Transcranial Direct Current Stimulation (tDCS)

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Never Stand Still | Faculty of Medicine

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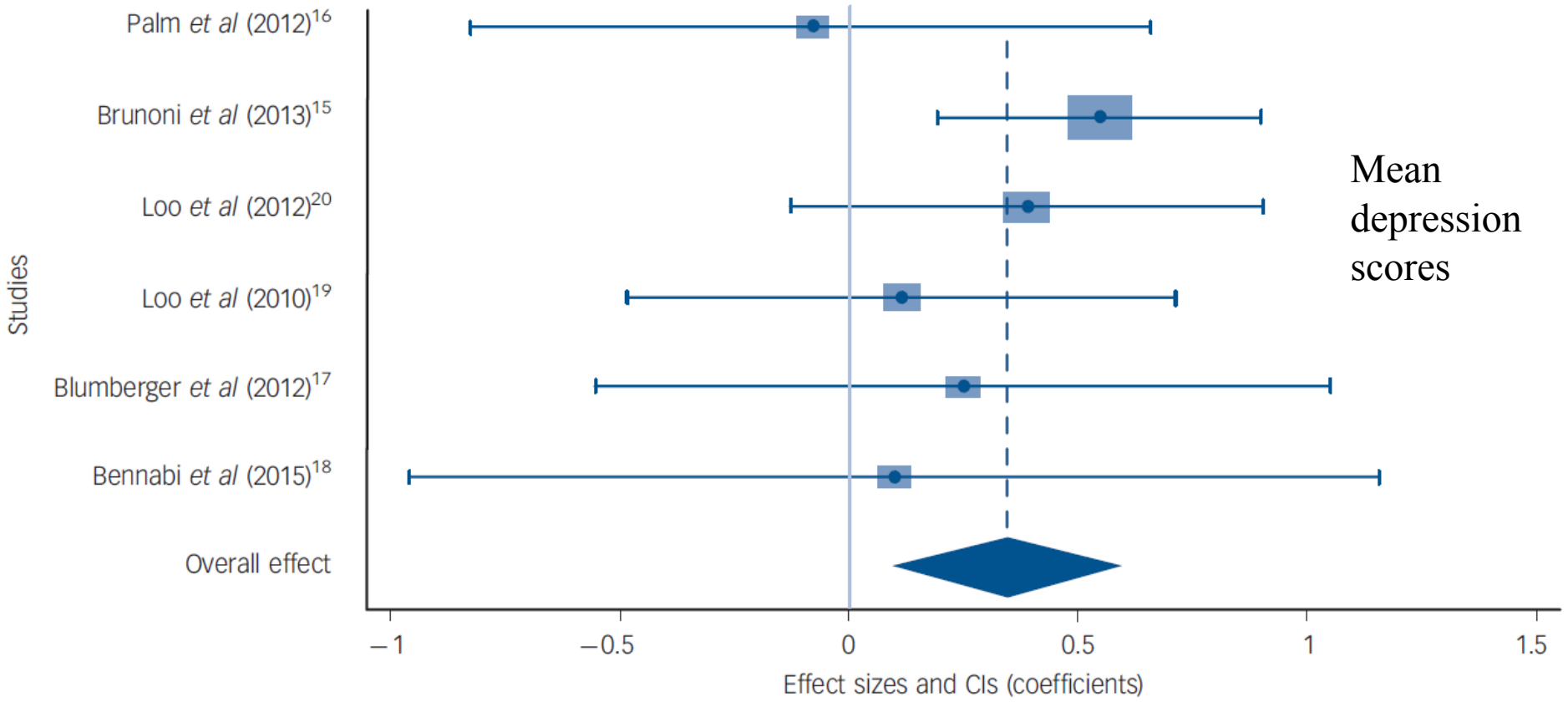
Disclosures

This talk will discuss the use of tDCS in depression – tDCS is not an approved treatment for depression.

Dr Loo has the following interests to disclose:

- tDCS equipment from Soterix for a clinical trial.

Brunoni……Loo, 2016. tDCS Efficacy in Depression Individual Patient Data Meta-Analysis



	Active	Sham	OR	CI	NNT
Response	34%	19%	2.44	1.38-4.32	7
Remission	23.1%	12.7%	2.38	1.22-4.64	9

Predictors: Treatment resistance, tDCS “dose”

tDCS meta-analysis, Brunoni et al, 2016, N=289

	Active	Sham	OR	CI	NNT
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Remission	23.1%	12.7%	2.38	1.22-4.64	9

TMS Neuronetics multicentre pivotal trial, O'Reardon et al, 2007, N=301

	Active	Sham	OR	CI	NNT
Response	23.9%	12.3%			9
Remission	14.2%	5.5%			

TMS NIMH multicentre trial, George et al, 2010, N=190

	Active	Sham	OR	CI	NNT
Response	15%	5%	4.6	1.47-14.42	
Remission	14.1%	5.1%	4.2	1.32-13.24	12

Antidepressant meds, NNT = 8, Thase et al, 2005

Design Multicentre Trial

Sample - treatment resistance

“Dose”

Durability - taper

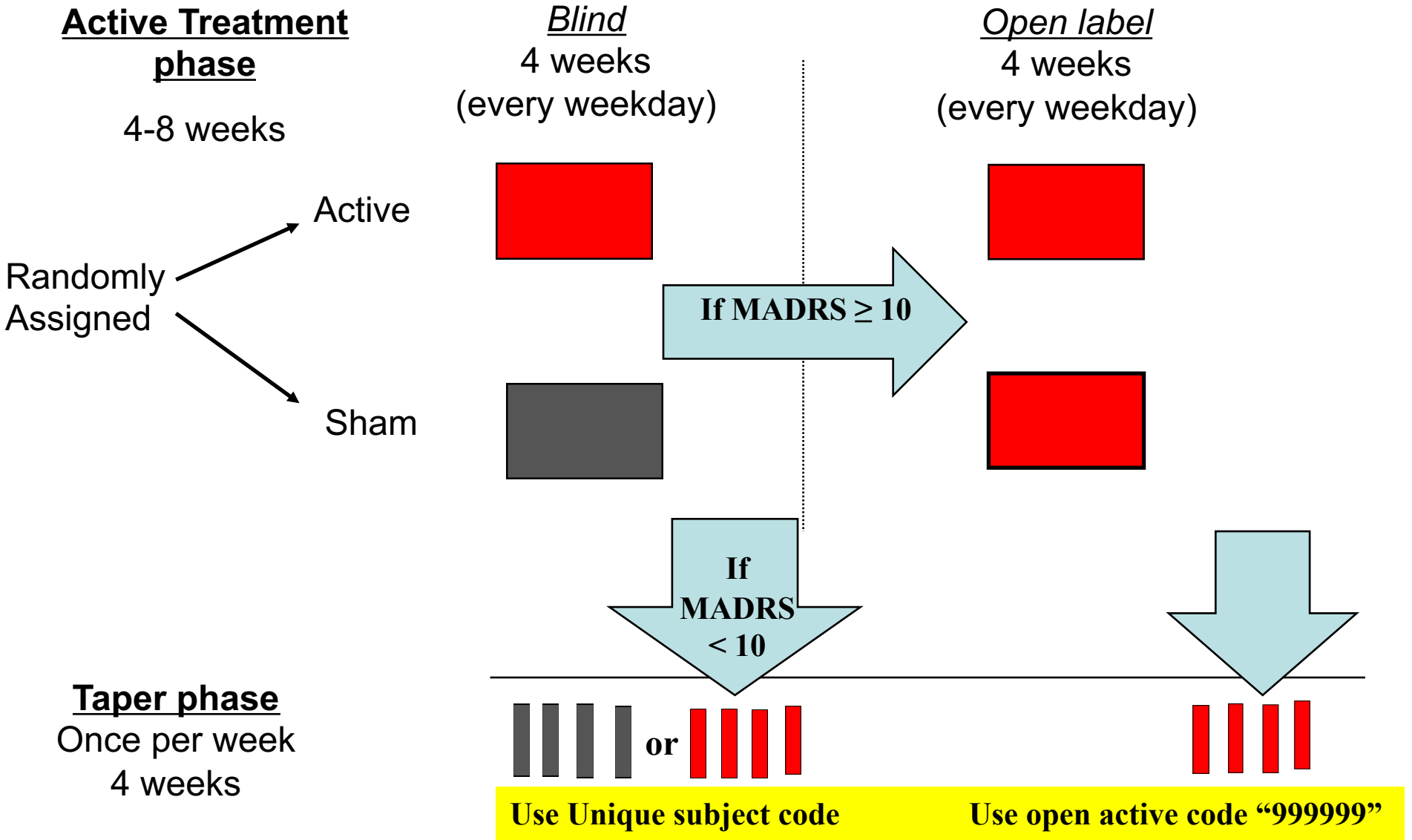
Blinding - Machine design

Montage

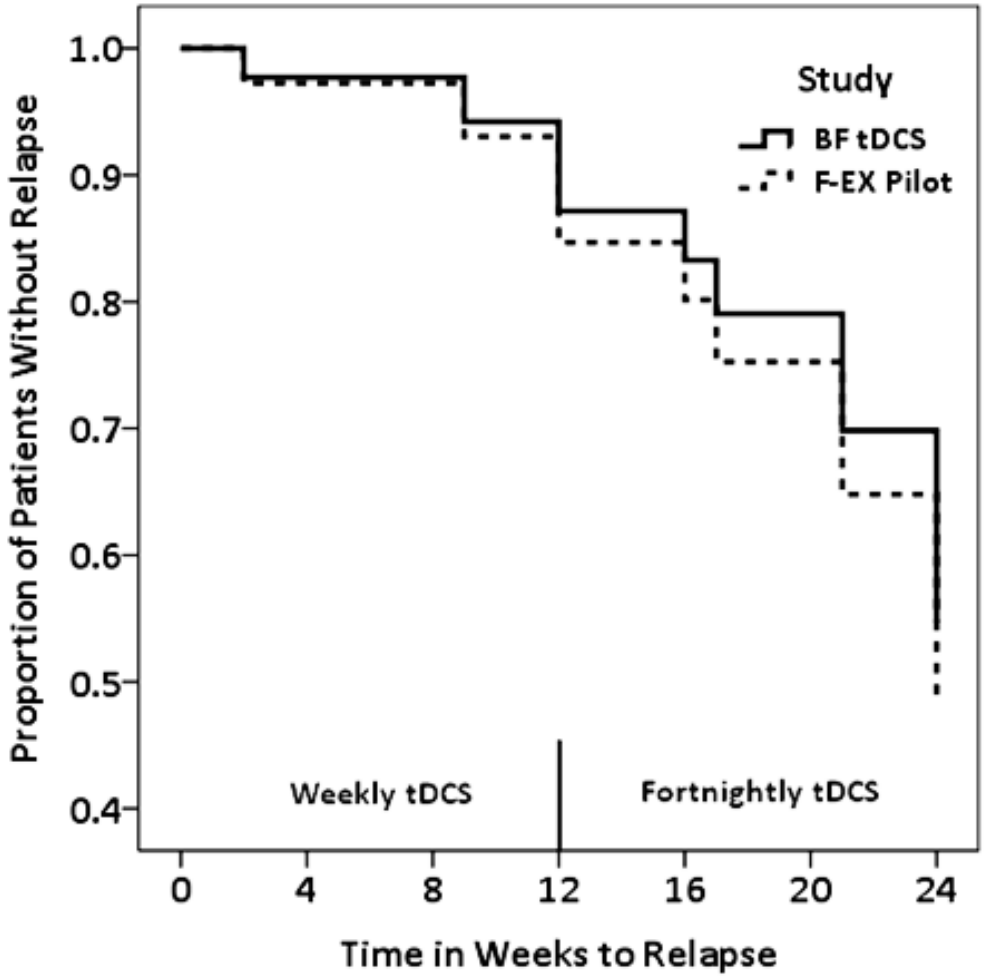
Sample

- N=120, aim 60 UP, 60 BP
- ≥ 18 years
- DSM IV Major Depressive Episode
- MADRS ≥ 20
- Current episode ≤ 3 years
- Failed ≤ 3 adequate antidepressant trials
- Not failed ECT in current episode
- Other exclusion: psychosis, drug/alcohol abuse, neurological disorder, skull defect/metal, long acting benzodiazepine, stimulants, pregnant.
- clinical assessment & structured scales

Study Design



Maintenance tDCS



N=26 responders from depression trials
30 courses maintenance tDCS

<u>Weekly x 3 months</u>
→ 84% no relapse @ 3/12

<u>Then fortnightly x 3 months</u>
→ 51% no relapse @ 6 months

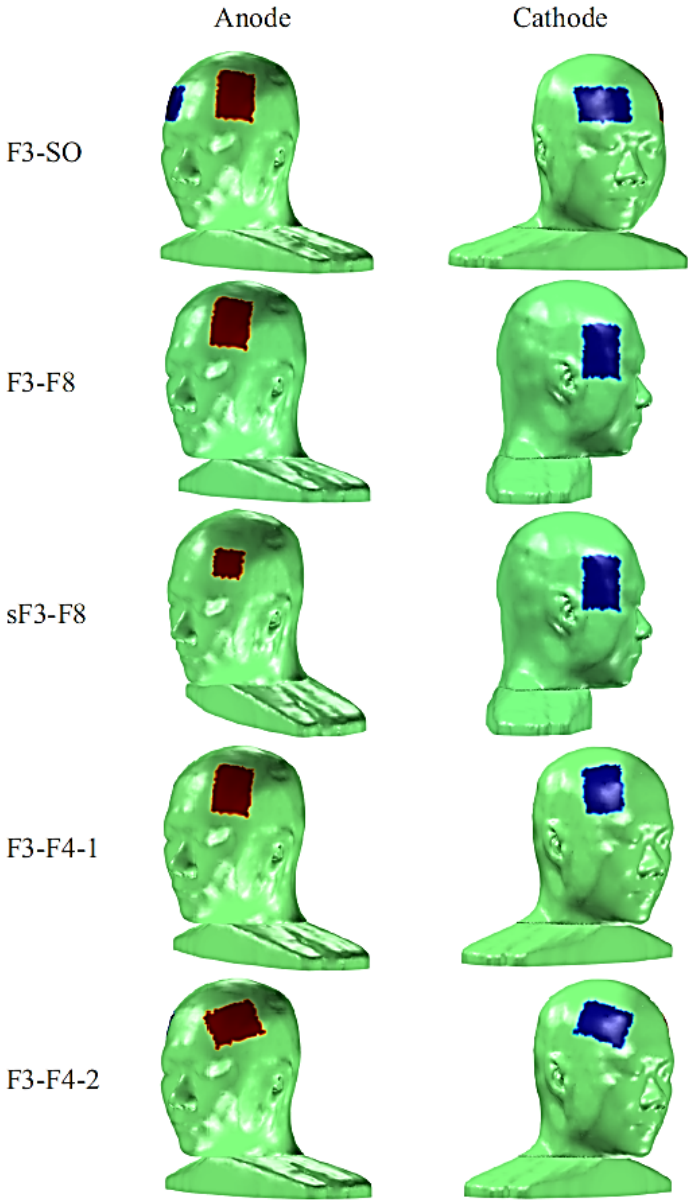
Martin et al, 2013

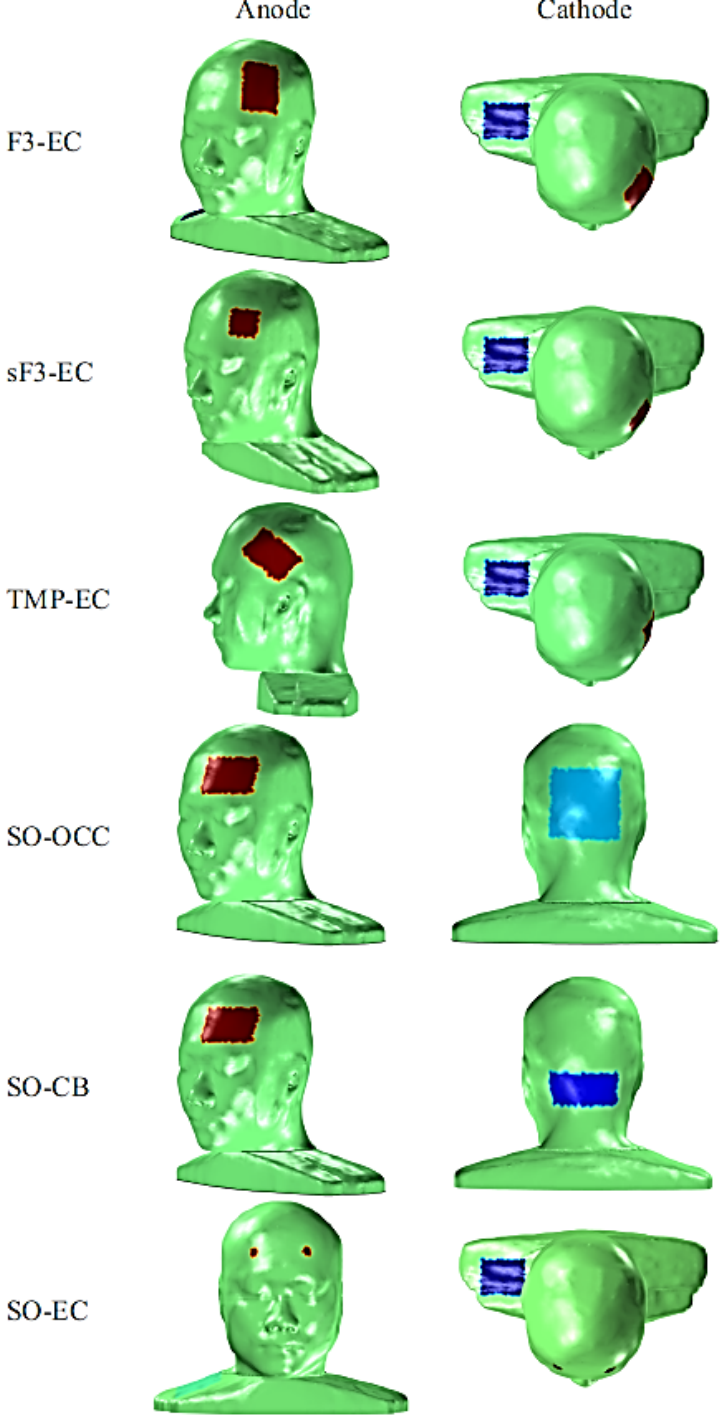
Machine

Blinding

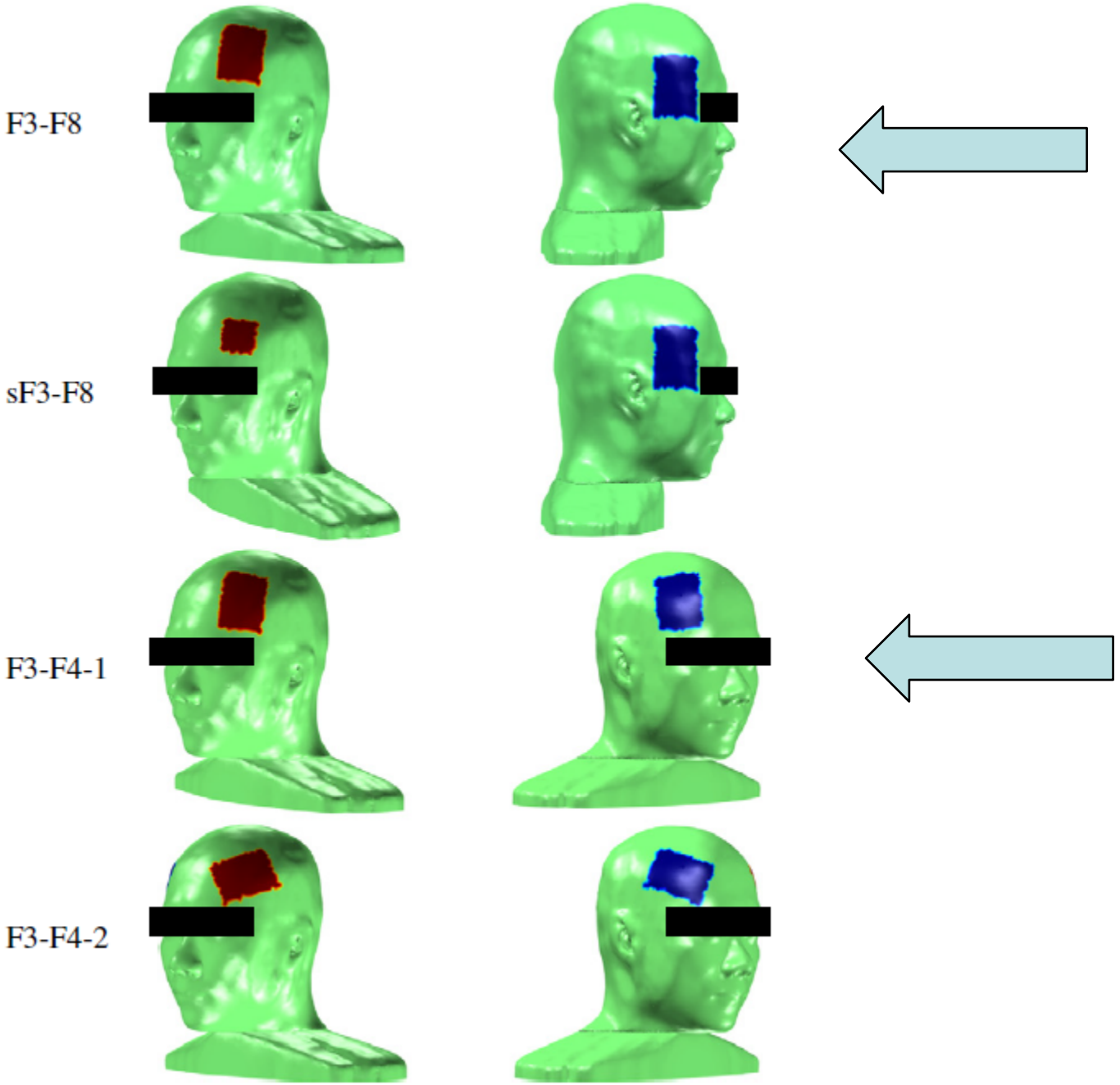
- Individual subject code. Multi digit – differ by ≥ 2 digits.
- Feedback during sham and active stimulation – test impedance
- Sham stimulation –Ramp. Microamp intensity.

tDCS Montages for Treating Depression

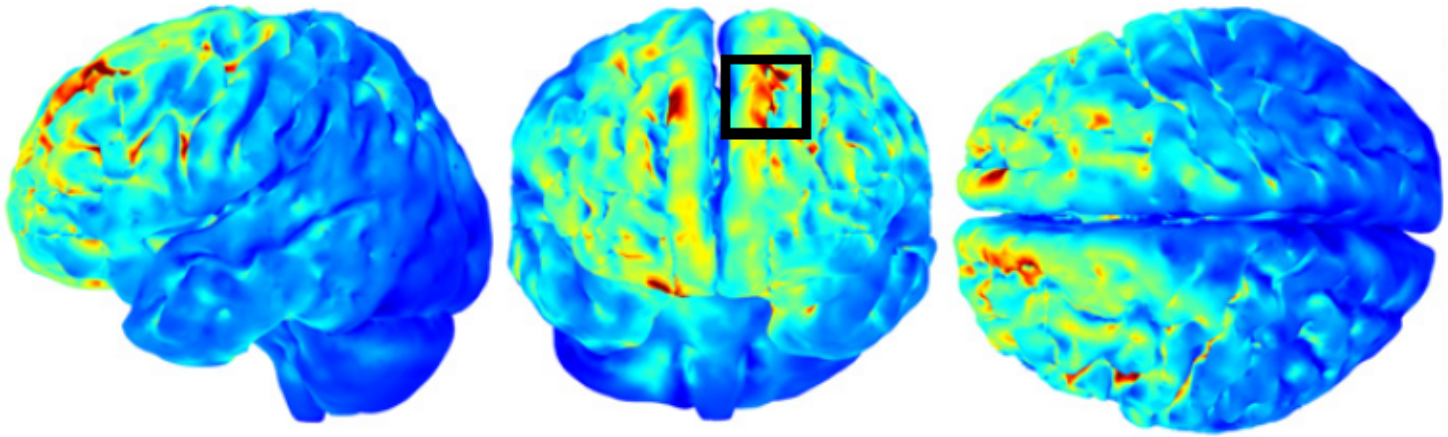




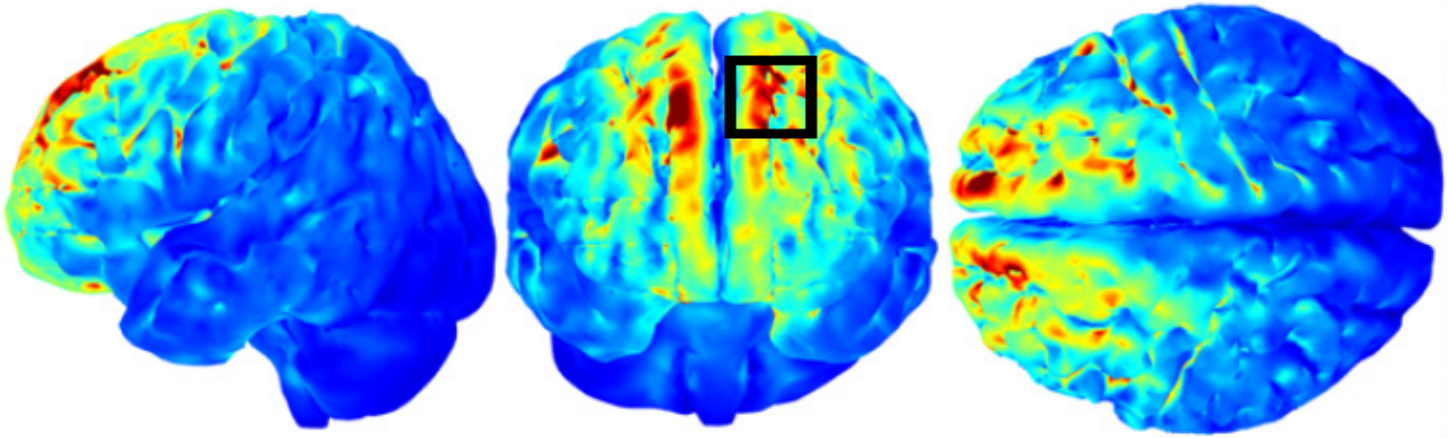
Bai et al, Neuroimage 2014


F3-F8
sF3-F8
F3-F4-1
F3-F4-2

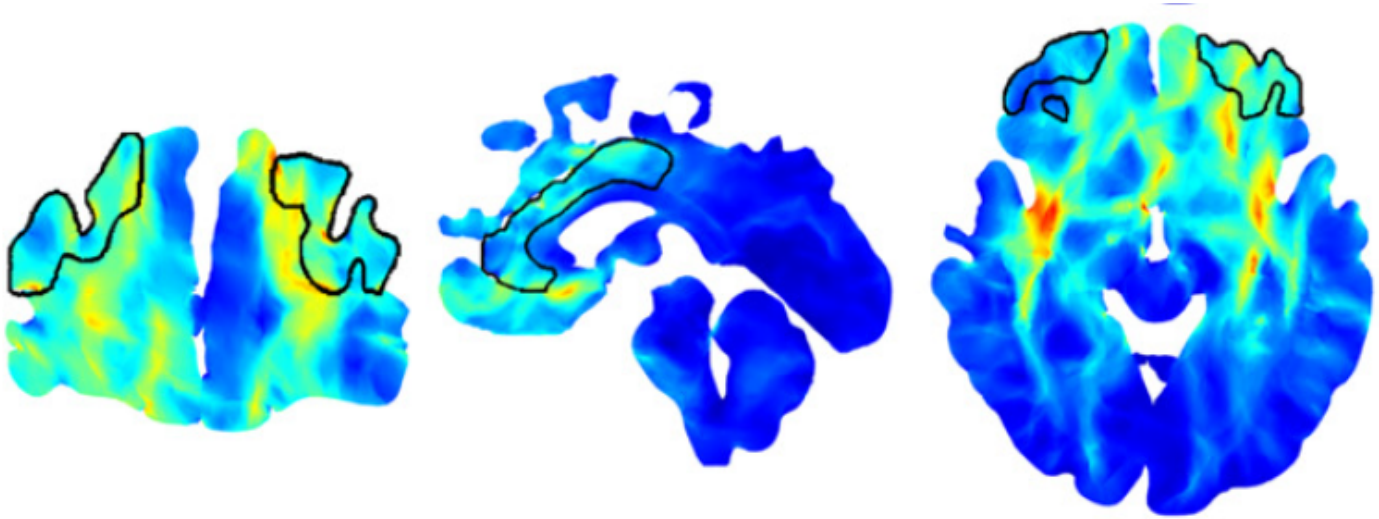
F3-F8



F3-F4-1



F3-F8



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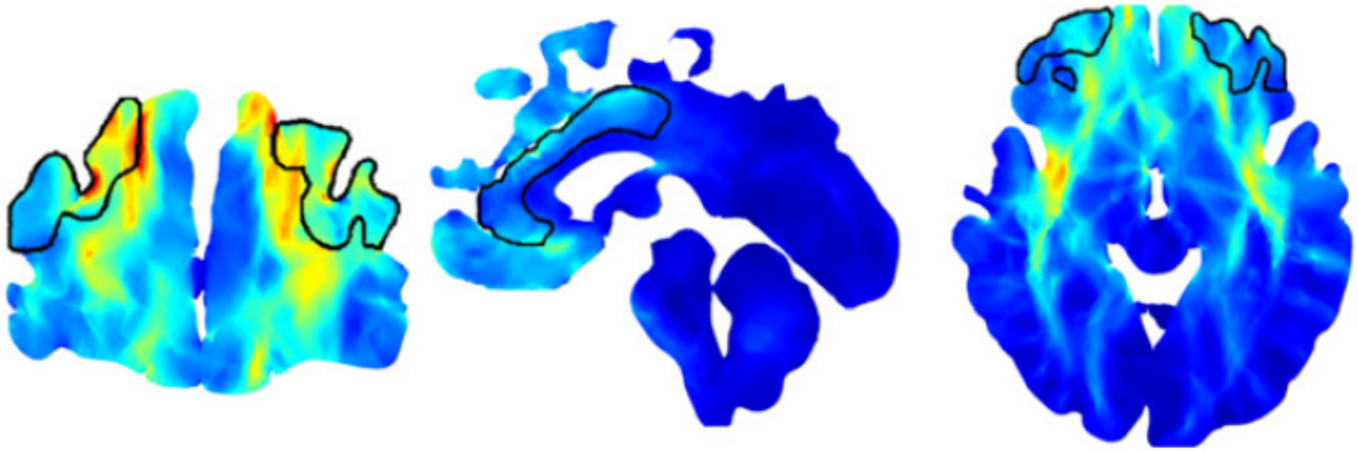
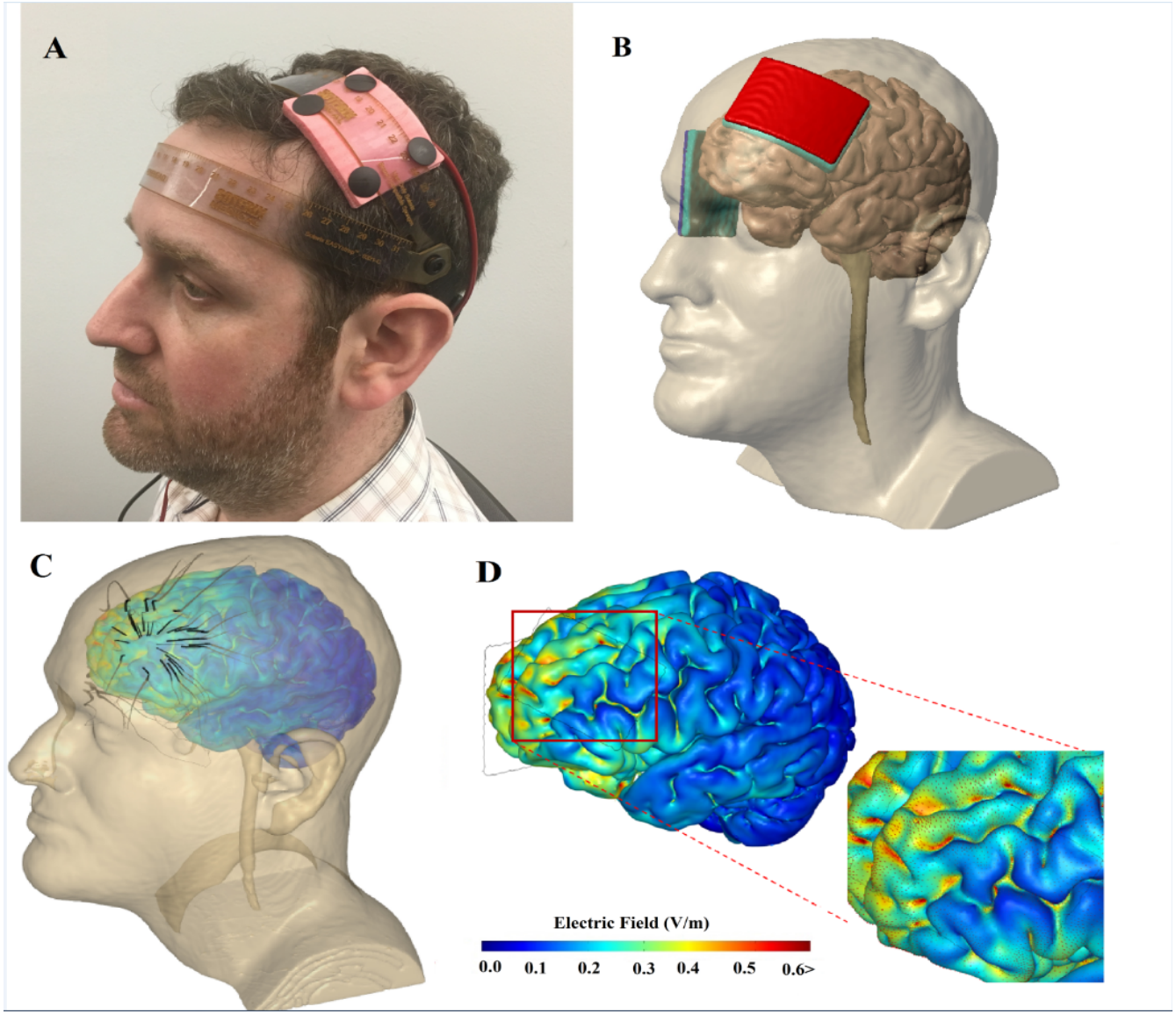
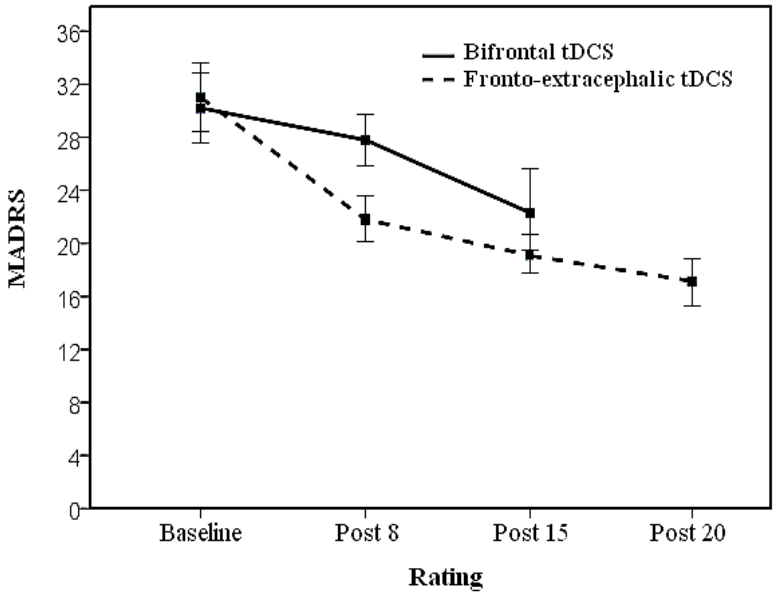


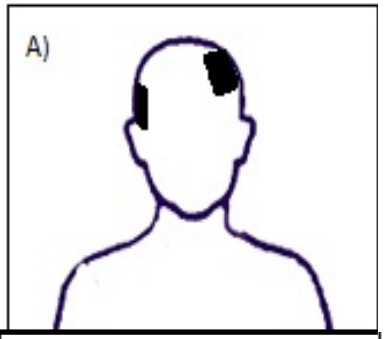

A
B
C
D
Electric Field (V/m)
0.0
0.1
0.2
0.3
0.4
0.5
0.6>

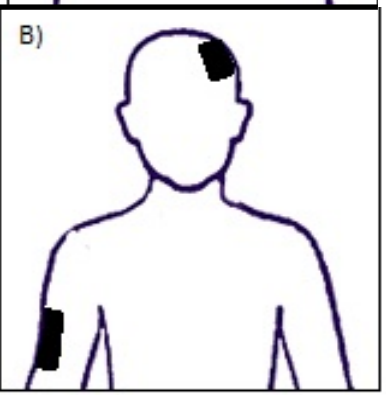
Electrode Montage



Martin et al, 2011

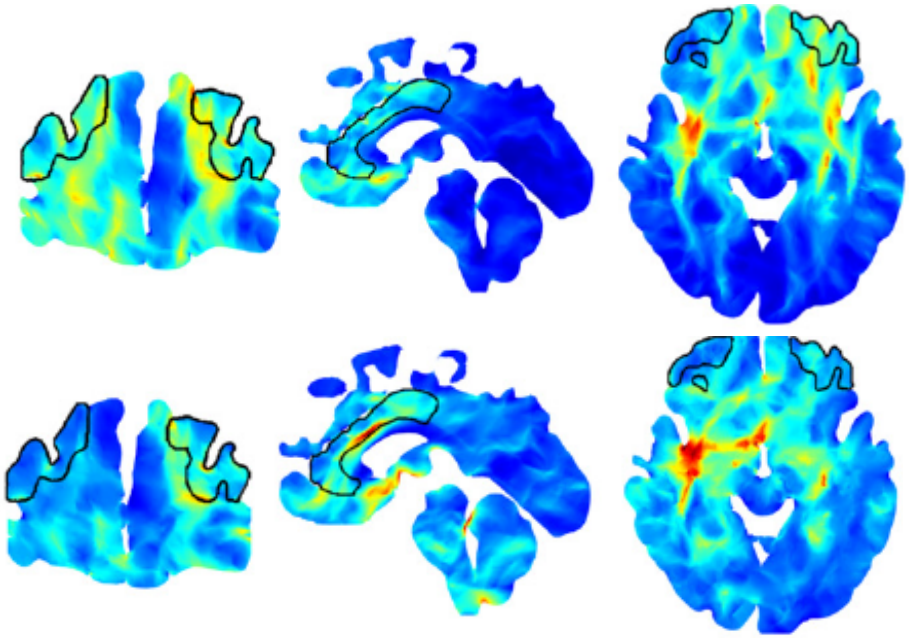
- N= 11 depressed
- 1st course Bifrontal
- 2nd course Fronto-Extracephalic
- 2mA tDCS, 20 mins daily
- N=1, hypomanic with F-Ex only

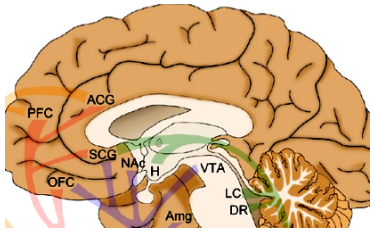




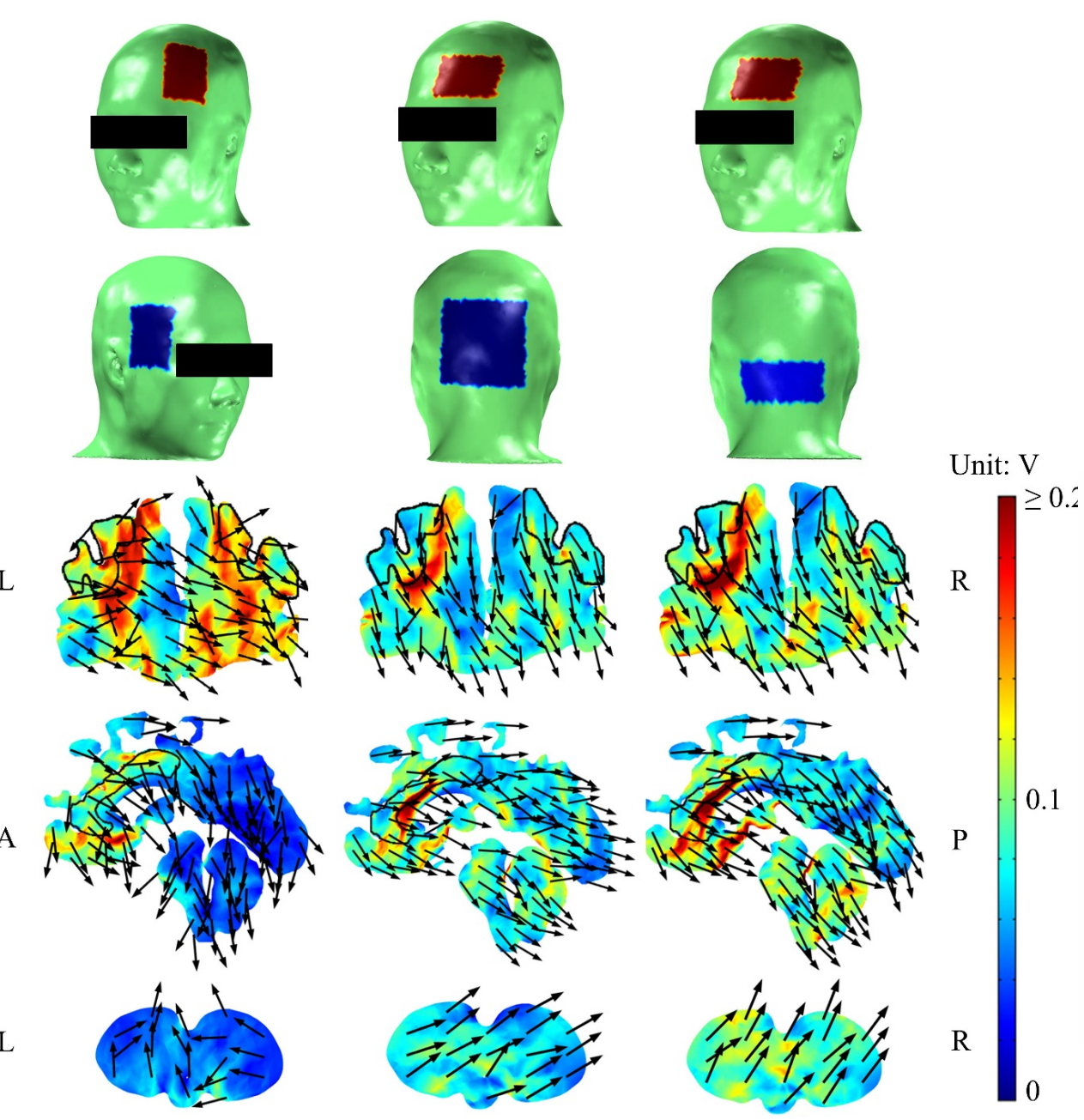
Bifrontal

Fronto-extracephalic





Bifrontal Fronto-Occipital Fronto-Cerebellar

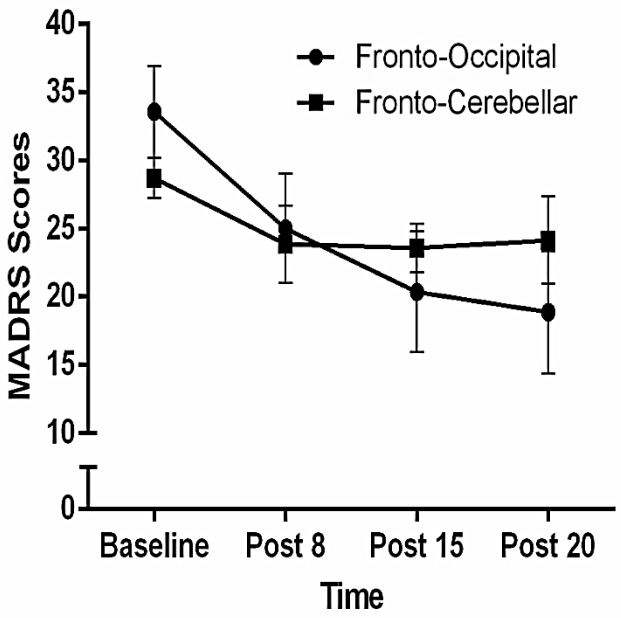


Ho et al, 2014

N=15 depressed

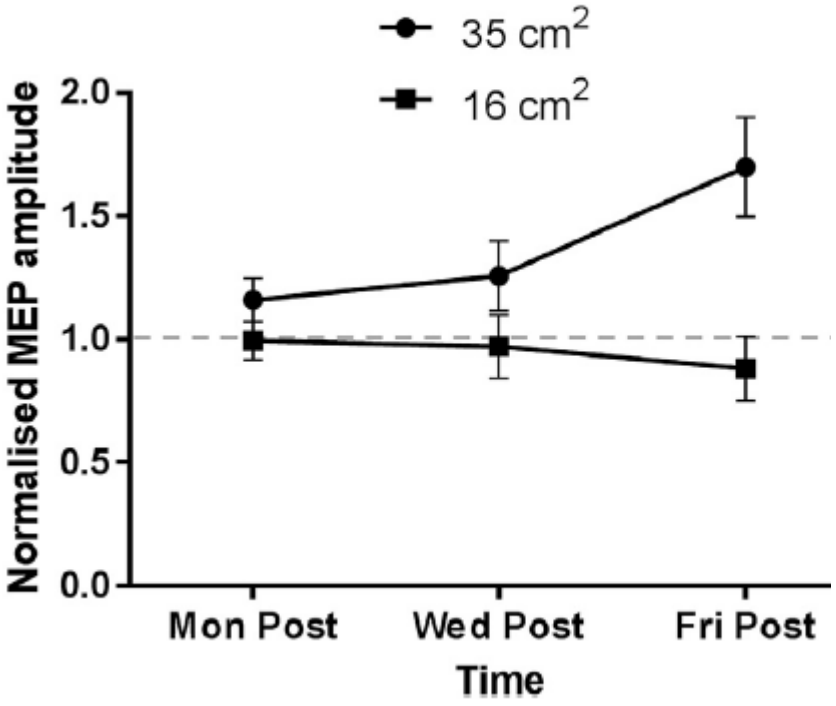
Pilot clinical trial

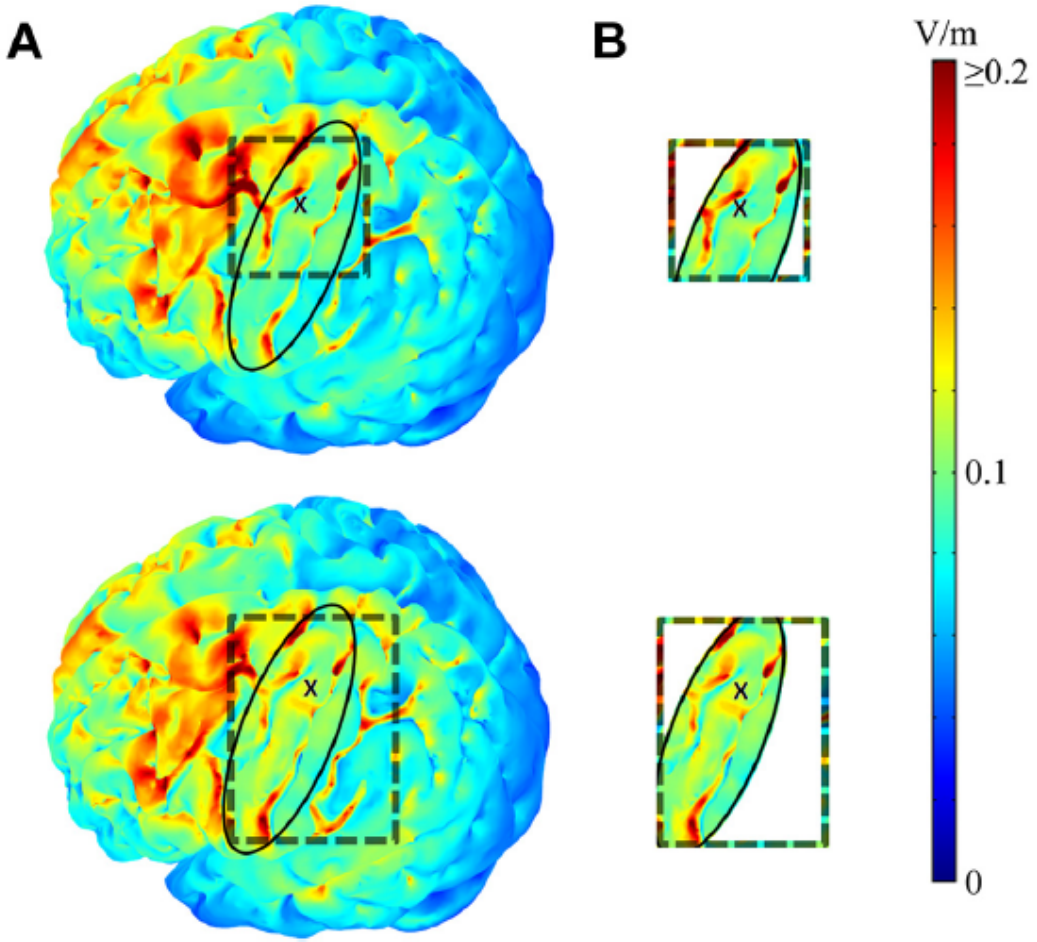
Fronto-occipital or fronto-cerebellar



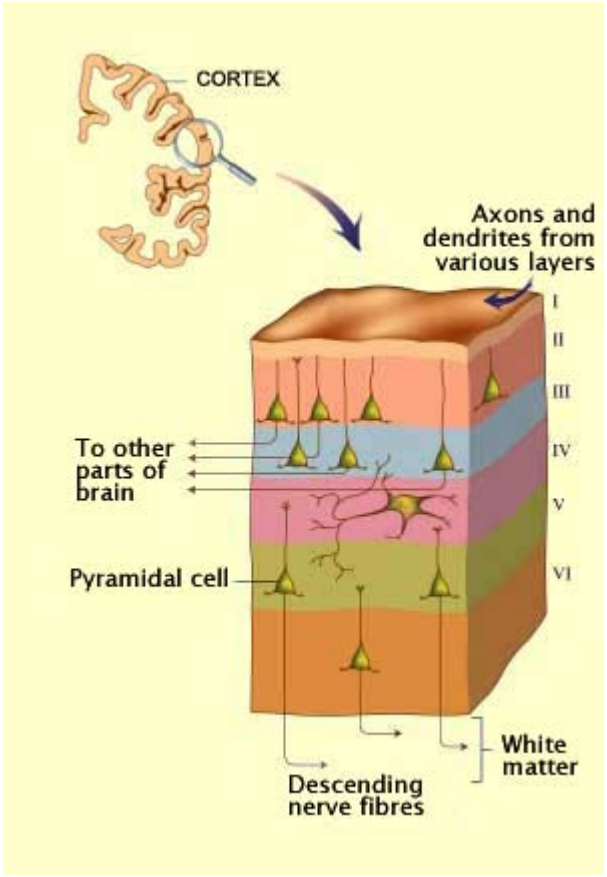
Electrode size- beyond "charge density"

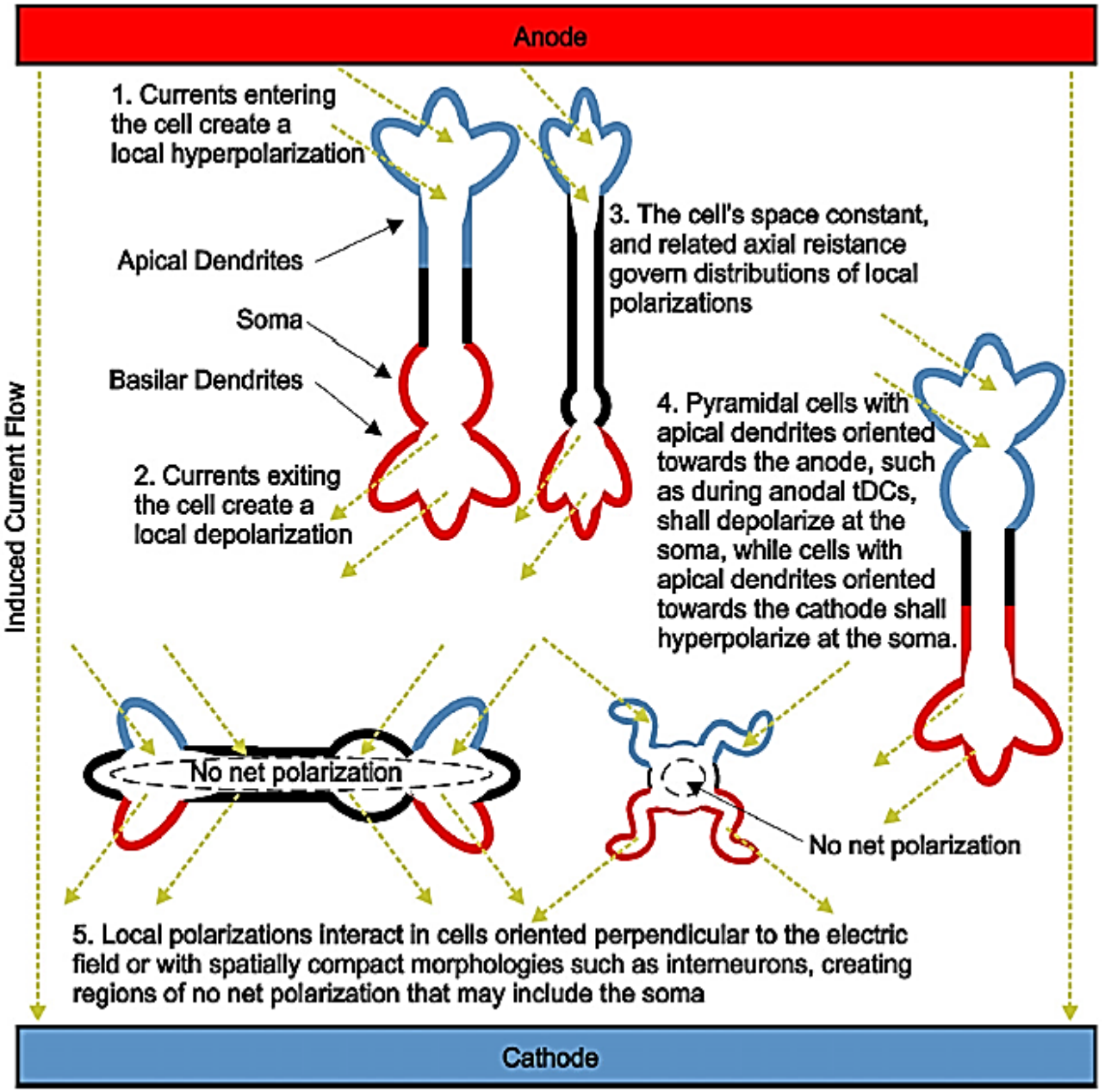
Data pooled from 7 studies
89 healthy, motor cortex





Ho,….Loo, 2016





Effects of Neuronal Anatomy

Radman et al, 2009

Dosing: RCTs of Active vs Placebo tDCS

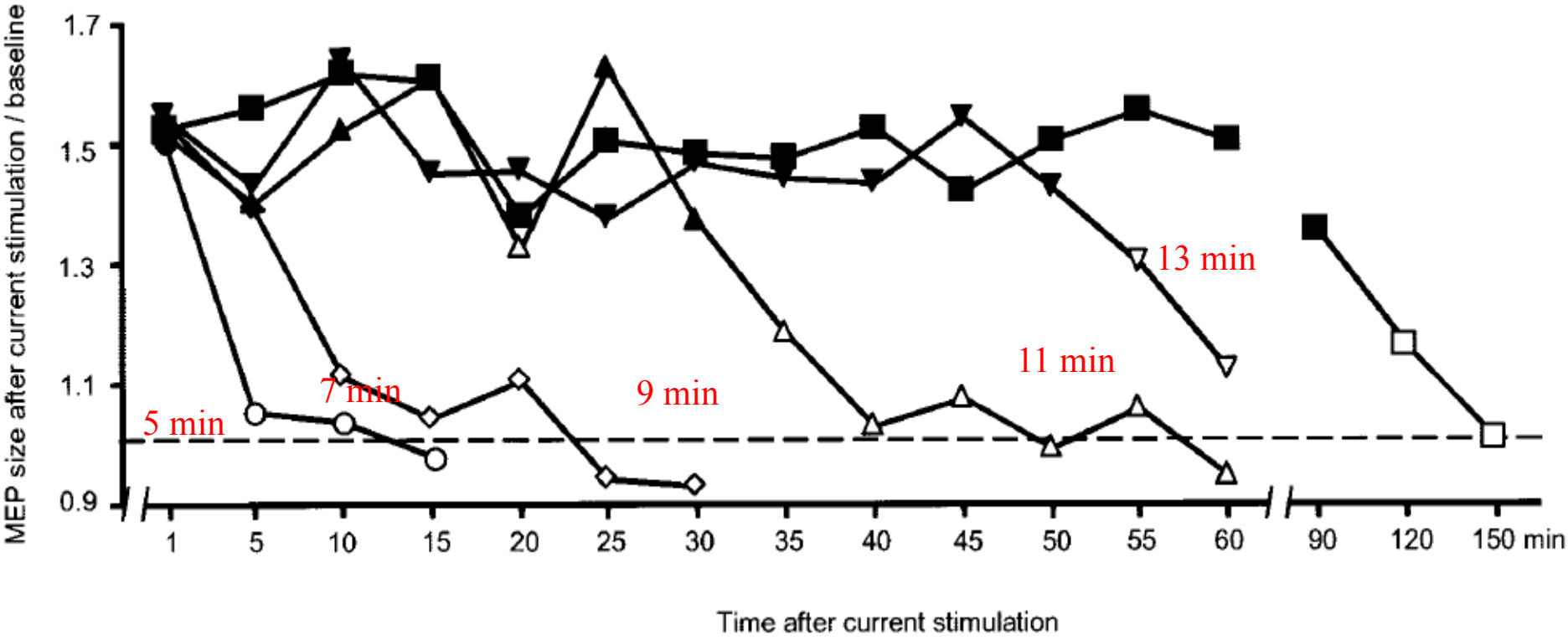
Study	N	Stimulation parameters/ sessions	Mean Δ depression scores	% Response	% Remitters
Fregni et al, 2006	10	1mA, 20 mins, 5 sessions/ 1.5 weeks	Active: 59% Sham: 13%	80 0	? ?
Boggio et al, 2008	40	2mA, 20 mins, 10 sessions/ 2 weeks	Active: 40% Sham: 10%	40 20	25 0
Loo et al, 2010	40	1 mA, 20 mins, 5 sessions/ 1.5 weeks	Active:20% Sham: 19%	0 0	0 0
Palm et al, 2011	22	1-2mA, 20 mins, 10 sessions/ 2 weeks crossover	Active (1mA): 15% Sham: (1mA): 9% Active (2mA): 17% Sham (2mA): 15%	0 0 17 0	0 0 0 0
Loo et al, 2012	64	2mA, 20 mins, 15 sessions/ 3 weeks	Active: 28% Sham 16%	13 [50] 14	0 [31] 0
Blumberger et al, 2013	24	2mA, 20 mins 15 sessions/3 weeks	Active:24% Sham: 25%	8 9	0 0
Brunoni et al, 2013	120	2mA, 30 mins 10 sessions/2 weeks Taper: 2 sessions/4 weeks	Active:40% Sham: 18%	9 [13] 11 [5]	4 [12] 6 [4]
Multicentre Trial	**120 UP/ BP**	**2.5 mA, 30 mins, 20 sessions/4 weeks Taper Phase**			

[ ] after 6 weeks

Dose – Stimulus Parameters

Intensity (mA)	Intensity x duration = charge
Duration (mins)	
Electrode size (cm2)	Charge/ electrode area = charge density
Number sessions	Intensity x duration x # sessions = total charge
	Total charge/electrode area = total charge density
Spacing of sessions	

Stimulation Duration

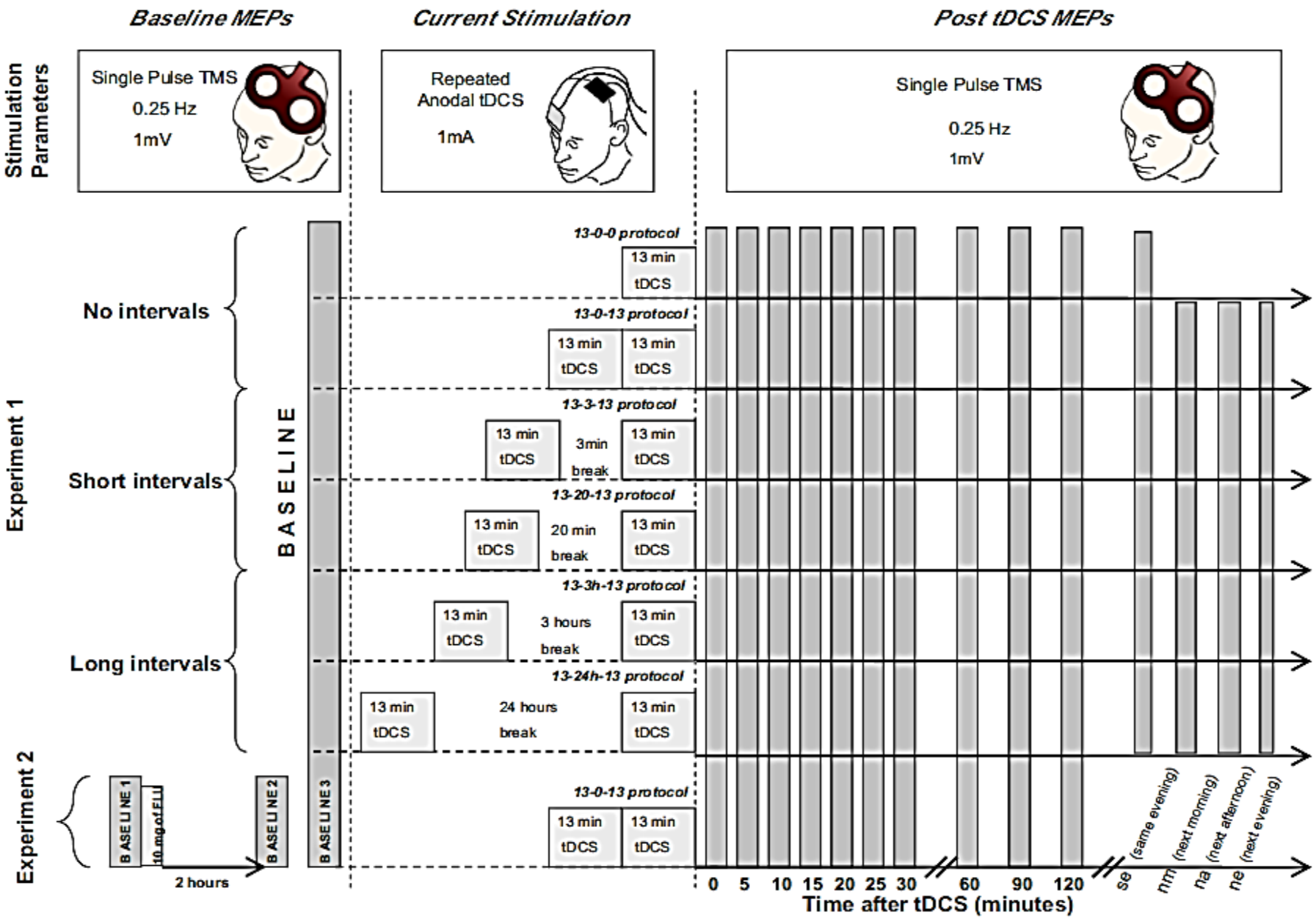


≥ 26 min?

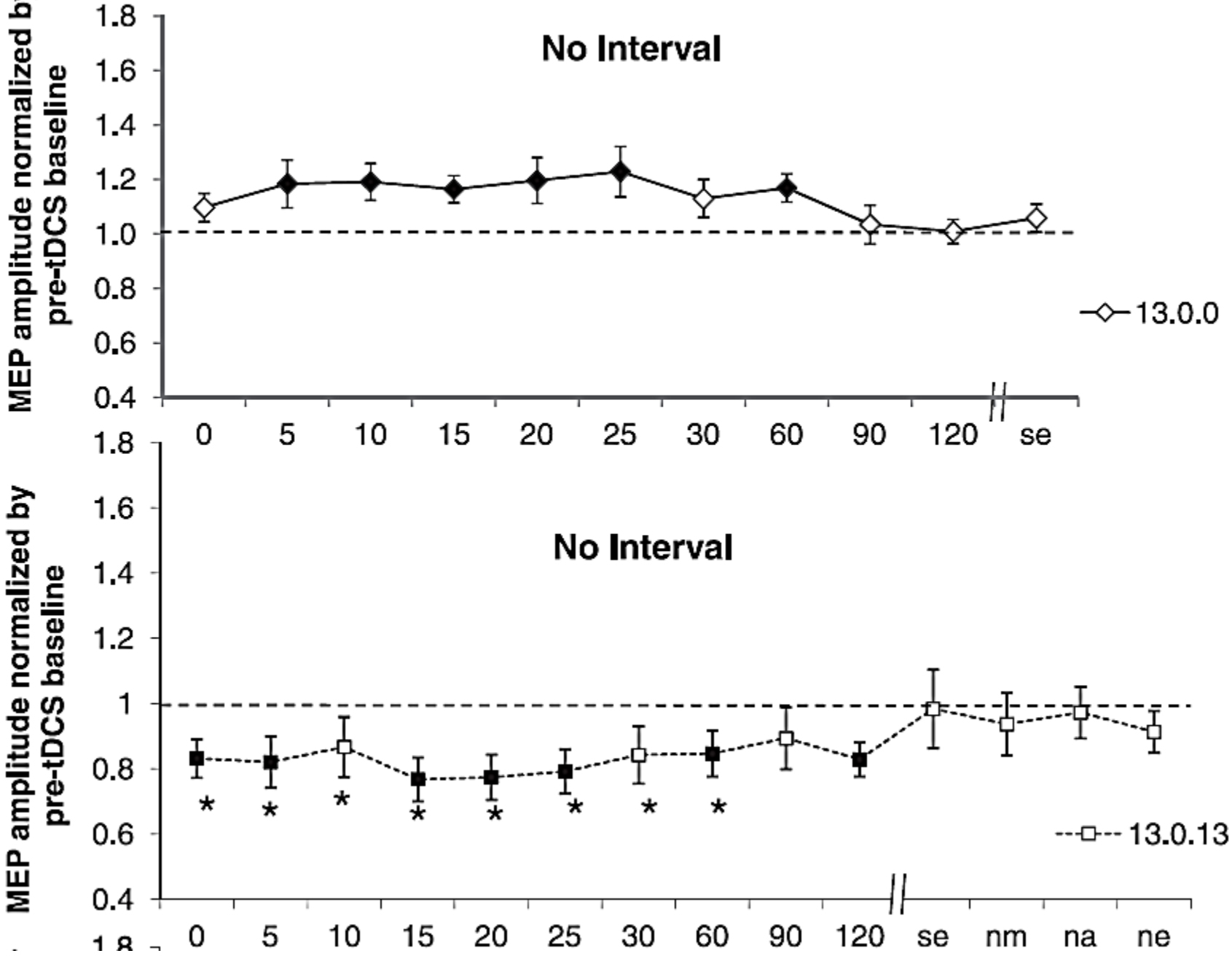
Anodal tDCS
Nitsche & Paulus, 2001

Session spacing

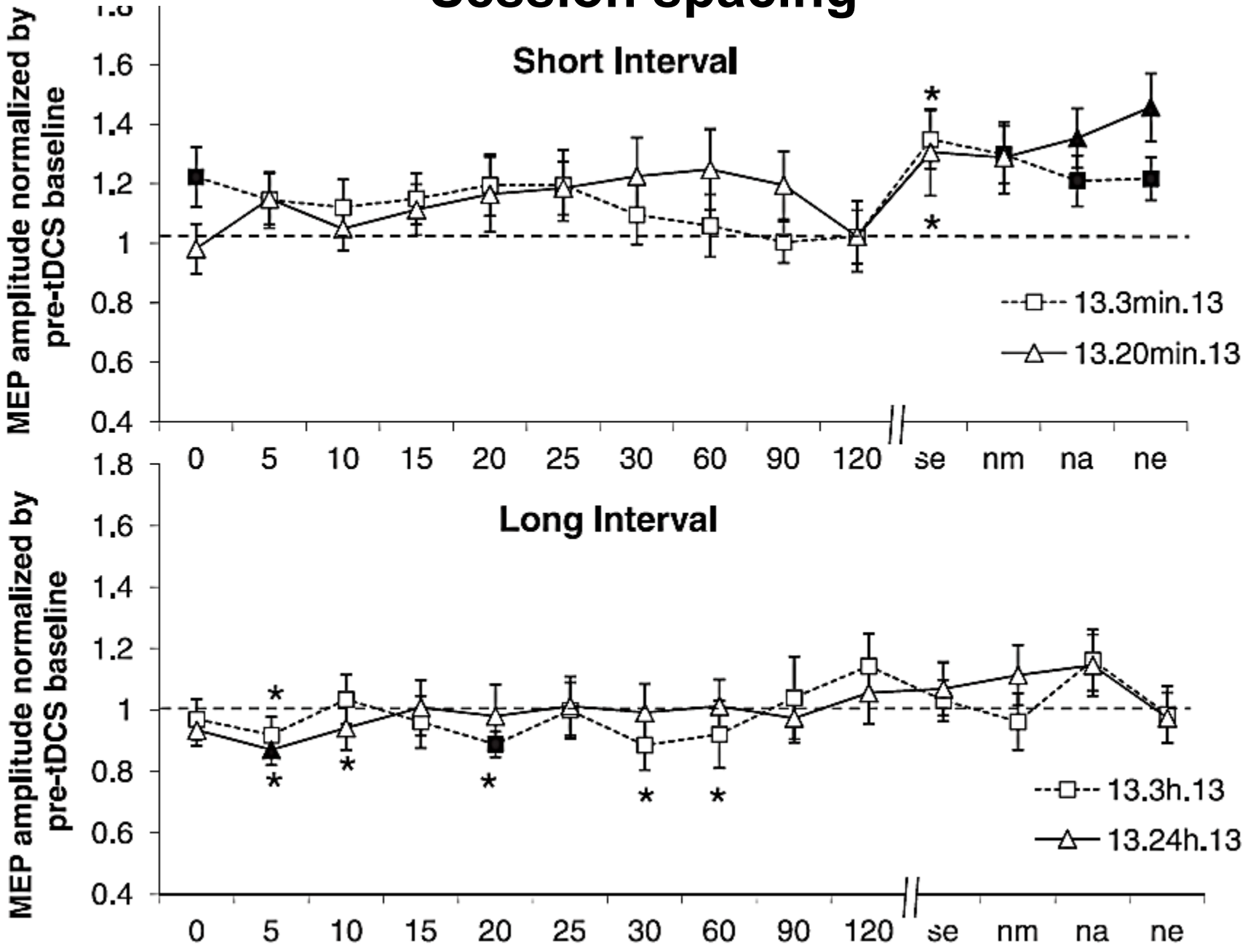
K. Monte-Silva et al. / Brain Stimulation 6 (2013) 424–432



Session spacing



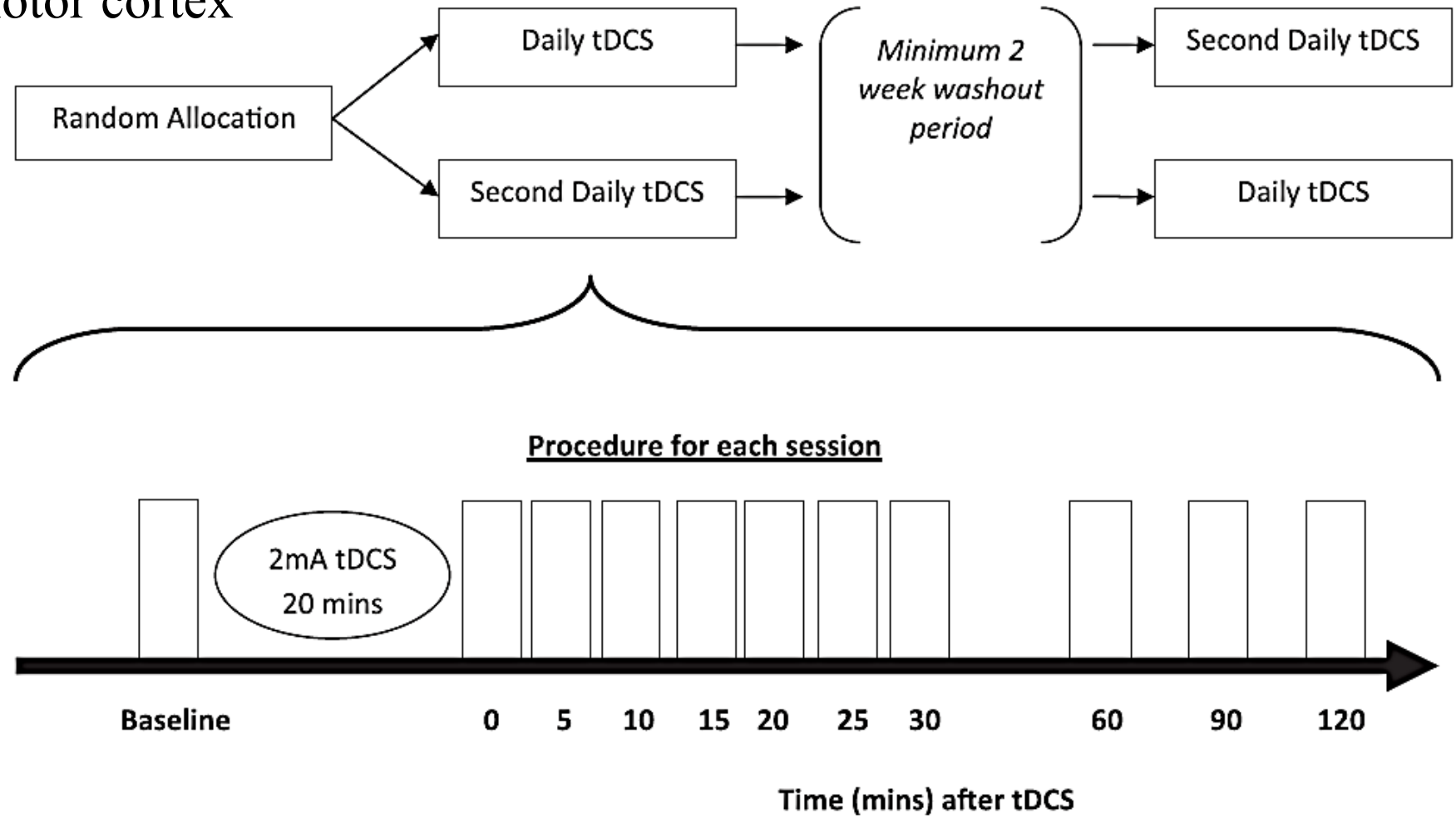
Session spacing



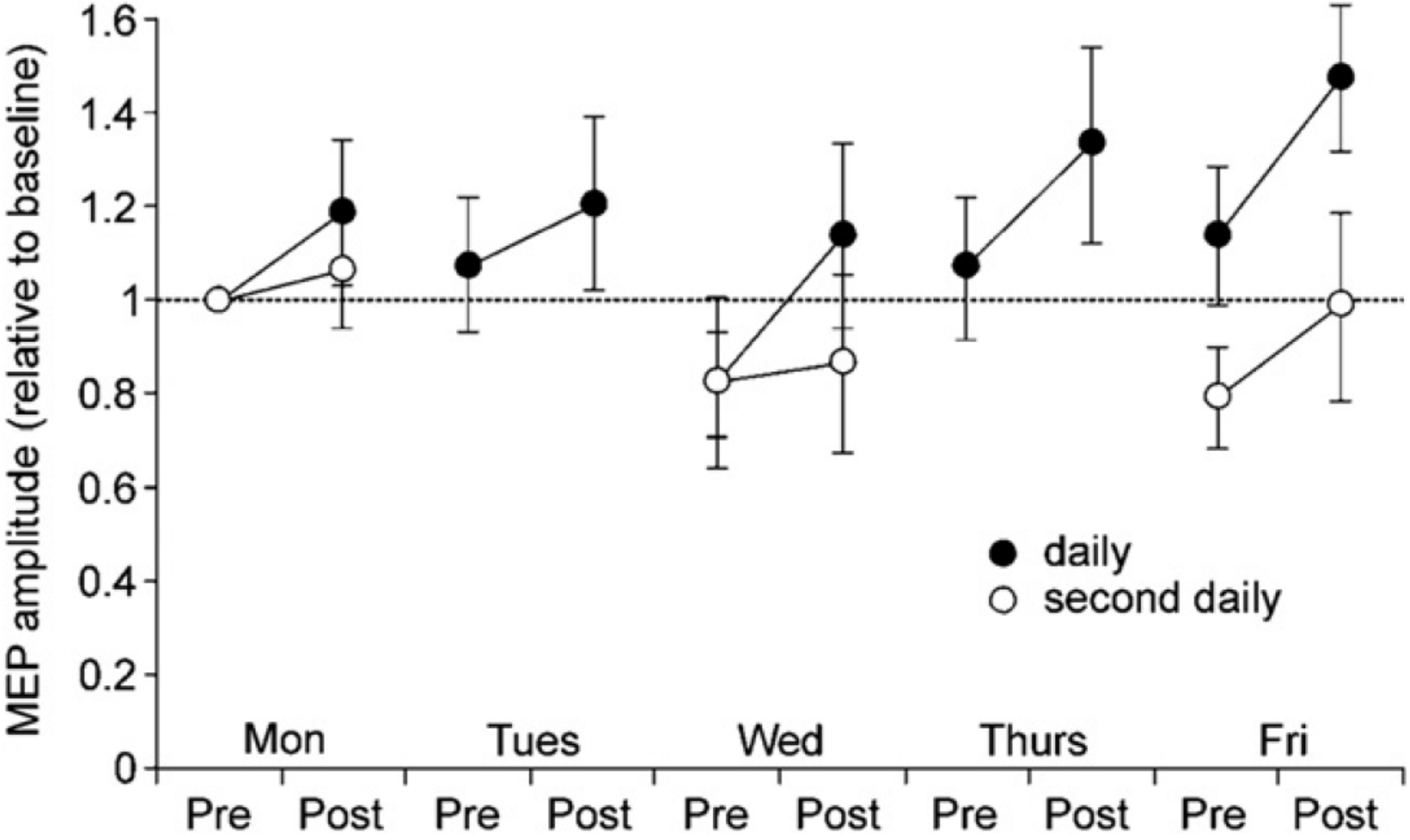
Strategies to Enhance Efficacy II

Daily vs 2nd Daily tDCS : Alonzo et al, 2011

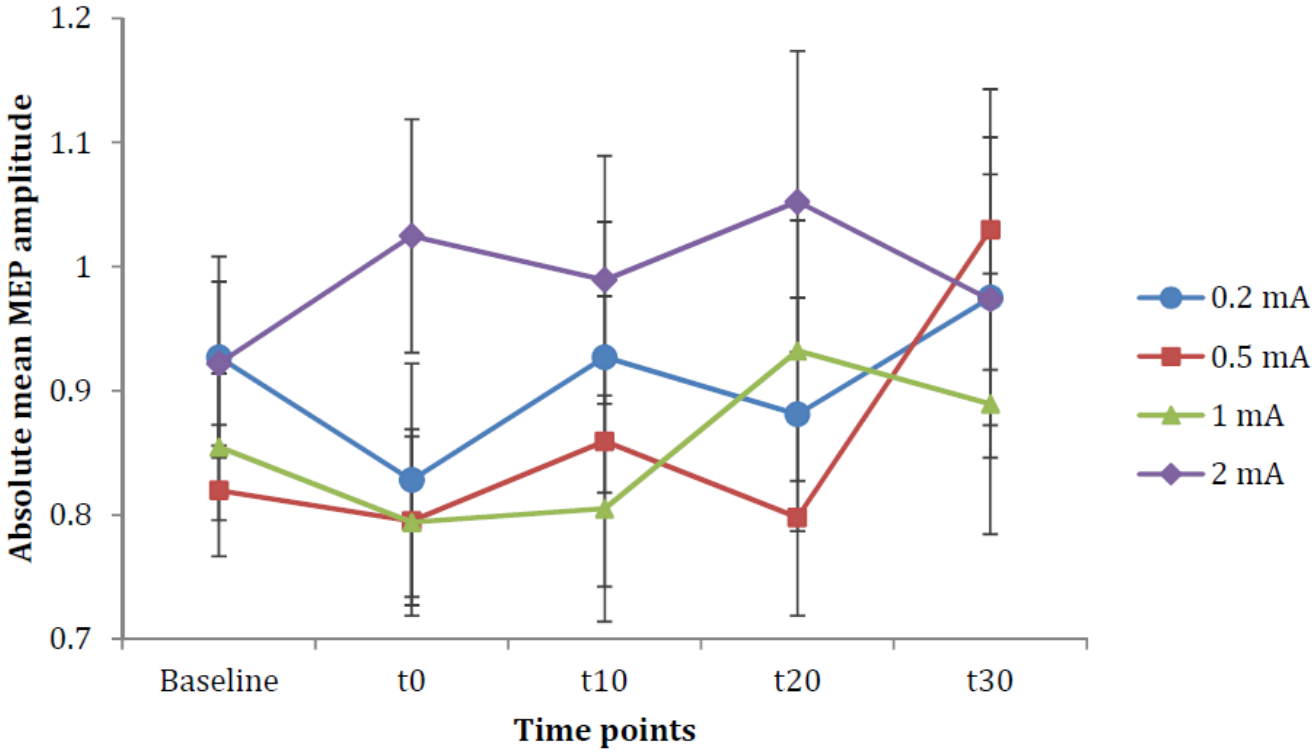
N=12, healthy
Crossover trial
Motor cortex

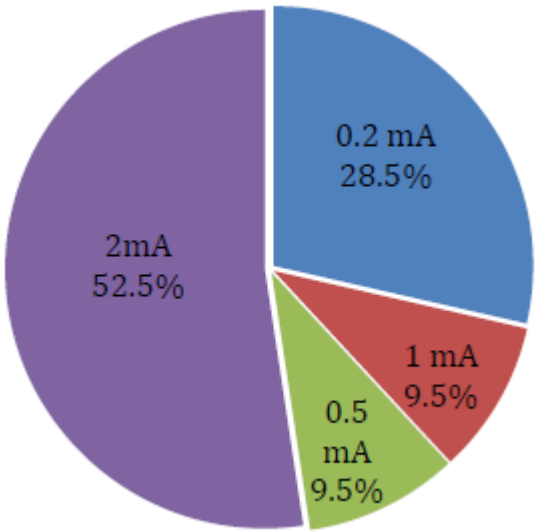


Daily vs 2nd Daily tDCS : Alonzo et al, 2011



Stimulus Intensity – Inter-individual variation





N=29, healthy
Motor cortex
5 sessions, multiple crossover

Chew….Loo, 2015

NB: Translational Pitfalls !

Healthy → clinical population eg stimulus intensity

Motor cortex → prefrontal cortex

Single sessions → multiple sessions

Target Engagement – Depression

Dosing

– stimulation metrics – current intensity, duration, electrode size, number/spacing sessions

- Stimulation montage

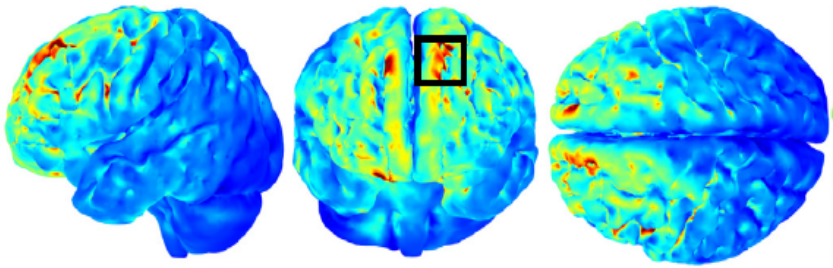
Assess Target Engagement (individual participant level)

- Neuroimaging (eg fMRI, PET)
  - During
  - Immediately after stimulation
  - After treatment course (eg next day)
- Behavioural outcomes – eg suicide rating, sleep etc
- Biomarkers, eg BDNF
- Neuro/psychological outcomes – eg response to positive/negative stimuli

Problem of Inter-individual Variability

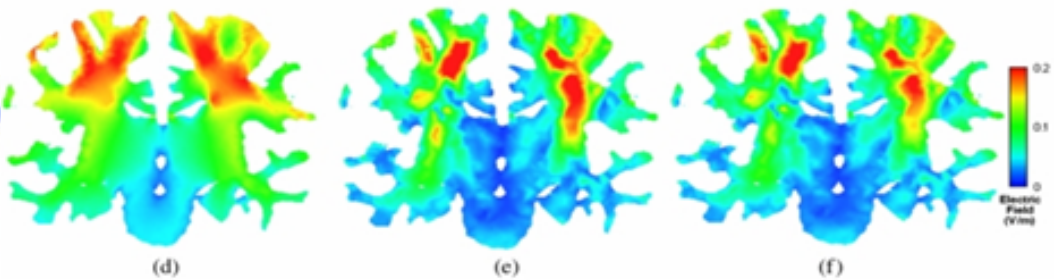
- Identify individual predictors of response to stimulation?
- Eg Pre-treatment letter fluency performance predicts antidepressant response to active tDCS [Martin et al, 2016]. N=104 depressed, pooled from 5 clinical trials: 57 active tDCS, 47 sham tDCS

Stimulated structures



Bai et al. 2014

Role of white matter



Suh et al. 2012

tDCS + Concurrent Intervention

Combine with, e.g.

- Medications, eg Nitsche study, Brunoni SELECT trial
- Psychotherapy (CBT)– postulated, yet to be demonstrated in RCT

Principles:

- tDCS alone subthreshold for neuronal firing/ synaptic plasticity
- tDCS lowers threshold for neuronal firing – preferentially enhance activated circuits
- tDCS enhances synaptic plasticity (Player et al, 2014)
- Frontal tDCS facilitates cognitive processing

Translational pitfalls

- Meds – naïve vs exposed brain, eg AD resistant
- Task eg Motor cx – tDCS during voluntary movement *reduced* cortical activity, measured by MEP (Antal et al, 2007, cf tDCS alone) BOLD fMRI (Antal et al, 2011, cf task alone)– ie complex interactions possible (likely?)

Summary –Optimising tDCS for Depression

- Dosing – stimulus parameters
- Individual variability in response. Individualise dosing?
- Electrode montage
- Combine with medication
- Combine with task
- Predictors of response