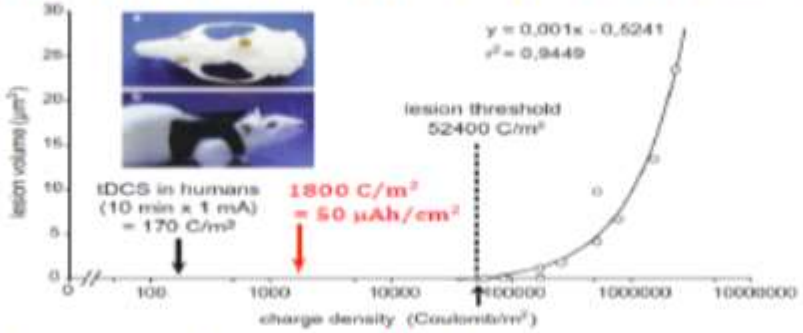
- Dosage
- Peripheral Rehab Therapy
- Montage
- Blinding
- Patient selection
- Outcome measure(s)

Dose of Brain Stimulation Emerges as an Important Modulator of the Effect

What is the effect of higher dose of tDCS?



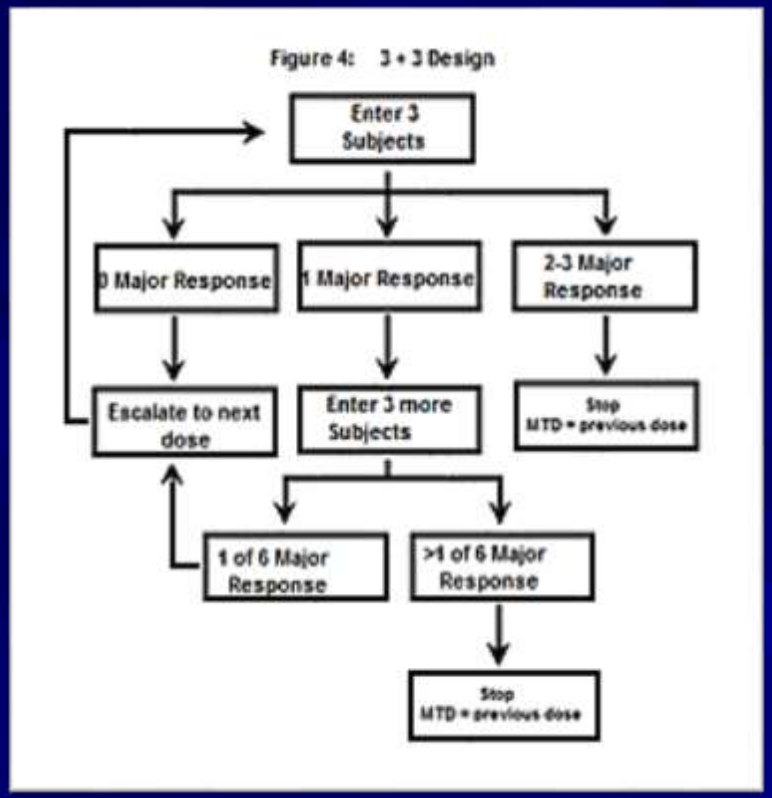
What is the safety profile of high-dose of tDCS?



Liebetanz et al., 2009, Clin. Neurophyiol.

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, *]



- Stopping Rules based on adverse events
  - 2nd degree scalp burn; seizure; new brain lesions; or discontinuation do to Aes.
- No dose limiting 'toxicities' that prevented escalation
  - 18 subjects enrolled
  - Treated up to 4.0 mA (3x / dose)
- Tolerability Issues
  - ≤ 2 subjects observed skin redness
  - Common across dose arms

Dose escalation: 1mA> 2mA> 2.5mA> 3.0mA> 3.5mA> 4.0mA

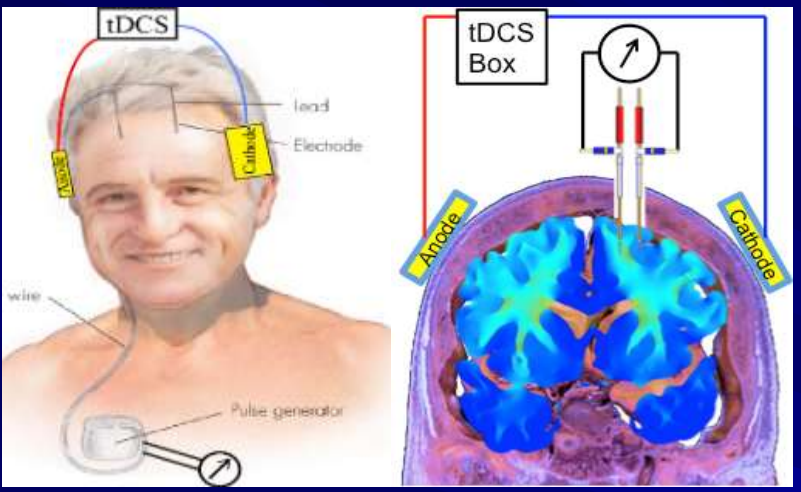
Funded by NIH: P20 GM109040 (FENG)

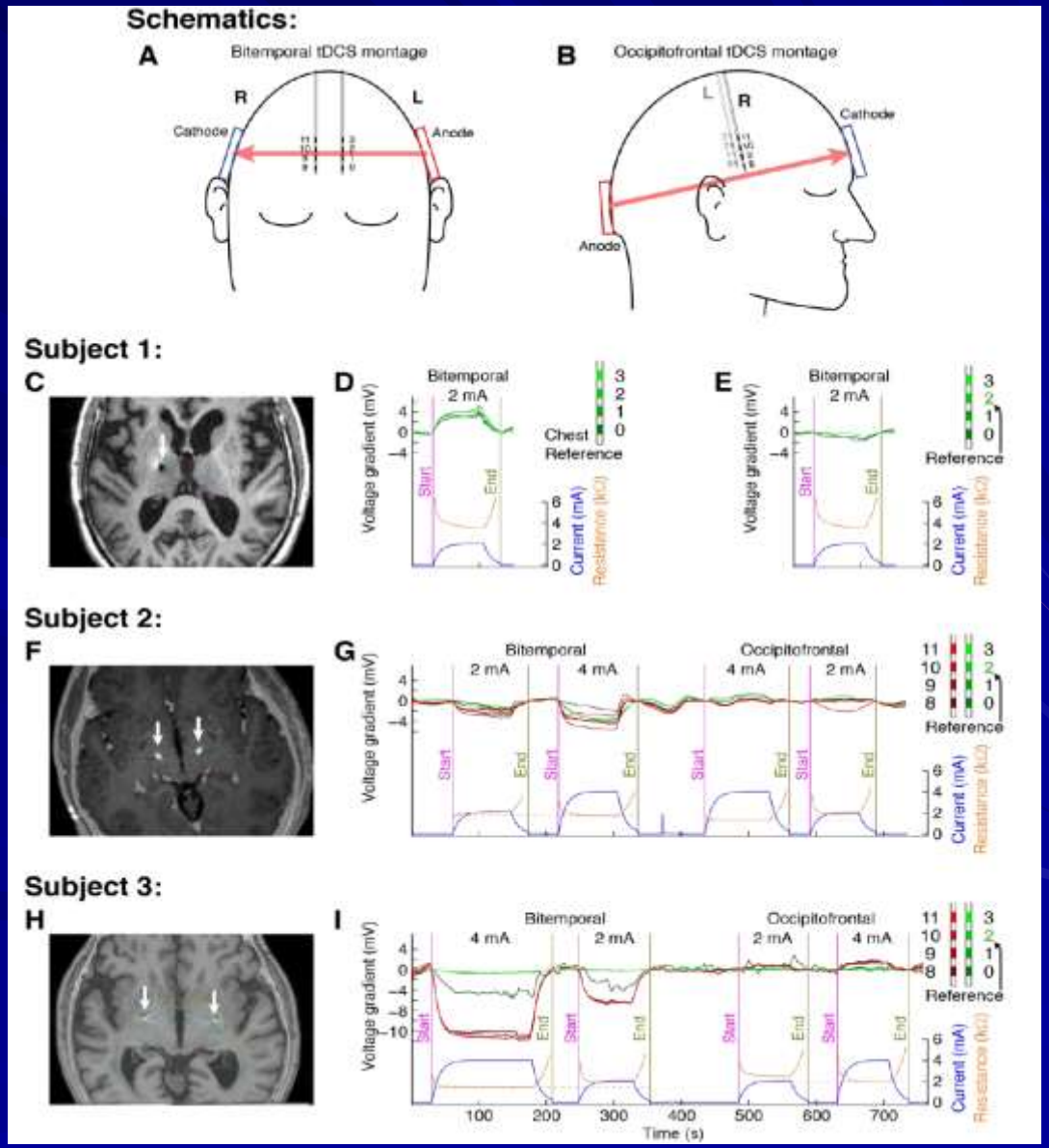
Extending the parameter range for tDCS: Safety and tolerability of 4 mA stimulation

"The study 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."

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, *]





Innovation project funded by NM4R (P2CHD086844)

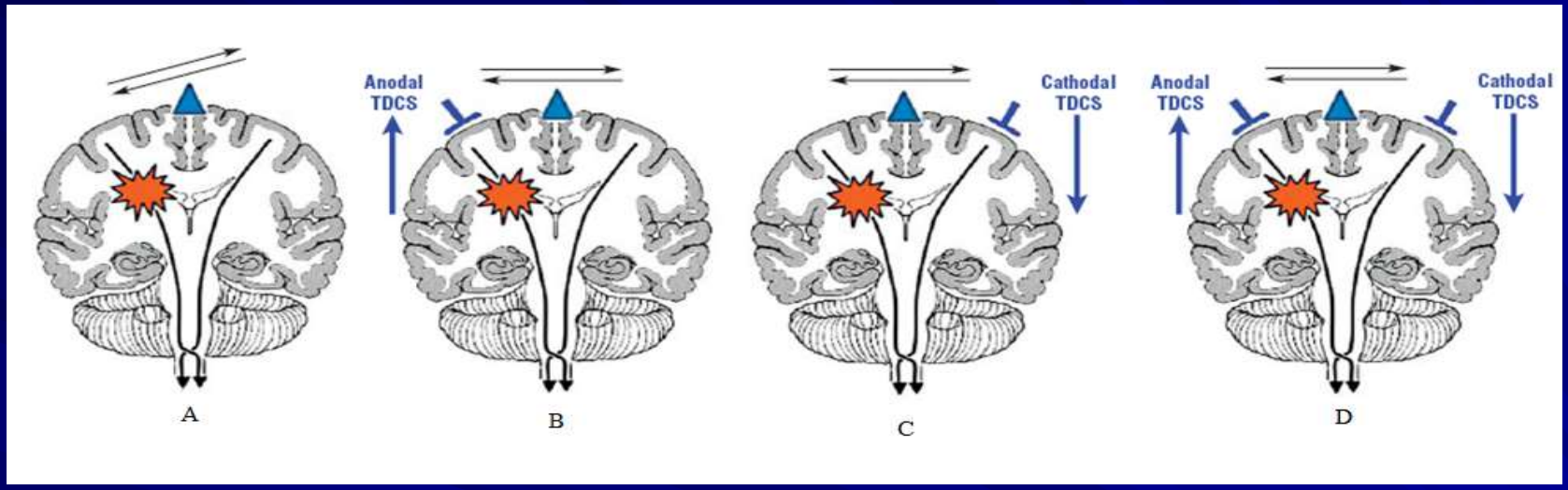
Selection of Rehabilitation Therapy

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

Key Features of CIMT

- Effective
- Standardized
- Quantifiable
- Available

Bihemispheric Montage is 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: $Tau^2 = 0.47$; $Chi^2 = 6.99$, df = 2 (P = 0.03); $I^2 = 71\%$								
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: $Tau^2 = 0.20$; $Chi^2 = 5.46$, df = 3 (P = 0.14); $I^2 = 45\%$								
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: $Tau^2 = 1.30$; $Chi^2 = 10.30$, df = 2 (P = 0.006); $I^2 = 81\%$								
Test for overall effect: Z = 1.77 (P = 0.08)								
Total (95% CI)			**124**			**128**	**100.0%**	**0.61 [0.08, 1.13]**
Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 30.51$, df = 9 (P = 0.0004); $I^2 = 71\%$								
Test for overall effect: Z = 2.25 (P = 0.02)								
Test for subgroup differences: $Chi^2 = 1.60$, df = 2 (P = 0.45), $I^2 = 0\%$								

Std. Mean Difference
IV, Random, 95% CI

−4 −2 0 2 4

Favors Sham Favors tDCS

Timing of Intervention

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

Blinding & Randomization

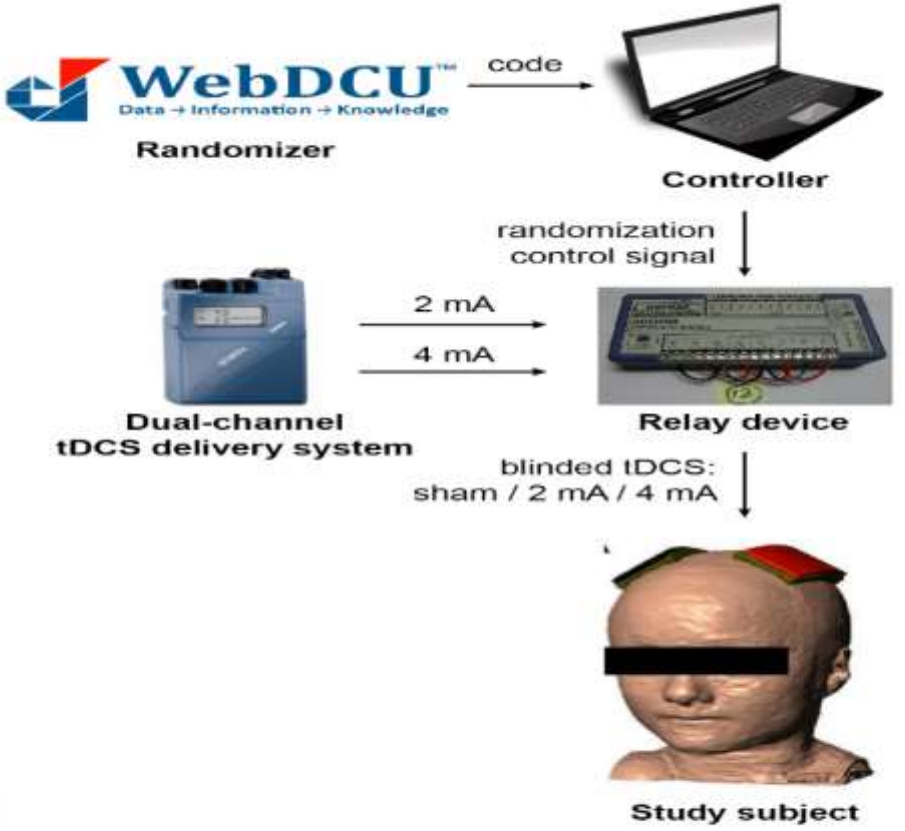


Fig 8. Schematic of interface between tDCS control, dual-channel tDCS delivery system, and WebDCU™ interface.

- Automation process
- Centrally controlled 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

- **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 primary outcomes
- Good psychometric property: ***reliability, validity and responsiveness***

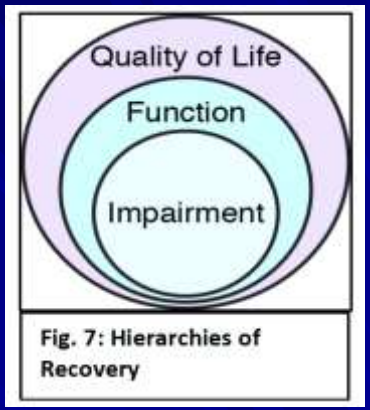
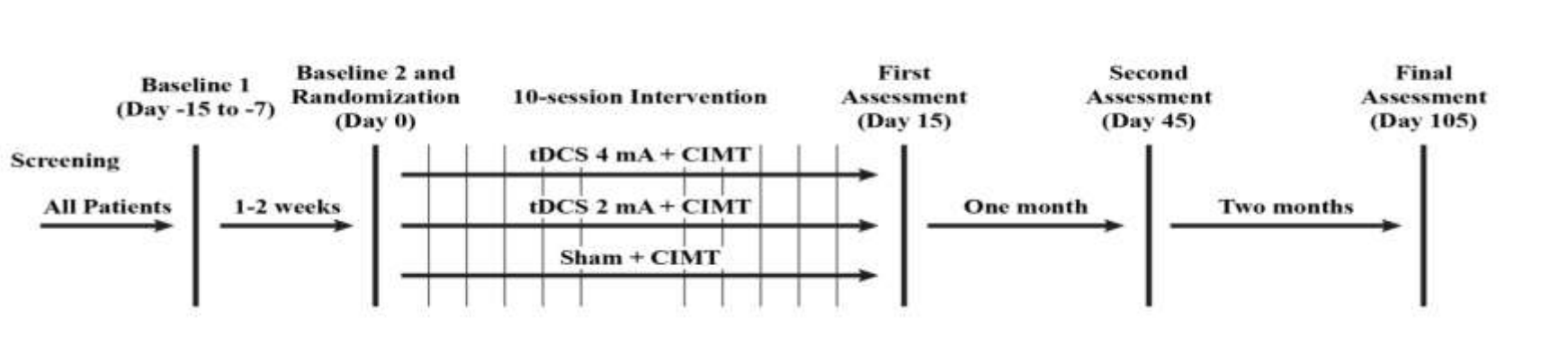


Fig. 7: Hierarchies of Recovery

TRANSPORT2 Study Design



- To determine whether there is an initial overall treatment effect (FM-UE) among 3 dosing groups:
  - sham + mCIMT
  - 2 mA + mCIMT
  - 4 mA + mCIMT
- Efficacy (FM-UE change) is measured at day 15 after the initiation of the 10-day intervention.
  - Both Intent-to-treat and per protocol analysis.

Sample Size Calculation

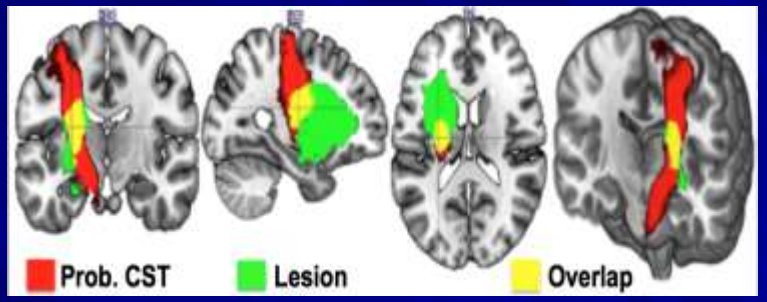
- A change of 4.25-7.25 points on the FM-UE scale is considered to be a meaningful clinically important difference (MCID). This study is powered under the assumption that mCIMT alone, will at least achieve this intervention effect (4.5) and furthermore intervention with either 2 mA or 4 mA tDCS will further increase the change in FM-UE scale from the baseline by 4.5 points (i.e., a minimum intervention effect of 9.0).
- Based on the meta-analysis of previous trials assessing tDCS in stroke patients, a conservative estimate of the intervention variability is defined as SD = 7. With a sample size of 31 subjects per group, a two-sided type I error rate of 10%, and standard deviation of 7, if the true pattern of mean changes is 4.5, 9.0, and 9.0 for the sham, 2 mA, and 4 mA groups respectively, we would have 83% power to reject the null hypothesis.
- Lost-of-follow up rates is controlled <=15%
- As a result, the final estimated sample size is 43 per group (129 in total).

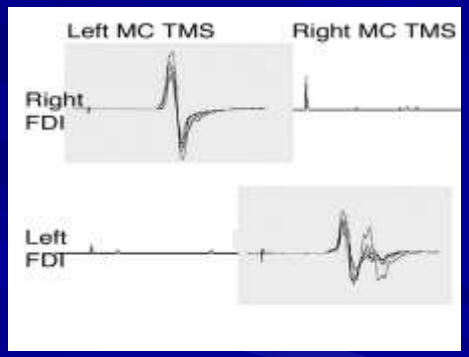
Secondary Aims

- To confirm that the proposed intervention is **safe**, **tolerable**, and **feasible** to administer in a multi-site trial setting
- **Endpoints**
  - Safety: Rate of Adverse Events
  - Tolerability: Visual Analog Scale
  - Feasibility: Treatment Completion Rate

Exploratory Aims

- 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.





Eligibility

Inclusion and exclusion will be presented by TRANSPORT2 Co-PI Dr. Gottfried Schlaug

Adverse Event Reporting

- Not Under IDE
- Determination and Classification based on NINDS Common Data Elements
- ***During the Intervention Period***
  - Adverse Events
  - Serious Adverse Events
- ***90 Day Follow-Up Period***
  - Serious Adverse Events
  - Clinically Related (Possibly or Definitely per investigator assessment) adverse events

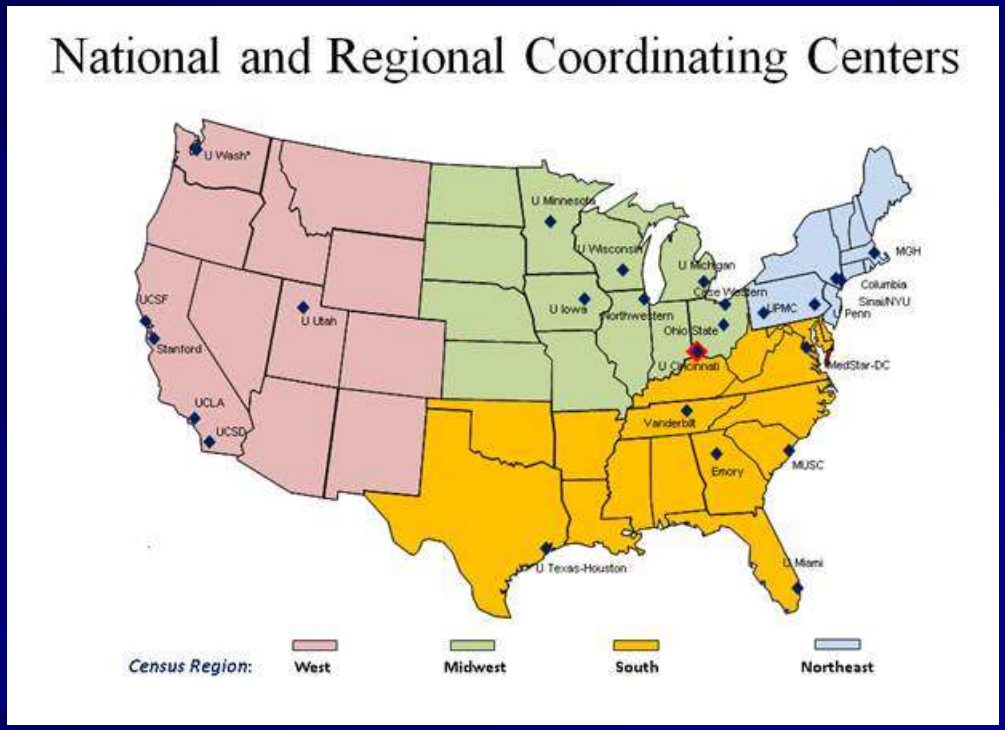
Go or No-go

	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*

The Network

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

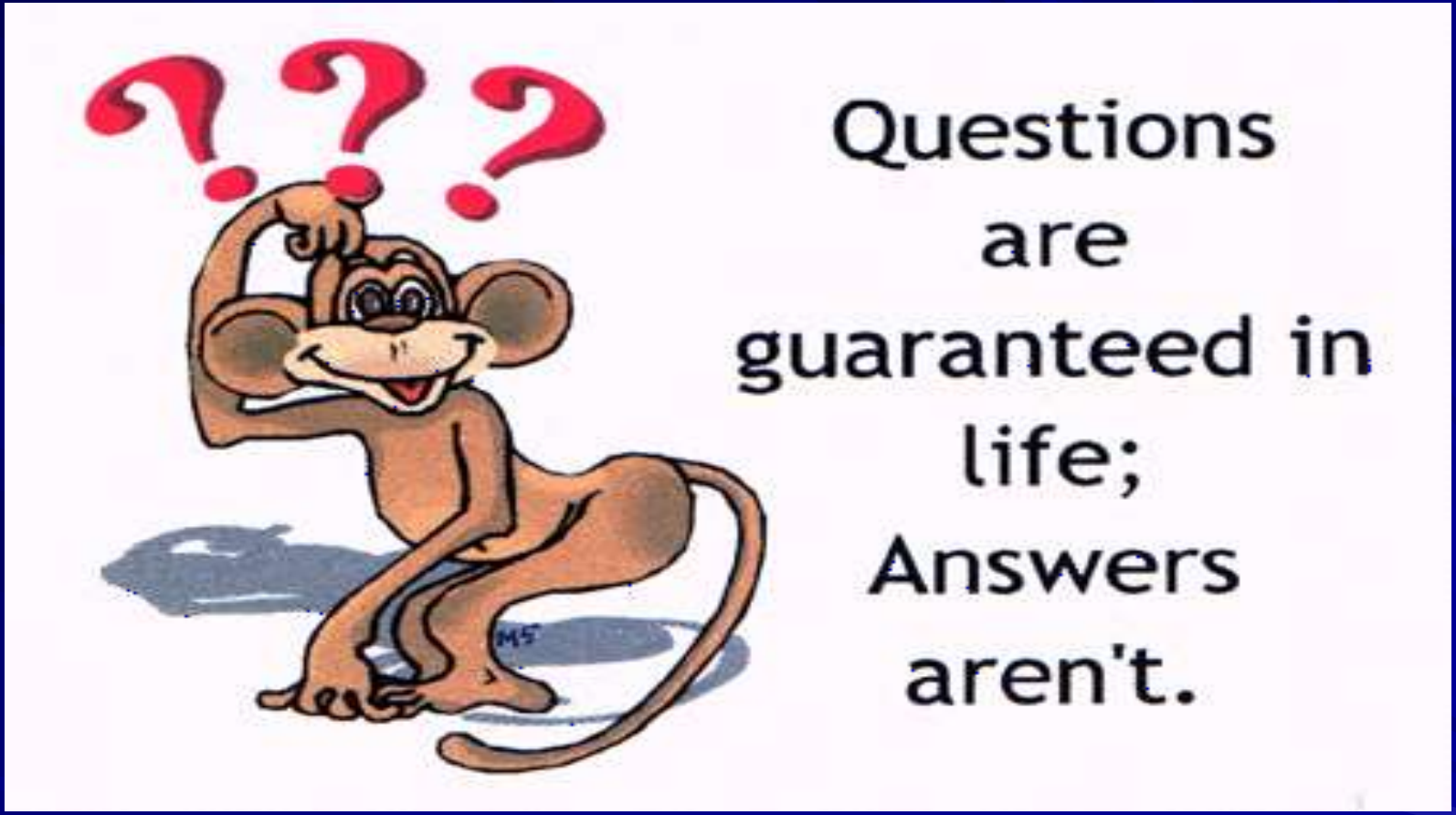
In September 2013, the National Institutes of Health funded the stroke trials network, "NIH StrokeNet". The StrokeNet infrastructure consists of 25 regional coordinating centers across the US, a national coordinating center at the University of Cincinnati, and a national data management center (Medical University of South Carolina). The primary goal of this network is to maximize efficiencies to develop, promote and conduct high-quality, multi-site clinical trials focused on key interventions in stroke prevention, treatment and recovery.



- ***Acute treatment:***
  - DEFUSE3
  - IDEF*
  - MISTIE3*
  - MOST
- ***Prevention***
  - CREST2*
  - CREST-H*
  - ARCADIA
  - SLEEPSMART
  - SATURN
- ***Recovery:***
  - TELEREHAB*
  - TRANSPORT2
  - IACQUIRE

TRANSPROT2 is the FIRST stroke recovery study concept originated in the Stroke Trial Network

Questions?



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