Transcranial Direct Current Stimulation (tDCS) – A Promising Treatment for Depression?

UNSW THE UNIVERSITY OF NEW SOUTH WALES

Never Stand Still | Faculty of Medicine

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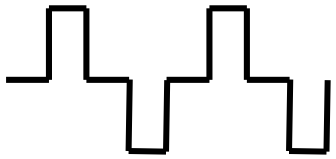
BLACK DOG INSTITUTE

transcranial Direct Current Stimulation (tDCS)



Alternating current (AC)

Direct Current (DC)

1-3 mA , 9V

Direct current: anode (+)

cathode (-)

Transcranial Direct Current Stimulation (tDCS)

Anode

Cathode

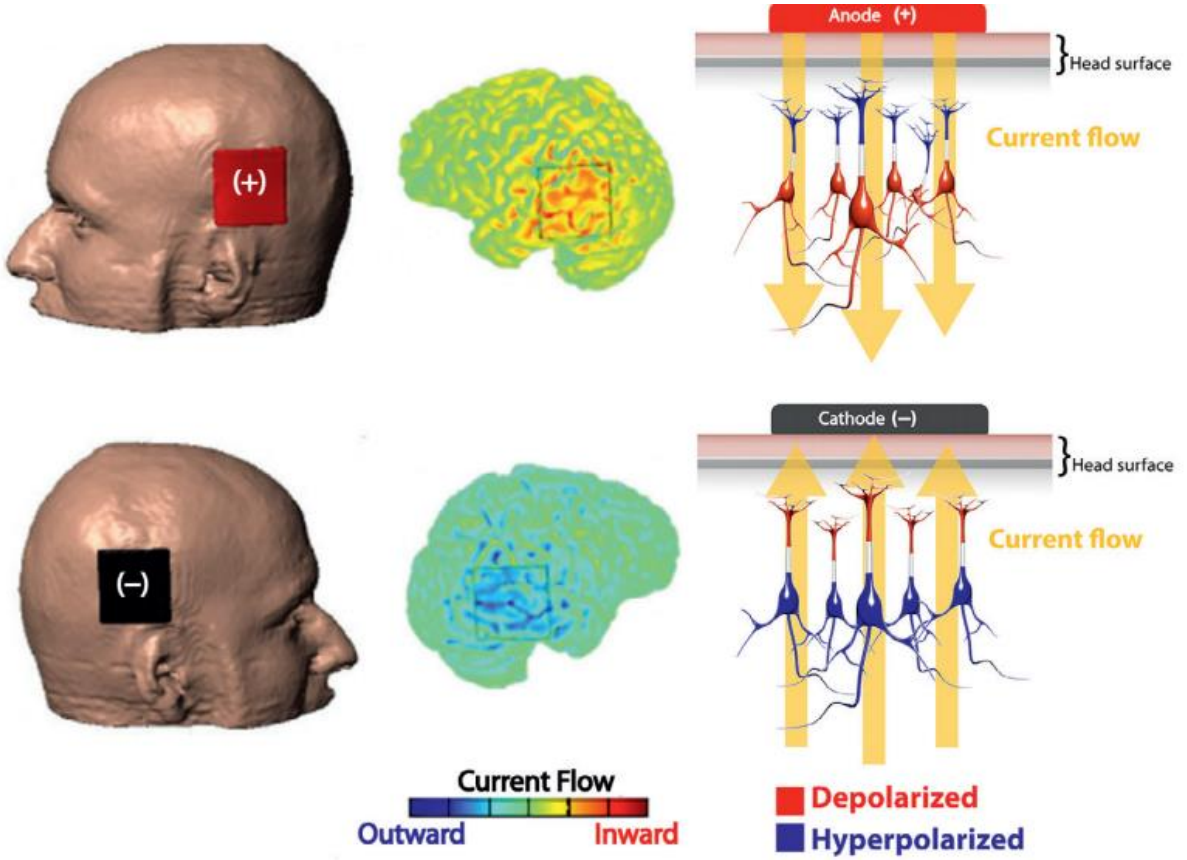


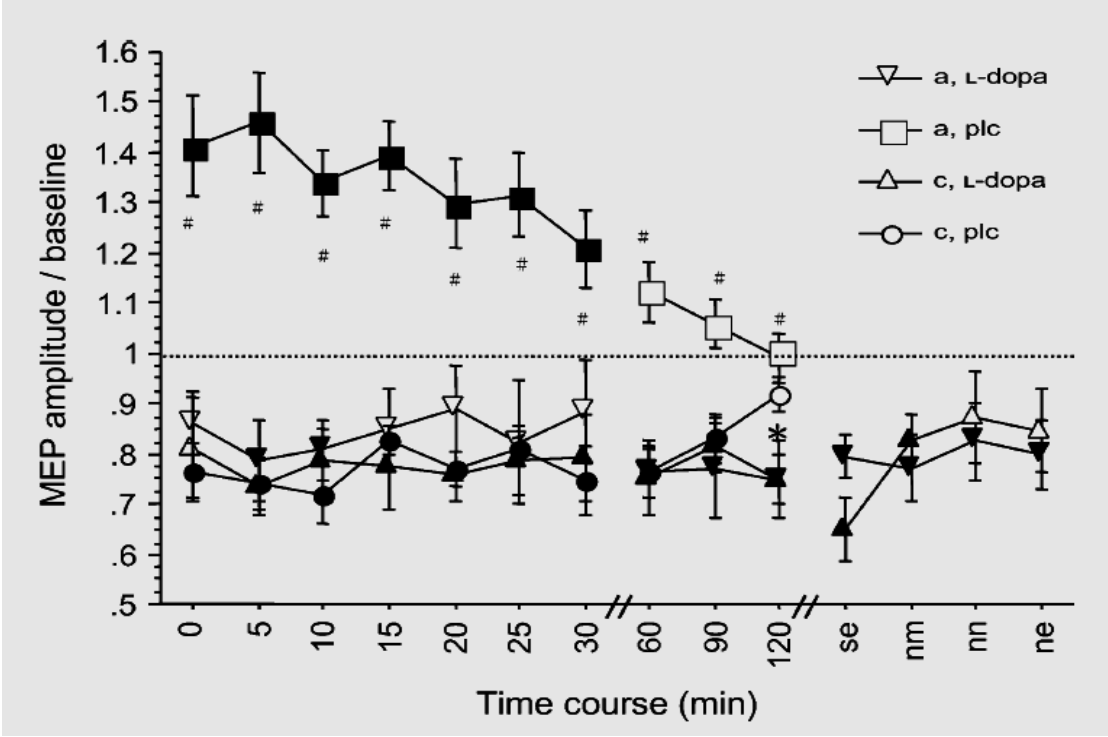
Figure 1. **Direction of current flow in anodal (top) and cathodal (bottom) tDCS.** Reprinted from *The Stimulated Brain* (p. 43), by I. Moreno-Duarte, 2014, San Diego: Academic Press. Copyright 2014 by Elsevier Inc.

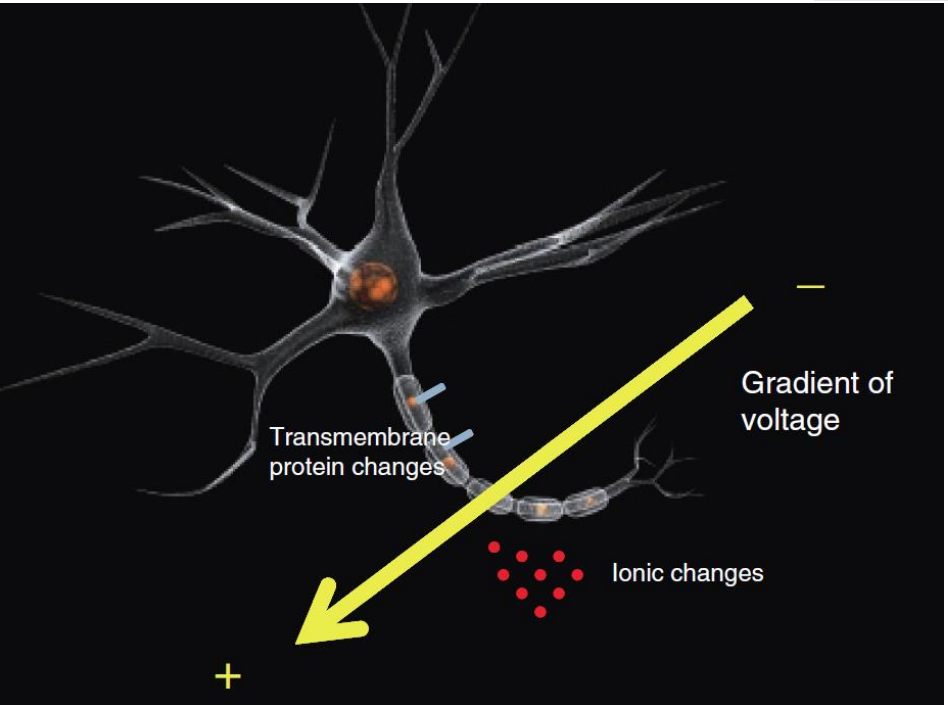
tDCS : Mechanisms

Membrane effects

(Figure from Zaghi et al, 2009)

Interactions:
Ca+ channel blocker
Na+ channel blocker



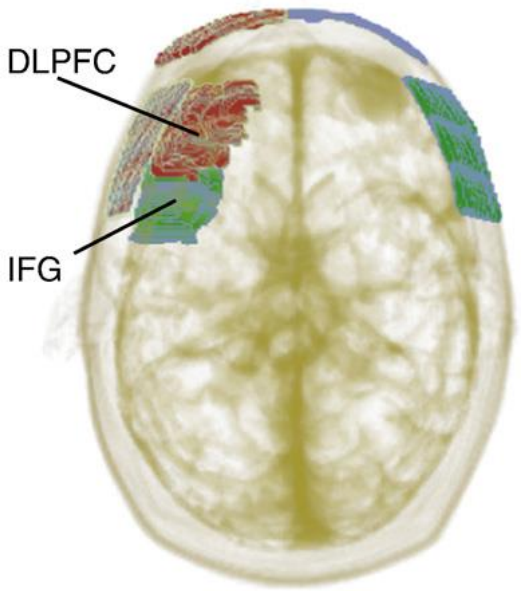


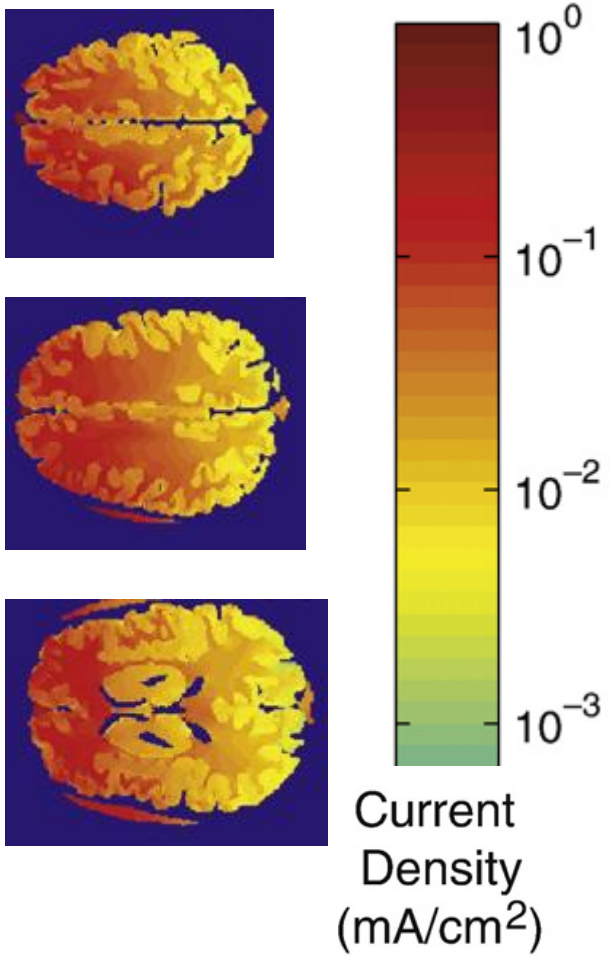
Synaptic effects

Eg Kuo et al, 2008

Interactions:
NMDA antagonist
D cycloserine
Amphetamine
Dopamine antagonist
L dopa
SSRI
Benzodiazepine

tDCS is relatively non focal

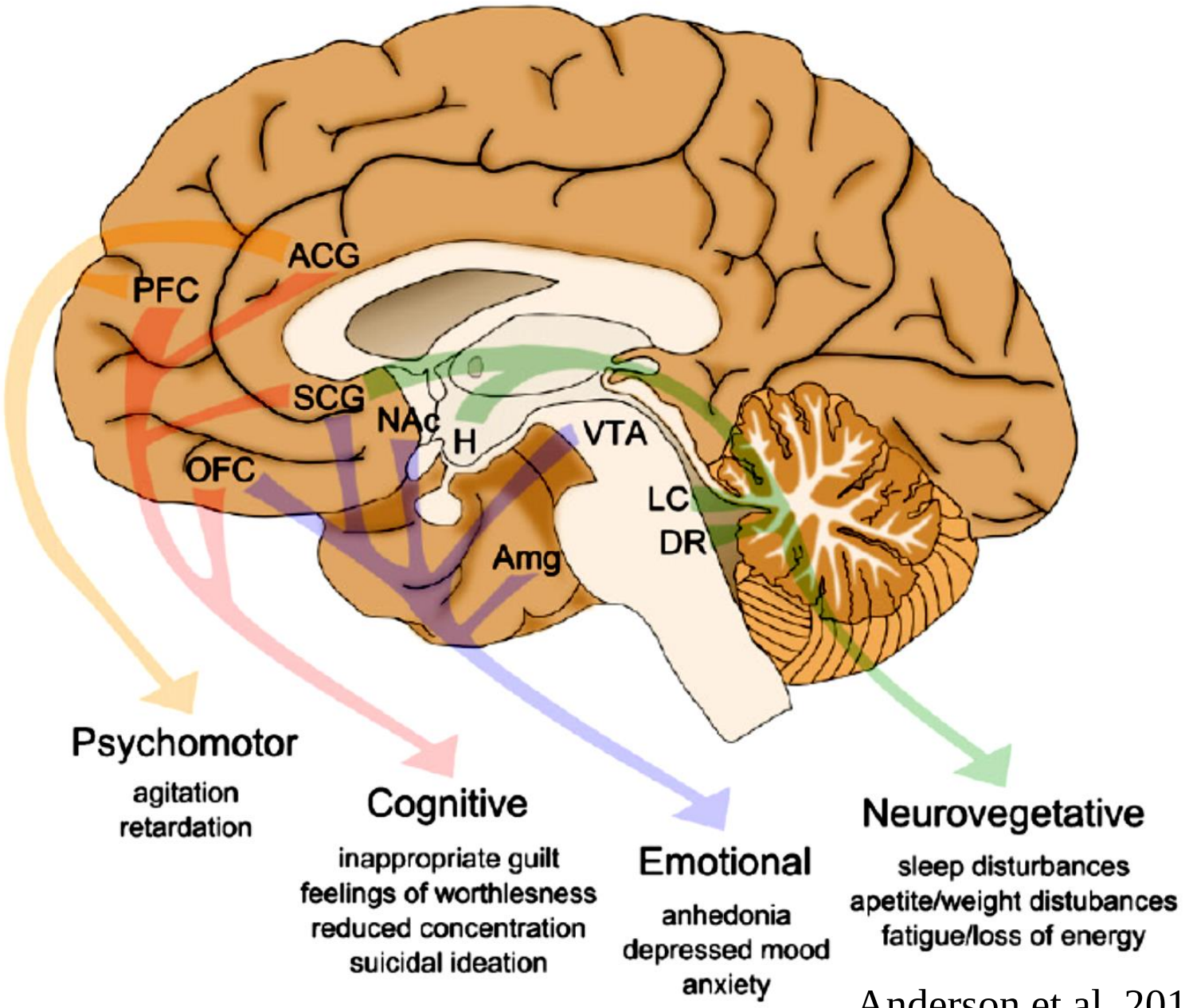




F3 – right supraorbital montage

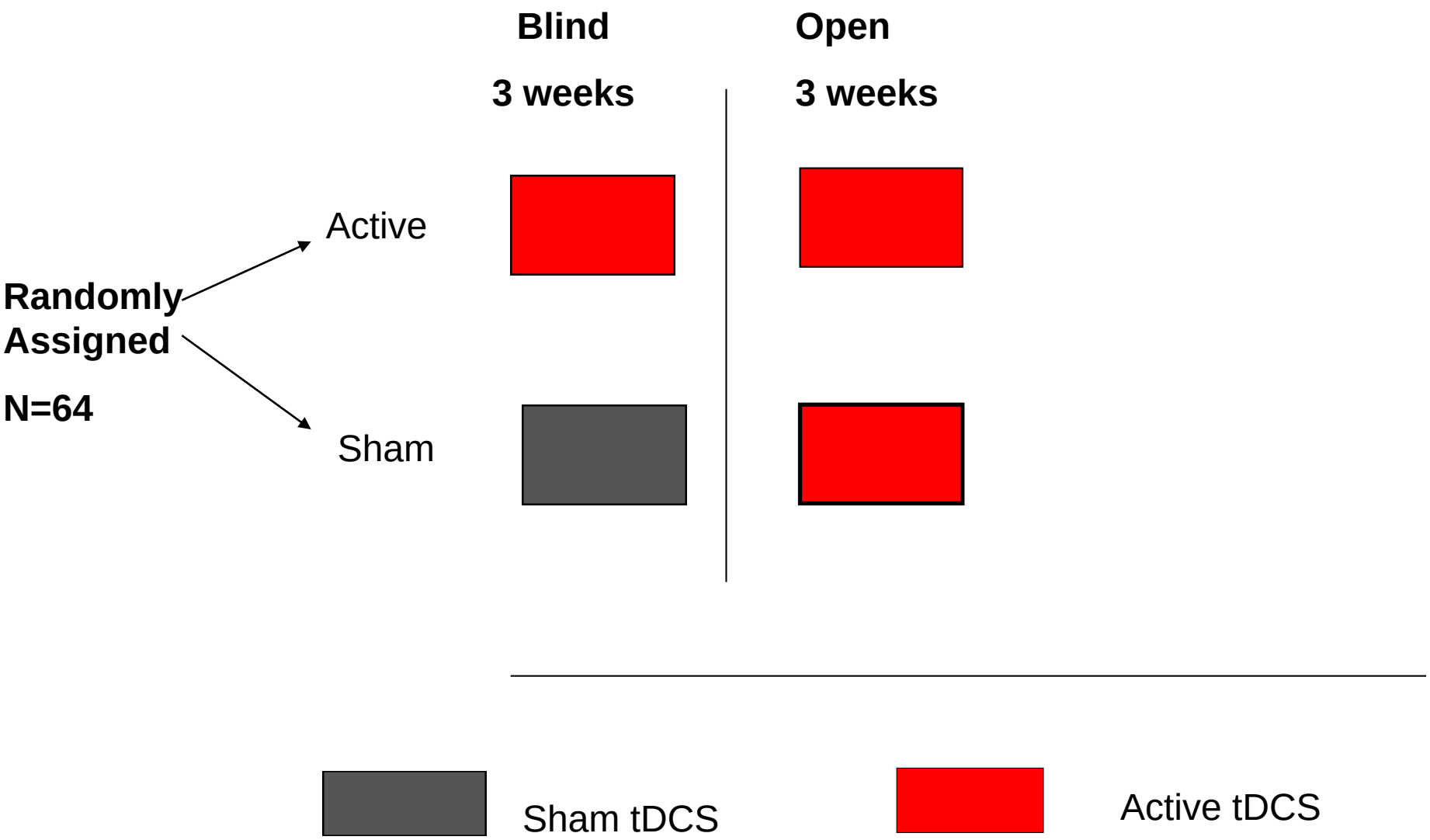
Sadleir et al, 2010

Brain circuits in depression



Anderson et al, 2012

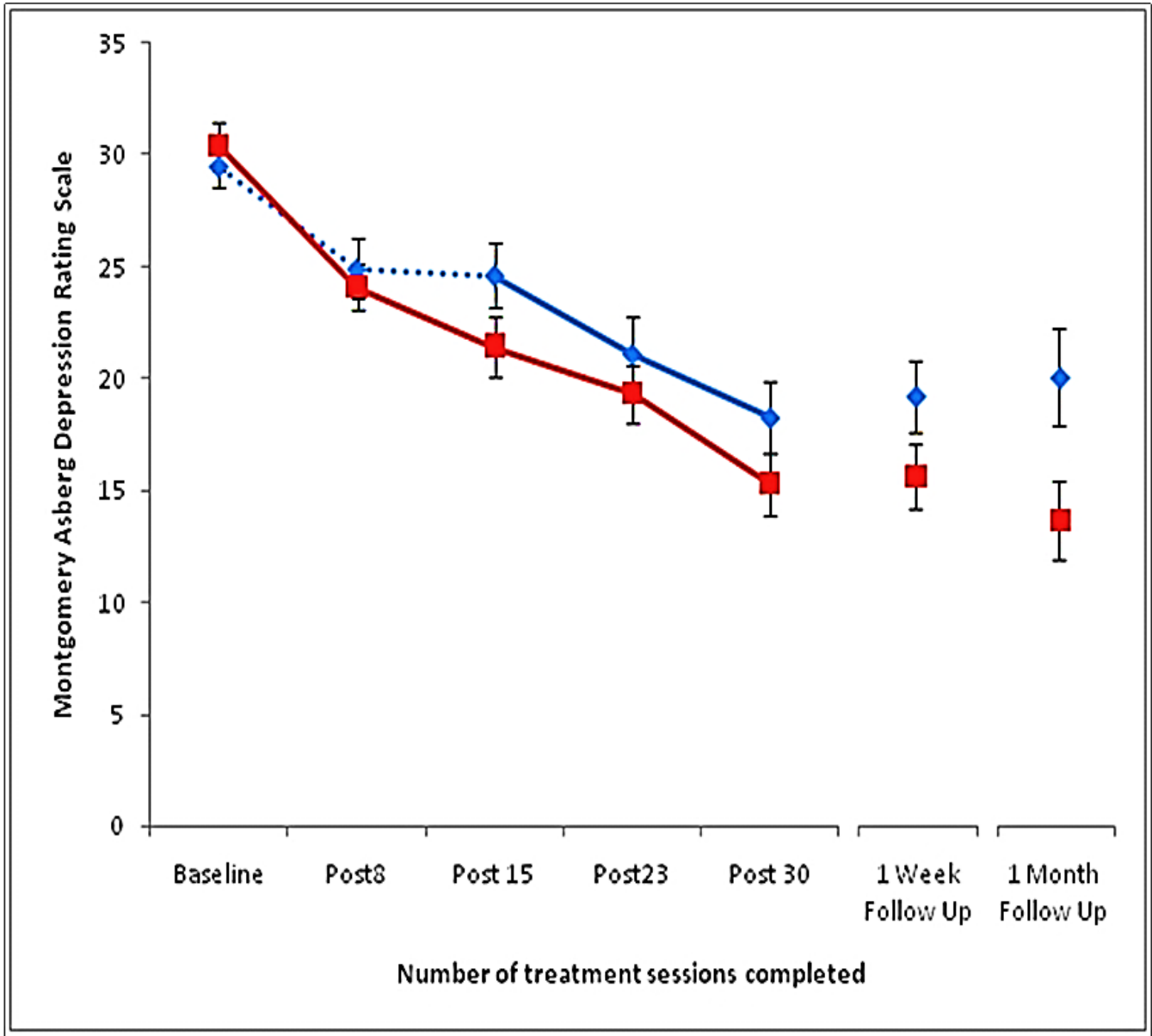
Loo et al, British J Psychiatry, 2012



Loo et al - RCT in Depression

British J Psychiatry 2012

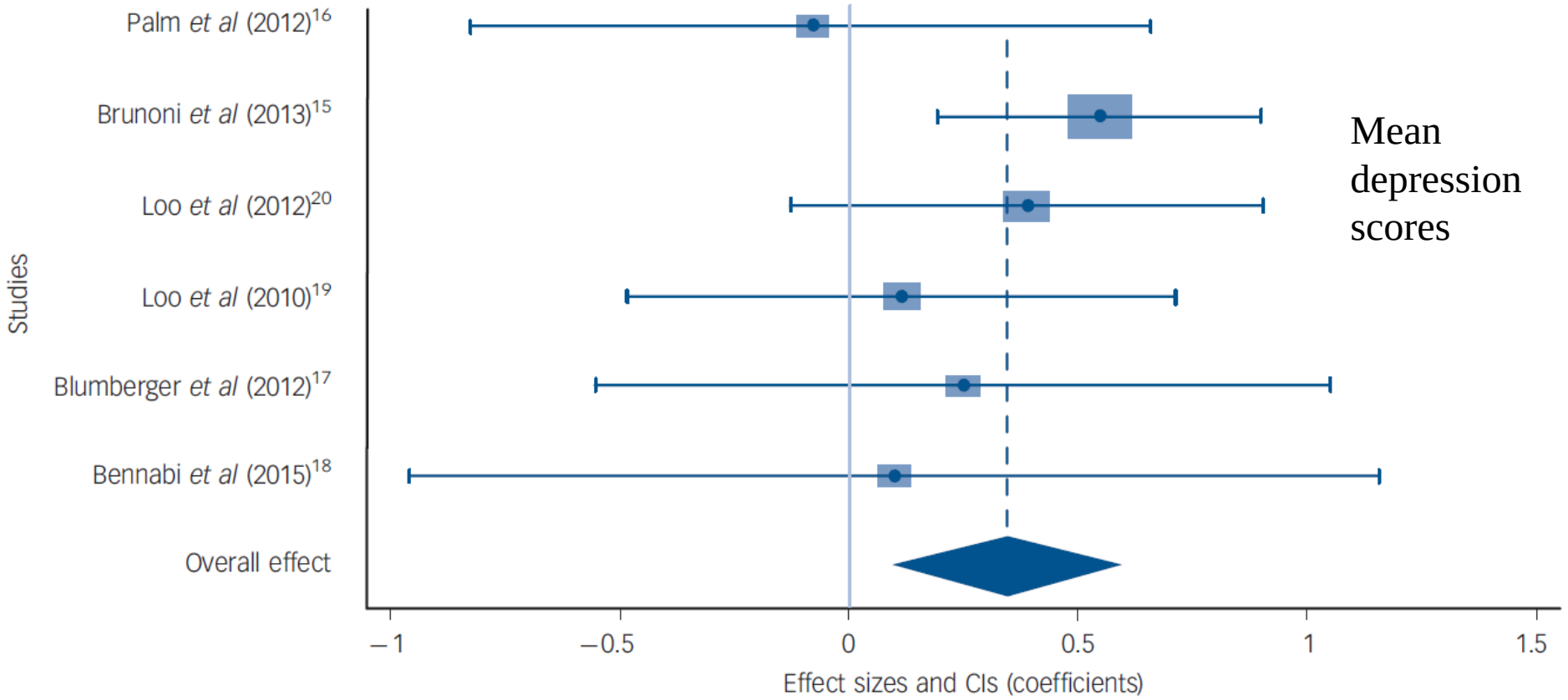
- N=64
- 2 mA, 20 minutes daily
- Placebo controlled RCT: 15 sessions/ 3 weeks
- Open label: +15 sessions



Responders

- After 3 weeks:
  - Active 4/31
  - Sham 4/29
- After 6 weeks:
  - Active (6 weeks active) 15/30
  - Sham (3 weeks sham + 3 weeks active) 12/29
  - Number needed to treat =2.6

Brunoni……Loo, 2016. tDCS 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
Response	34%	19%	2.44	1.38-4.32	7
Remission	23.1%	12.7%	2.38	1.22-4.64	9

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

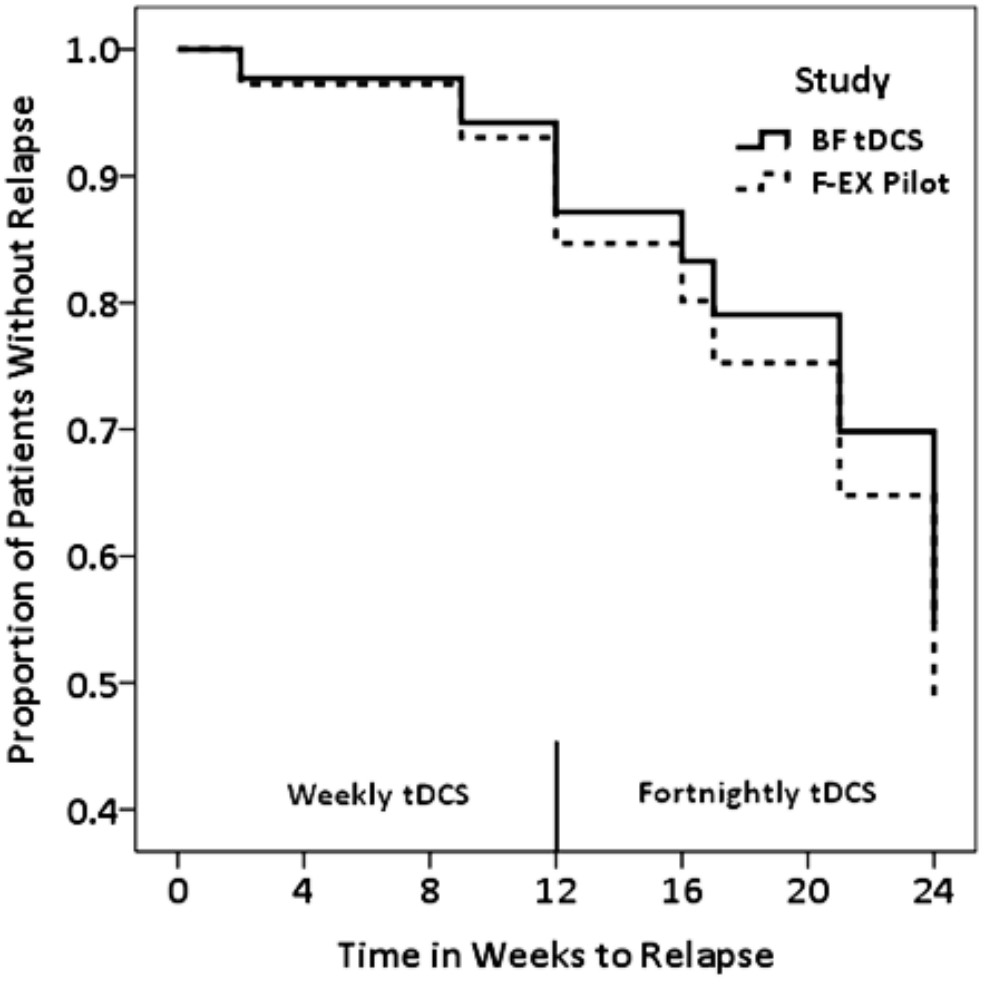
	Active	Sham	OR	CI	NNT
Response	23.9%	12.3%			9
Remission	14.2%	5.5%			

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

Do Effects Last?
Maintenance tDCS



N=26 responders from depression trials
30 courses maintenance tDCS

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

Then fortnightly x 3 months
→ 51% no relapse @ 6 months

Martin et al, 2013

Side Effects

Side Effect	Active Condition (N=33)	Sham Condition (N=31)
Skin redness	30	29
Tingling	26	27
Itching	23	22
Burning/Heating sensation	14	7
Pulsing sensation	2	2
Headache	12	10
Dizziness/ lightheaded-ness	10	6
Fatigue	7	4
Nausea	3	0

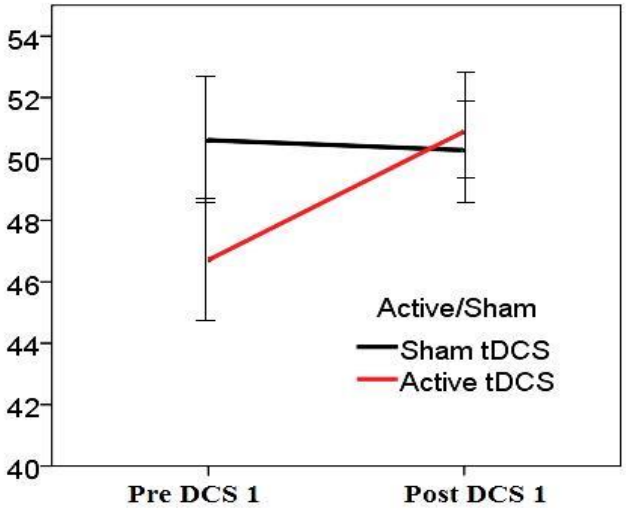
Side Effects	Active condition (N=33)	Sham Condition (N=31)
Related to vision	Blurred vision (N=3); visual effects when eyes closed (N=1); Seeing dots in periphery (N = 1); watery eyes (N = 1)	N=0
Related to ears	N=0	Right ear ache (N=1); ringing in ears (N=1)
Related to neck	Neck soreness (N=1)	Stiffness in neck and shoulders (N=1); tingling on neck (N=1)
Other	Giddiness (N=1); flaky skin (N=1); feeling spaced out (N=1); shakiness (N=1); transient hypomania (N=1)	Twitching of right arm (N=1); tingling on tongue (N=1); a ‘funny feeling’ in head (N=1); facial numbness (N=1); reflux (N=1)

Cognitive test results over 15-session study period: sham *vs.* active

	Main effect Sham *vs.* Active		Main effect Time		Time x group interaction	
Measure	***F***	***p***	***F***	***p***	***F***	***p***
RAVLT						
Total	**1.53**	**0.22**	**0.00**	**0.96**	**0.08**	**0.78**
Delay	**2.82**	**0.10**	**0.58**	**0.45**	**0.88**	**0.35**
Digit Span						
Forward	**0.52**	**0.48**	**1.16**	**0.29**	**0.67**	**0.42**
Backward	**0.22**	**0.64**	**0.01**	**0.92**	**0.47**	**0.50**
Letter Number Sequencing	**1.78**	**0.19**	**0.00**	**0.93**	**0.23**	**0.63**
COWAT						
Letter (total)	**1.25**	**0.27**	**3.00**	**0.09**	**2.49**	**0.12**
Stroop (Interference)	**0.87**	**0.36**	**5.24**	**0.03**	**0.80**	**0.73**

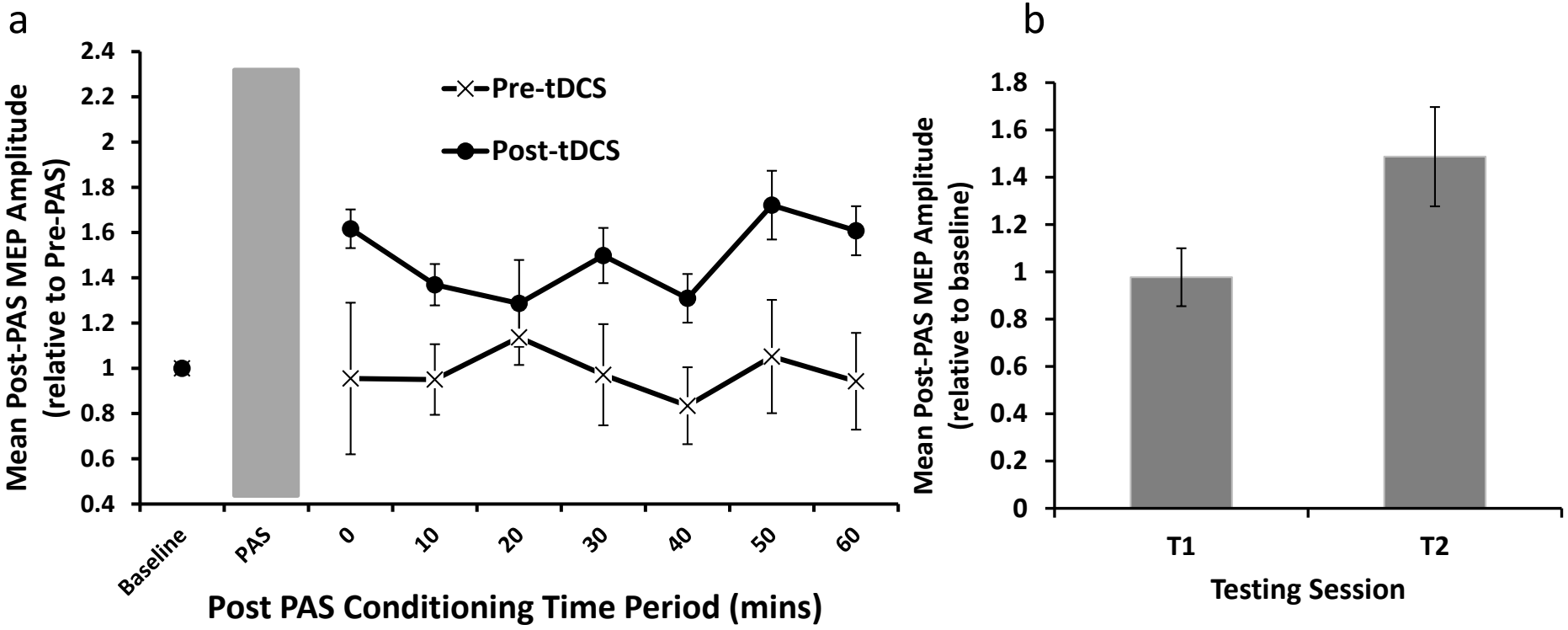
Cognitive tests results immediately before and after DCS sessions 1 and 15: sham *vs*. active

Measure	Main effect : group		Main effect: Time		Time x group interaction	
	F	*p*	*F*	*p*	*F*	*p*
DCS 1						
SDMT	0.37	0.54	10.1	<0.01	10.0	<0.01
Simple RT (msec)	0.88	0.35	3.31	0.08	0.39	0.53
Choice RT (msec)	0.22	0.64	0.32	0.58	0.62	0.43
DCS 15						
SDMT	0.04	0.84	2.90	0.09	0.08	0.79
Simple RT (msec)	0.11	0.75	0.08	0.79	0.04	0.84
Choice RT (msec)	0.14	0.71	0.47	0.50	0.06	0.81



Loo et al. (2012)

18 Depressed Subjects
Before and After 4 Weeks tDCS Treatment



Change in MEP after PAS, pre tDCS vs post tDCS, p = 0.017

Player,….& Loo; J Affective Disorders, 2014

A Systematic Review on the Acceptability and Tolerability of Transcranial Direct Current Stimulation Treatment in Neuropsychiatry Trials

Luana V.M. Aparício [a,b], Fabiana Guarienti [a,b], Lais Boralli Razza [a,b], André F. Carvalho [c], Felipe Fregni [d], André Russowsky Brunoni [a,b,e,*]

Brain Stimulation

Background: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation investigated as a treatment for several neuropsychiatric disorders. Notwithstanding tDCS-induced adverse events (AEs) are considered to be low and transient, systematic review analyses on safety and tolerability of tDCS derive mostly from single-session studies.

Objective: To investigate the tolerability (rate of AEs) and acceptability (rate of dropouts) of tDCS.

Methods: Systematic review and meta-analysis of tDCS randomized, sham-controlled trials in healthy or neuropsychiatric adult samples from the first date available to March 9, 2016. We only included parallel studies performing at least 5 tDCS sessions. An adapted version of CONSORT guidelines for reporting harms outcomes was used to evaluate AE reporting.

Results: Sixty-four studies (2262 participants) were included. They had a low risk of publication bias and methodological bias for the items assessed. Dropout rates in active and sham tDCS groups were, respectively, 6% and 7.2% (OR = 0.82 [0.59–1.14]). However, almost half of studies reported no dropouts and only 23.4% reported its reasons; when reported, the most frequent reasons were AEs and protocol violation. A tolerability meta-analysis was not performed, as most studies did not report AEs. The quality of AEs reporting was also limited, particularly in smaller studies and stroke studies.

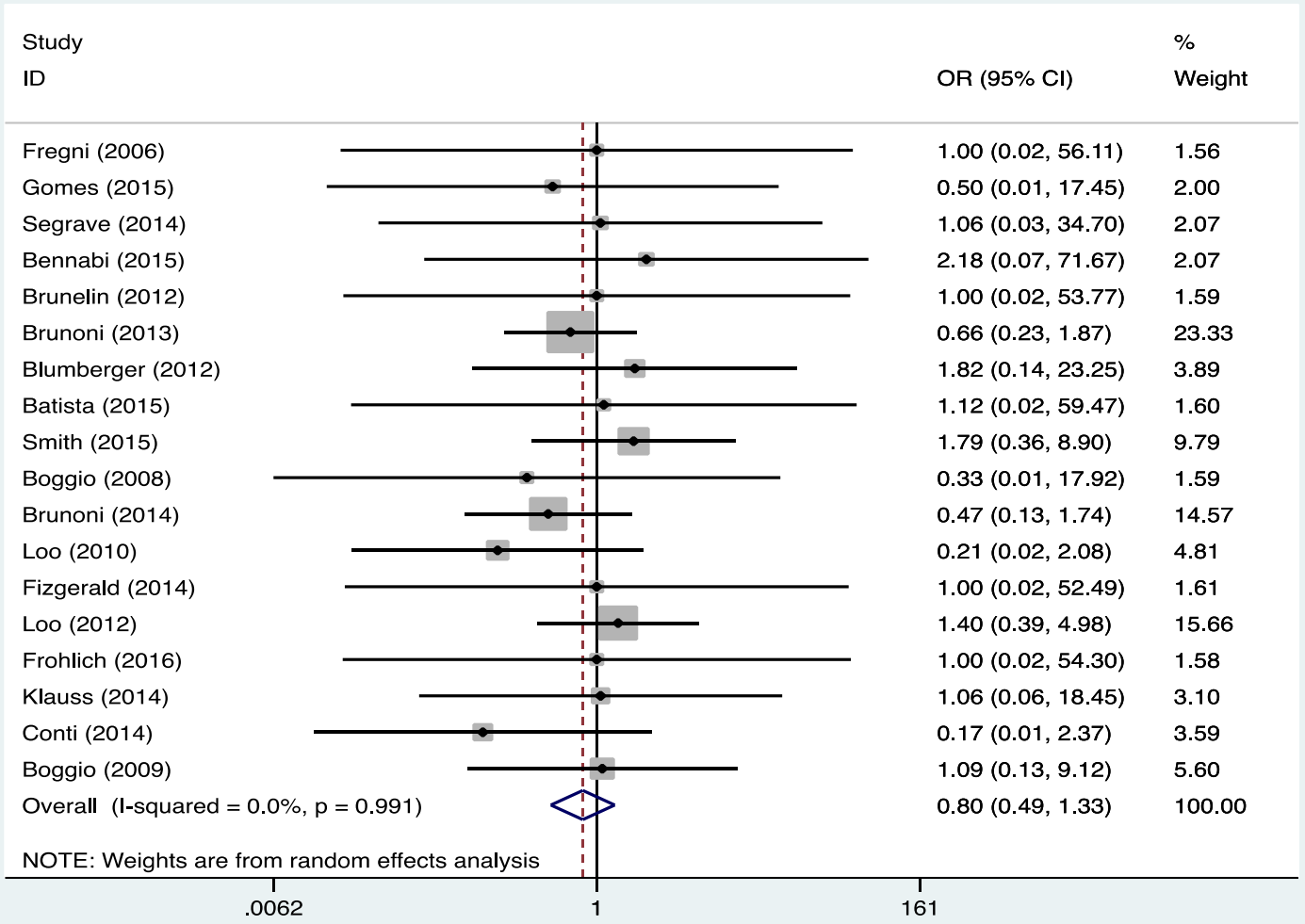
Conclusions: Although overall dropout rate was low and similar in active and sham groups, studies did not adequately describe AEs. An updated questionnaire and guidelines for assessment of AEs in tDCS trials are proposed in order to standardize the reporting of AE in the field.

Safety – tDCS in Depression

	Itching		Burning		Headache		Fatigue		Sleepiness		Skin redness		Tingling		Pain	
	Active	Sham	Active	Sham	Active	Sham	Active	Sham	Active	Sham	Active	Sham	Active	Sham	Active	Sham
Boggio 2008	23.3	20	0	0	13.3	10	0	0	0	0	6.6	10.1	0	0	0	0
Blumberger 2012	0	0	0	0	23	0	0	0	0	0	0	0	30.7	36.3	0	0
Fregni 2006	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Loo 2010	38.2	35	0	0	35.3	30	0	0	0	0	94.1	60	17.6	40	0	0
Loo 2012	74.1	75.9	45.2	24.1	45.2	34.5	22.6	13.8	0	0	96.8	100	83.9	93.1	6.5	0
Brunoni 2013	37	25	0	0	22	19	0	0	44	29	25	8	13	9	6.5	0
Brunoni 2014	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Segrave 2014	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Bennabi 2015	0	0	N/A	N/A	0	0	0	0	0	0	N/A	N/A	0	0	0	0

Brunoni et al 2016

Acceptability – tDCS in Psychiatric Disorders (Frequency of dropouts)



OR = 0.8 (95%CI 0.49 – 1.33) (10.3% active vs. 12.7% sham)

Brunoni et al 2016

DIY tDCS !!!

Sun Herald
30 June 2013
↓

Nature
20 June 2013 →

Brain blast

DIY attempts at electrical brain stimulation to improve cognition are to get easier.

Buyer beware. For US$249 a company in the United States is promising to send curious and competitive players of computer games an unusual headset. The device, the company claims, will convert electronic gamers into electronic-gamers. At the touch of a button, the headset will send a surge of electricity through their prefrontal cortex. It promises to increase brain plasticity and make synapses fire faster, to help gamers repel more space invaders and raid more tombs. And, according to the publicity shots on the website, it comes in a choice of red or black.

The company is accepting orders, but says that it will not ship its first headsets to customers until next month. Some are unwilling to wait. Videos on the Internet already show people who have cobbled together their own version with a 9-volt battery and some electrical wire. If you are not fussy about the colour scheme, other online firms already promise to supply the components and instructions you need to make your own. Or you could rummage around in the garage.

That's 'could' as in 'you might be able to', by the way; not 'could' as

Warning over gamers' headset

TIM BARLASS

A headset with four electrodes to zap the brain with a surge of electricity offers to improve computer gamers' response time so they can eliminate more zombies and raid more tombs.

The $US249 ($273) device, which is available on the internet, passes a current to the prefrontal cortex using a stimulation technique that is also used to treat depression.

But a Sydney world leader in the use of the procedure has warned of the unknown side effects of using the headset and its long-term impact on brain function.

The company website says: "Overclock your brain using transcranial Direct Current Stimulation to increase the plasticity of your brain. Make your synapses fire faster."

The company says the headset is not a medical device and is not regulated by the US Food and Drug Administration. It also says the device meets all regulated safety standards but warns against its use by epilepsy sufferers or anyone with implants.

Professor Colleen Loo, from the University of NSW school of psychiatry and clinical and research psychiatrist with the Black Dog Institute said the effect on the brain was dependent on where and how the electrodes were positioned. "It's a bit like having an accelerator and brake in a car," she said. "Neither is bad and both are very useful but applying them judiciously at the right time and in the right context is absolutely essential. I think stimulation of yourself with do-it-yourself kits is potentially quite dangerous.

"Even with a single session, I am concerned about people doing some mischief to themselves ... if you did this while playing a game and then you went out and drove a car and had an accident, did it affect your reaction time, your co-ordination?"

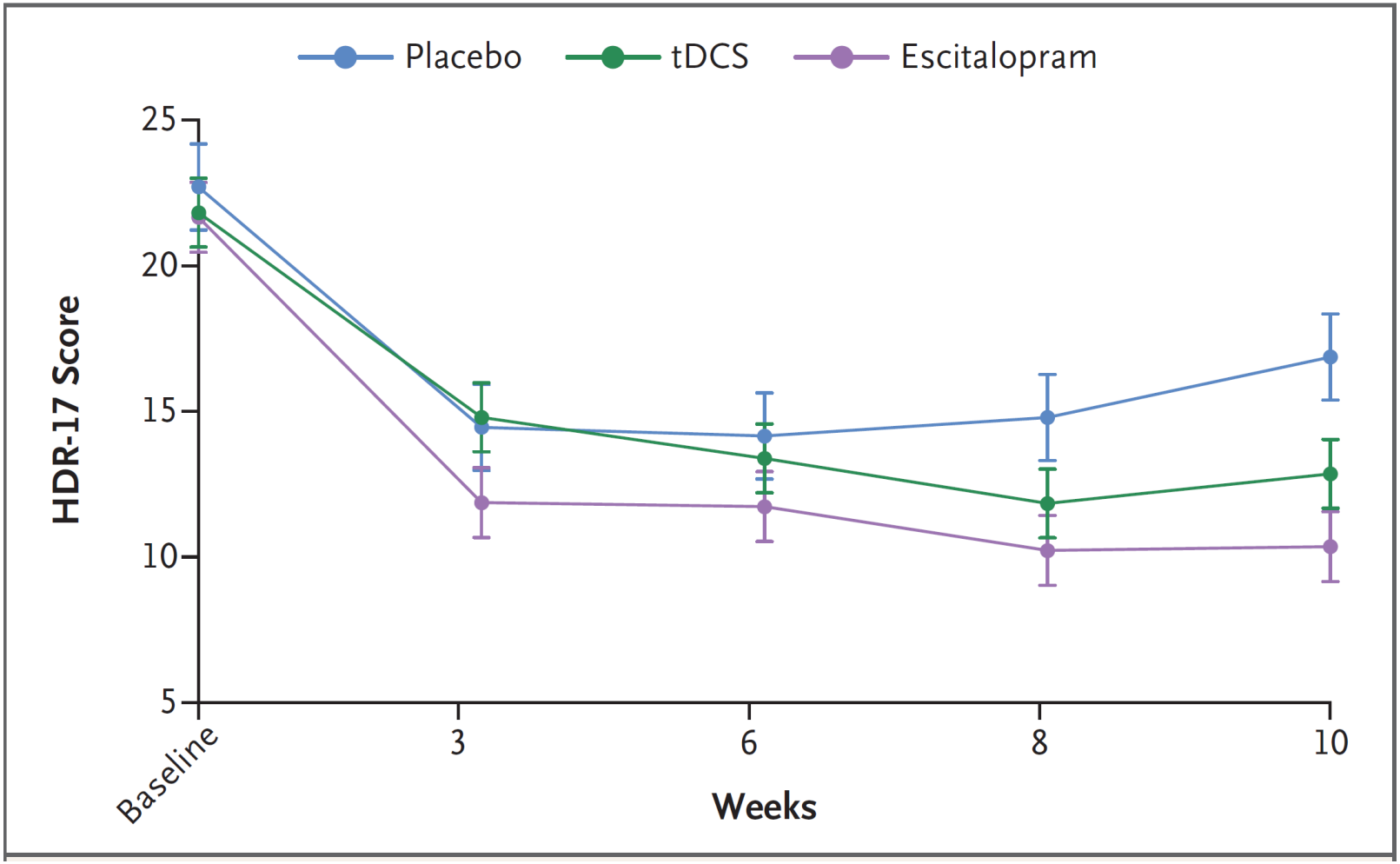
Jolt: The headset zaps gamers with electricity. Photo: Ivan Bajinovfoc

Brunoni et al “ELECT” Trial, 2017

N=245

Escitalopram 10 mg 3/53, then 20 mg

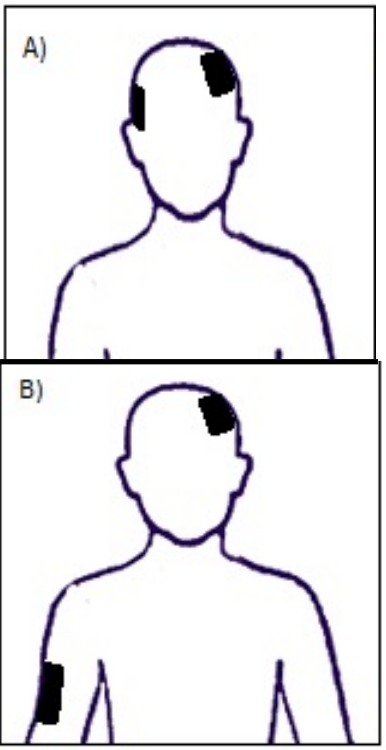
tDCS 2 mA, 30 min – 3 weeks, then weekly x7



Optimising tDCS for Depression

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

Electrode Montage



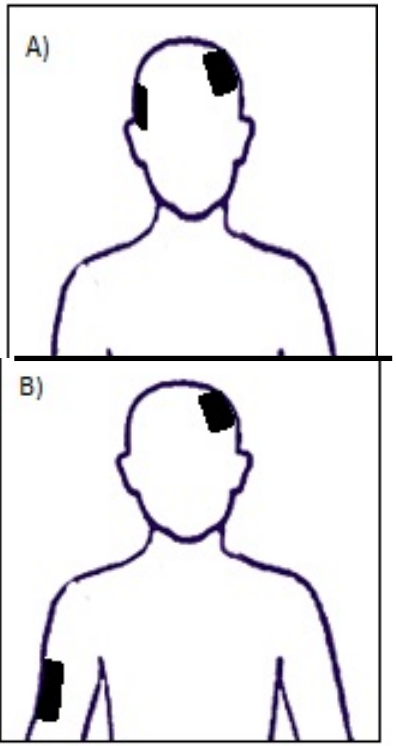
Bifrontal

Fronto-extracephalic

Martin et al, 2011

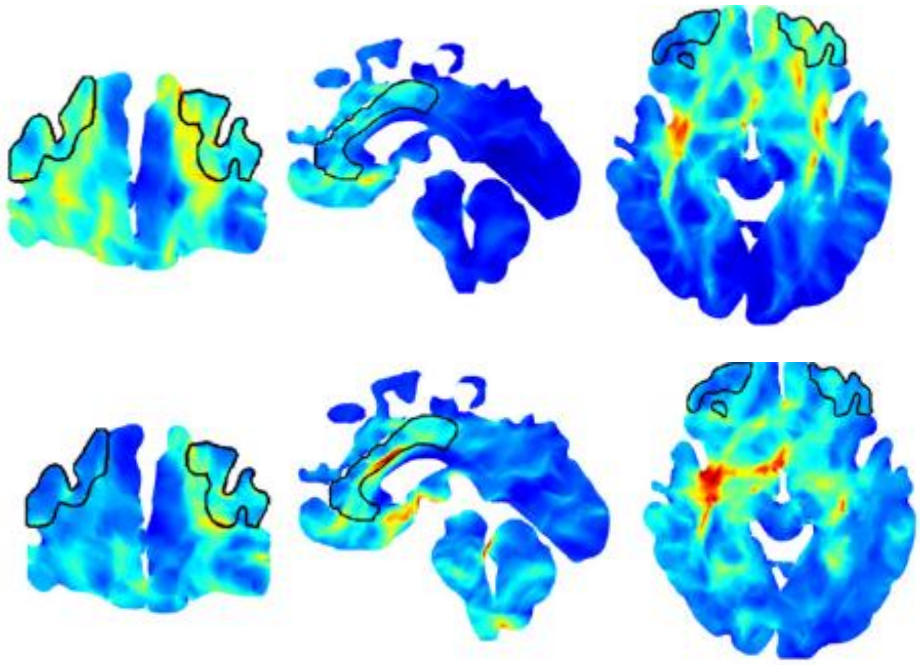
- N= 11 depressed
- 1st course Bifrontal
- 2nd course Fronto-Extracephalic
- 2mA tDCS, 20 mins daily
- N=1, hypomanic with F-Ex only

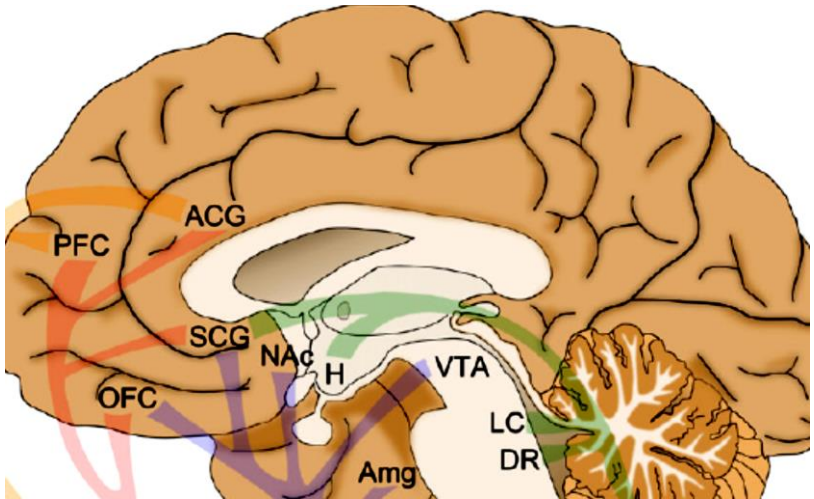
Electrode Montage

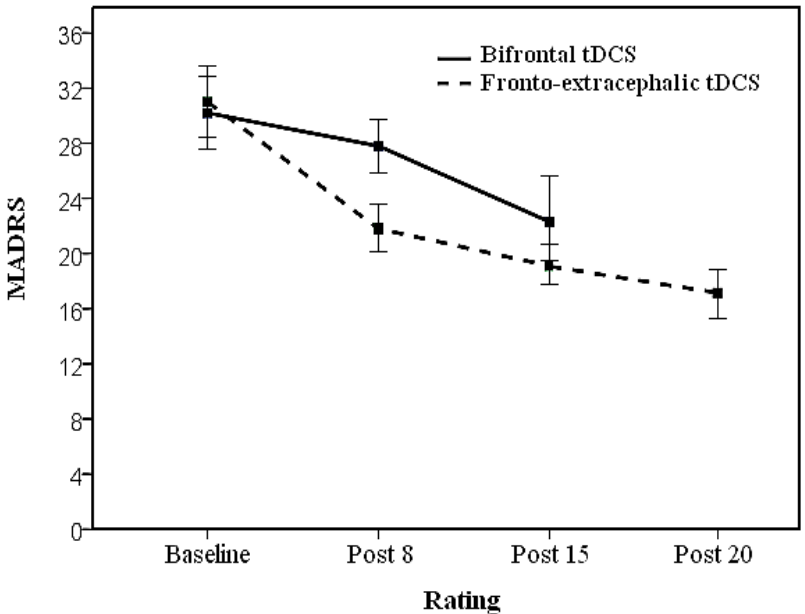


Bifrontal

Fronto-extracephalic







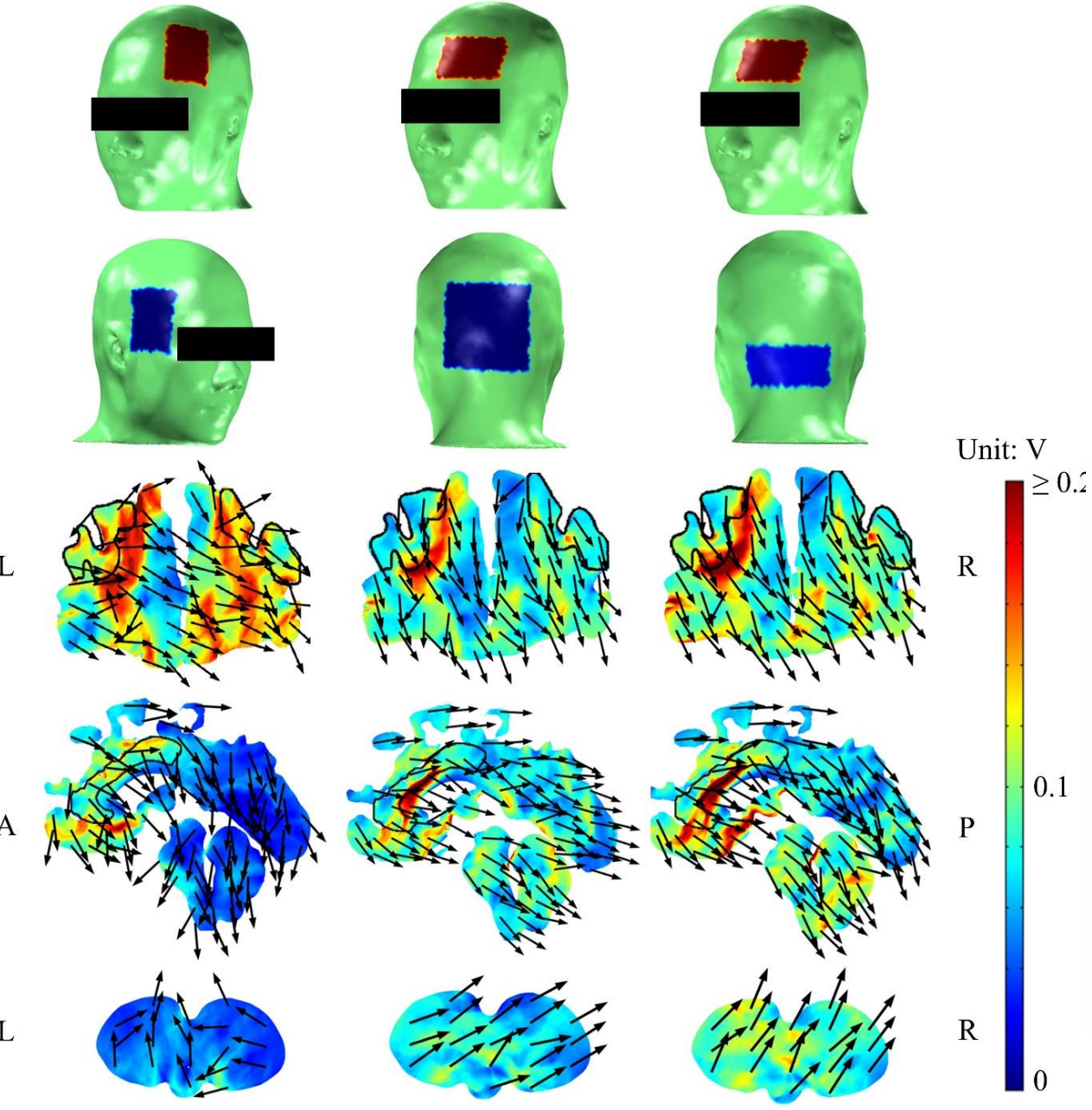
Bifrontal Fronto-Occipital Fronto-Cerebellar

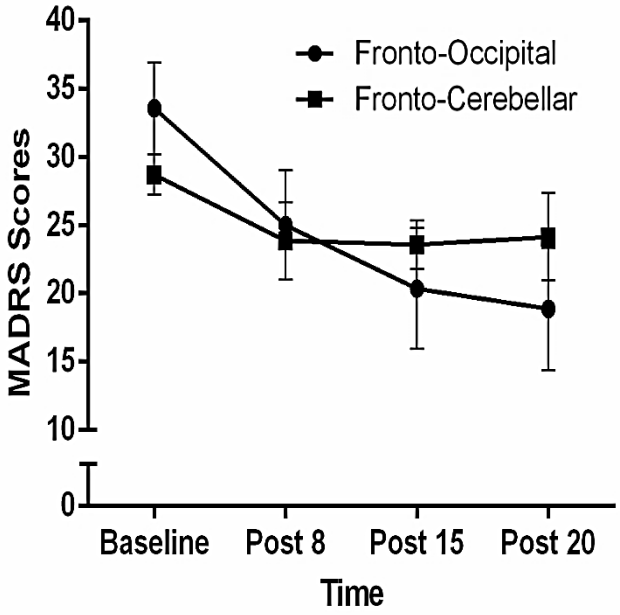
Ho et al, 2014

N=15 depressed

Pilot clinical trial

Fronto-occipital or fronto-cerebellar



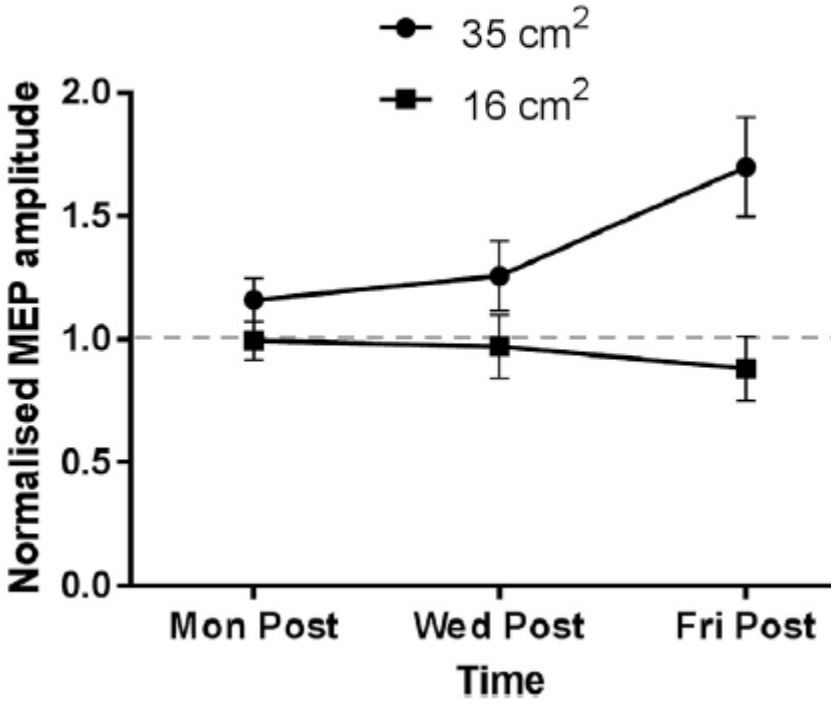


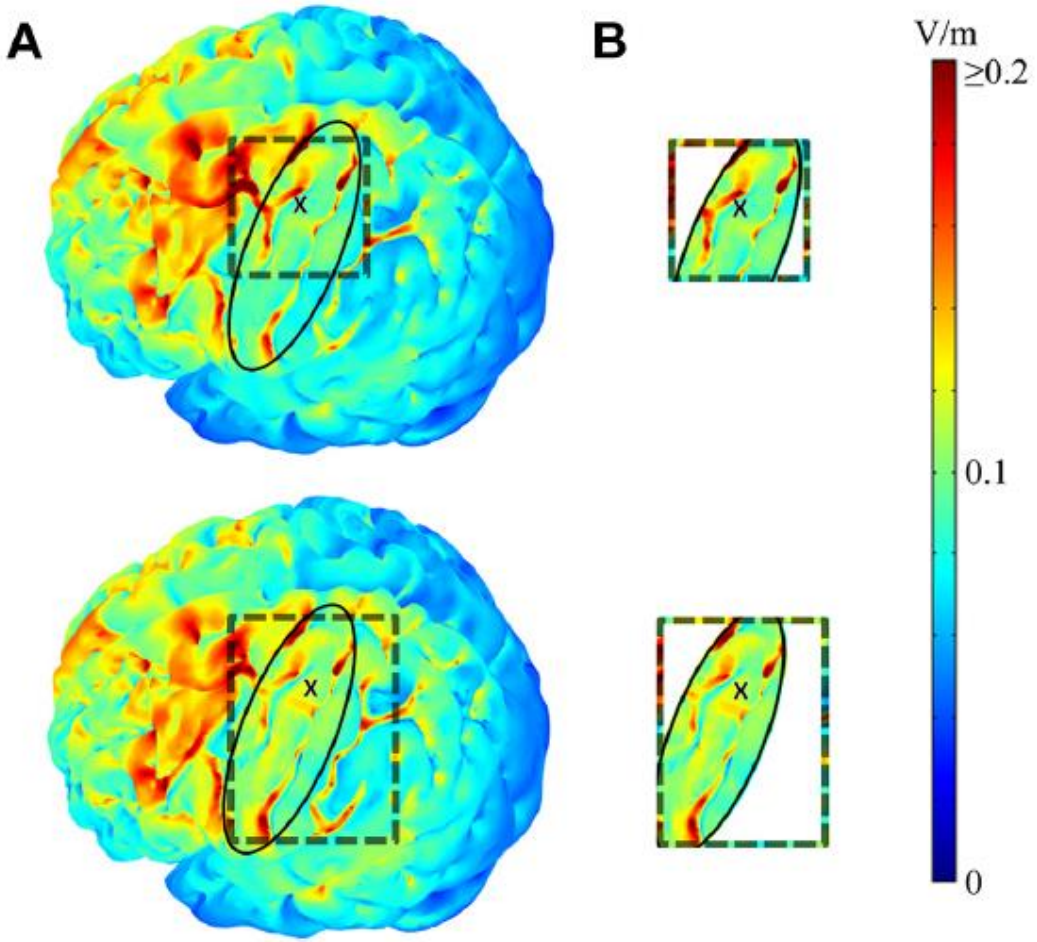
Dose – Stimulus Parameters

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	

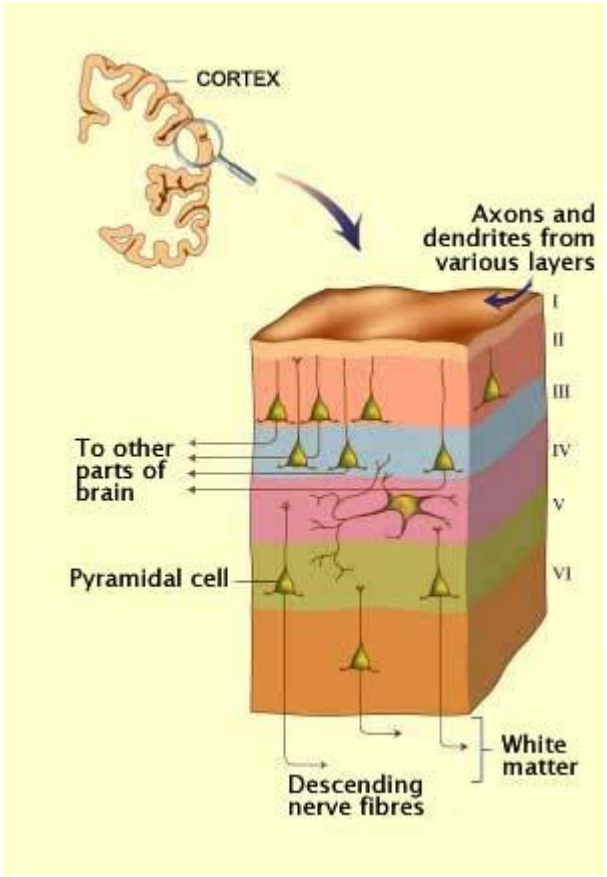
Electrode size- beyond "charge density"

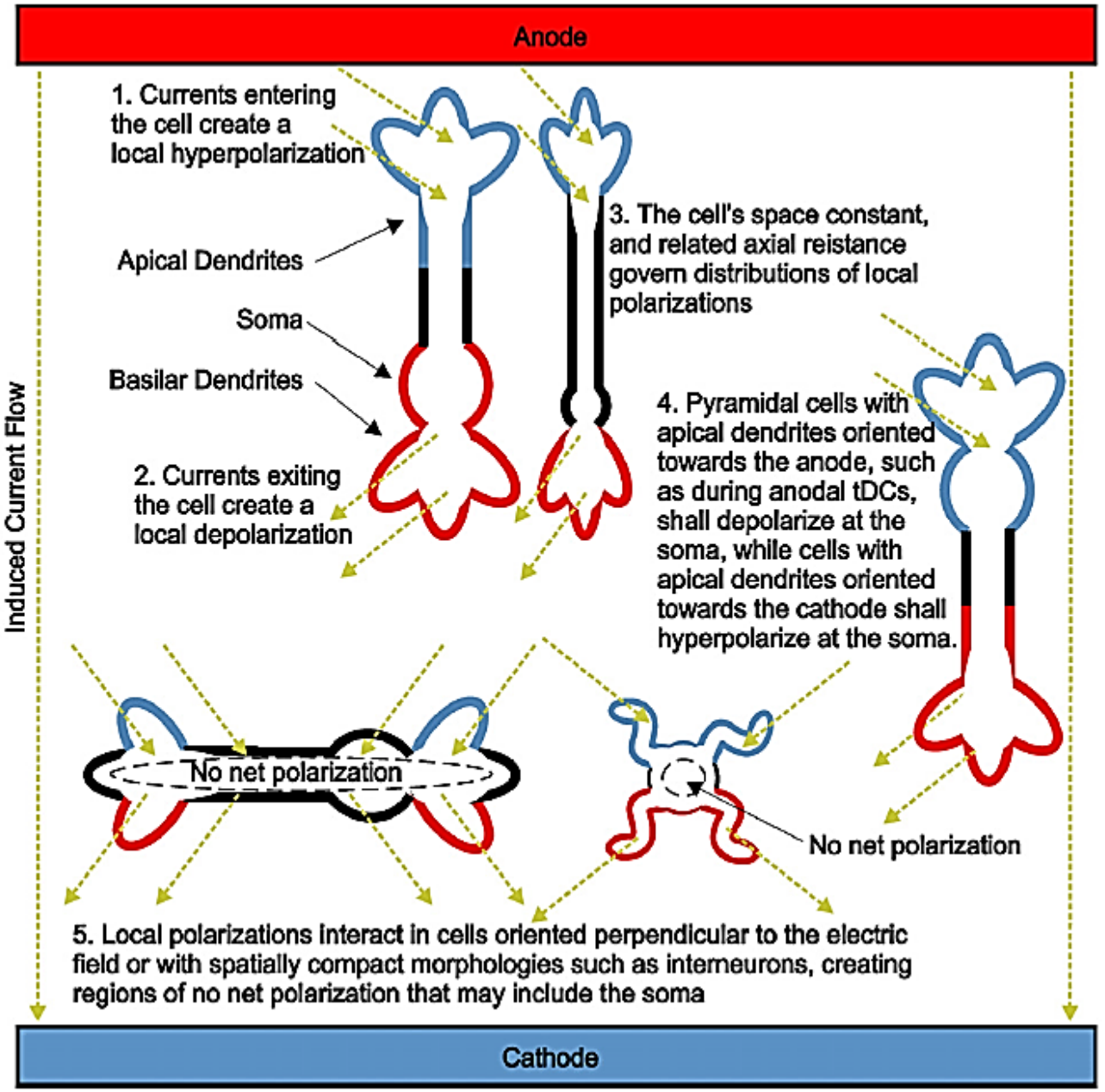
Data pooled from 7 studies
89 healthy, motor cortex





Ho,….Loo, 2016

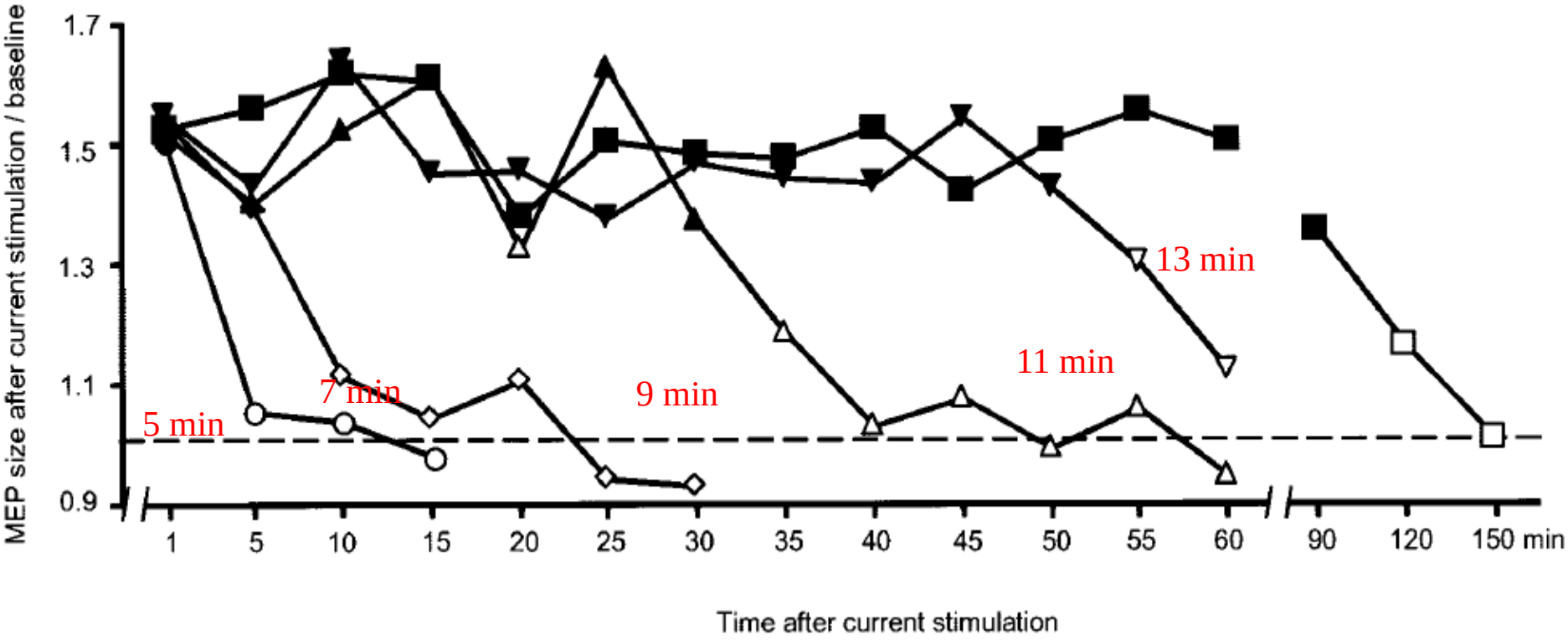




Effects of Neuronal Anatomy

Radman et al, 2009

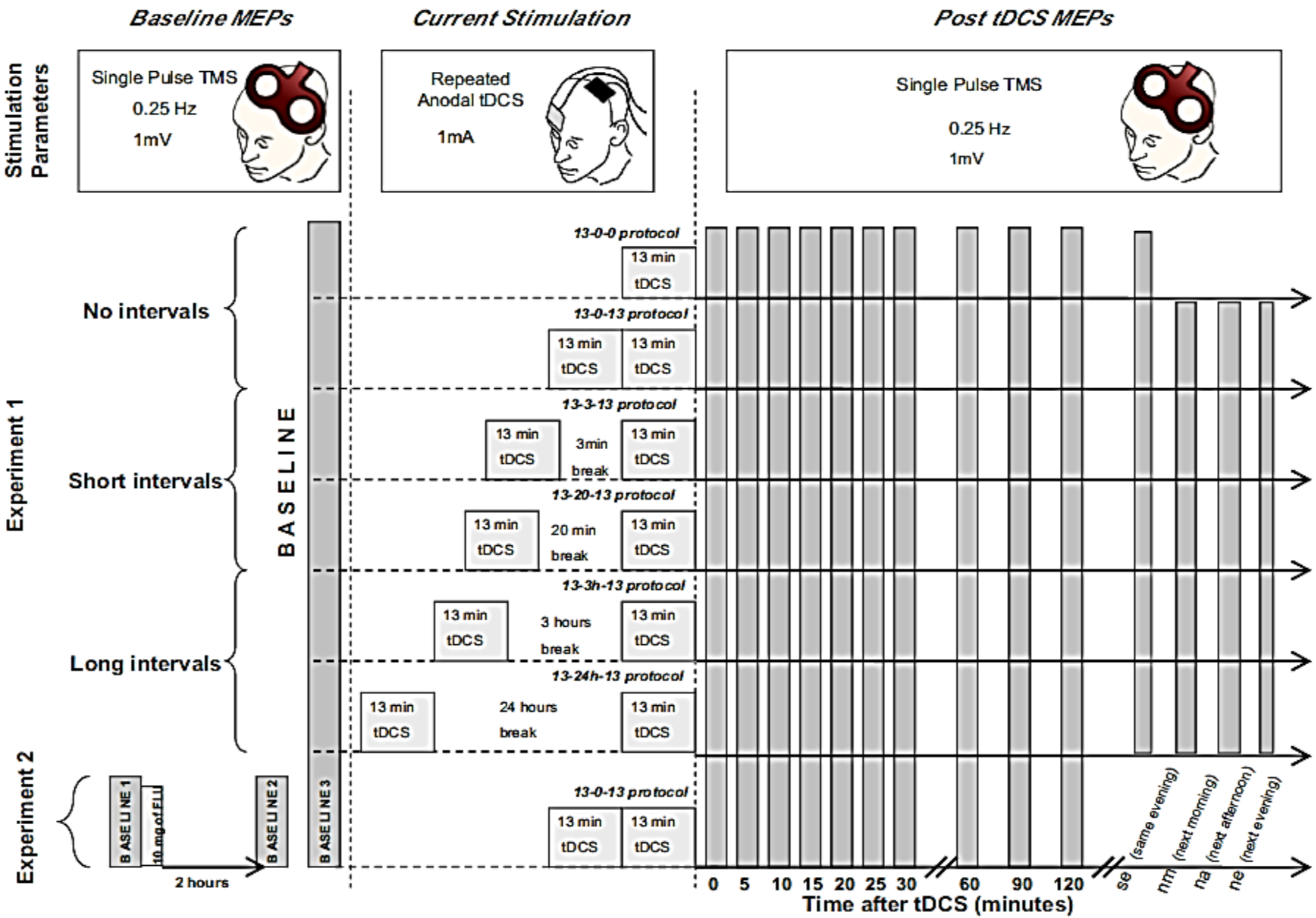
Stimulation Duration



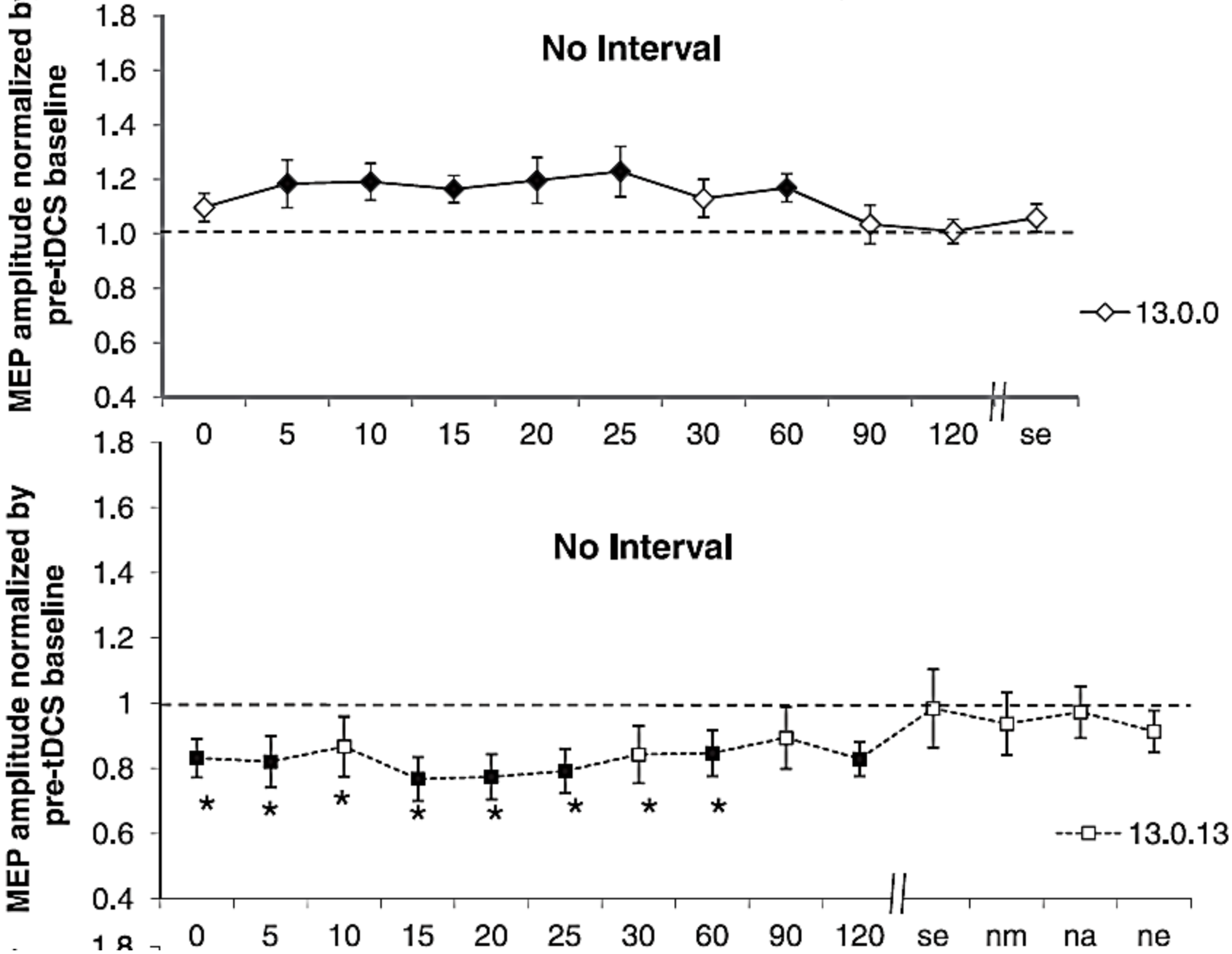
$\geq$ 26 min?

Anodal tDCS
Nitsche & Paulus, 2001

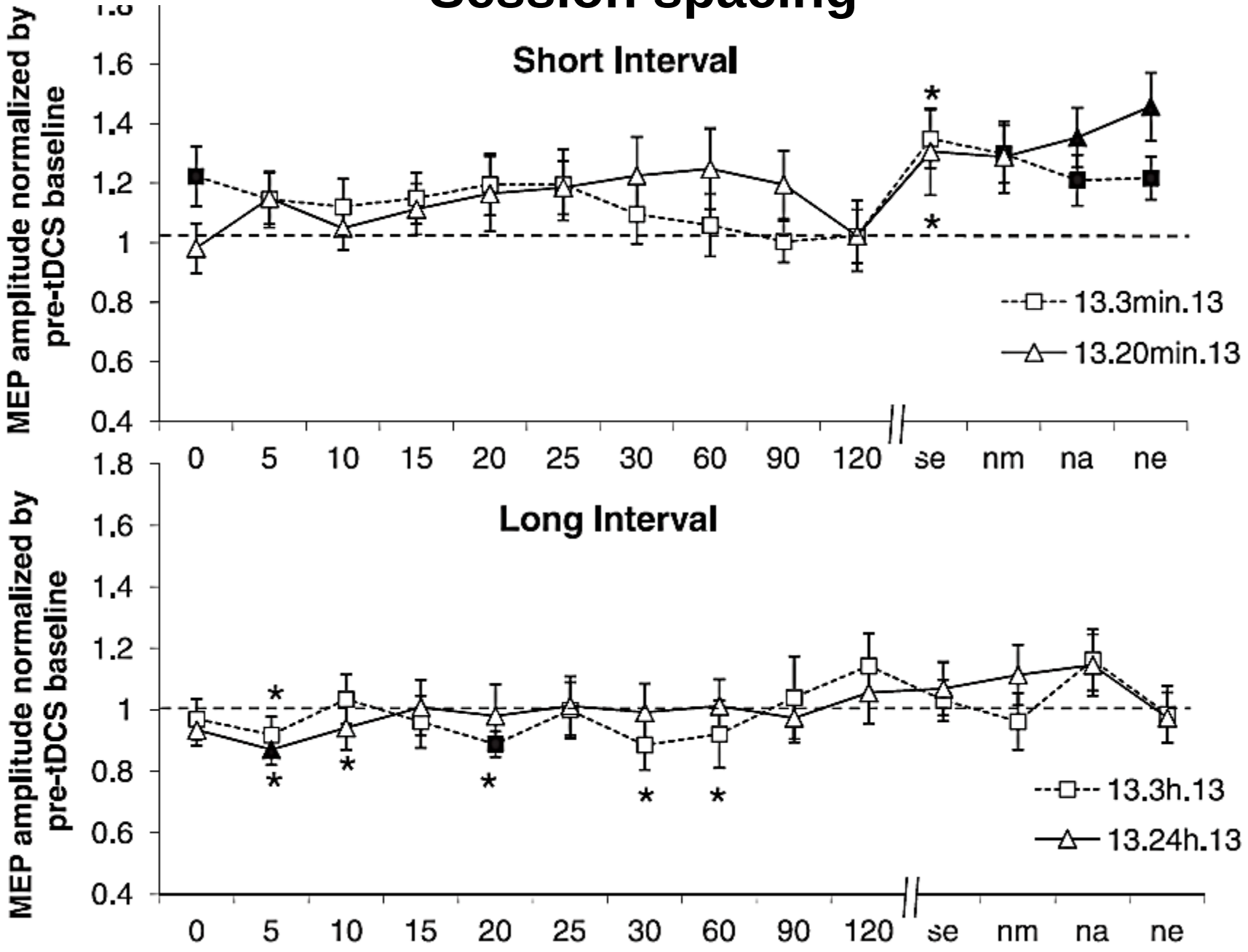
Session spacing



Session spacing



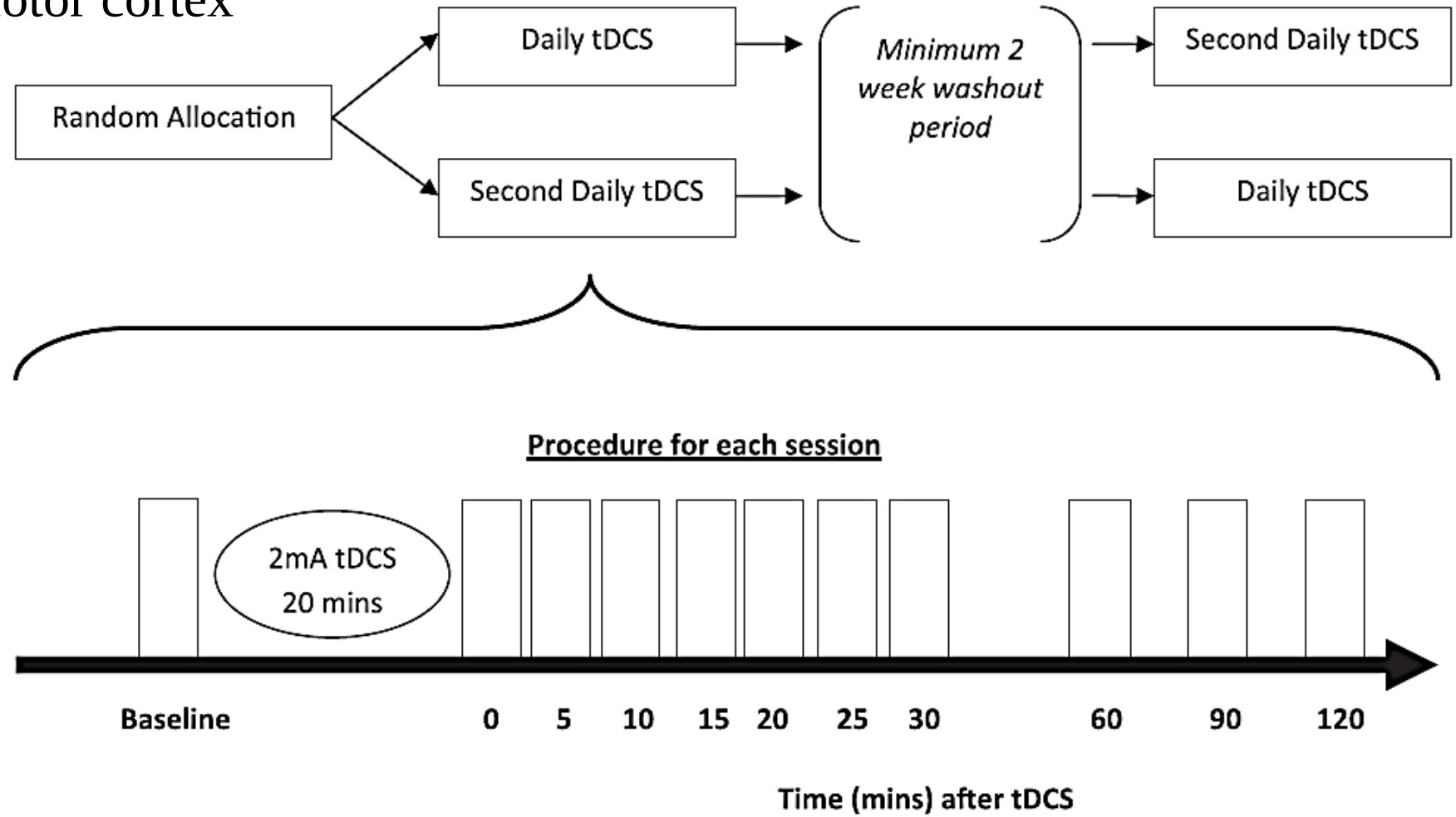
Session spacing



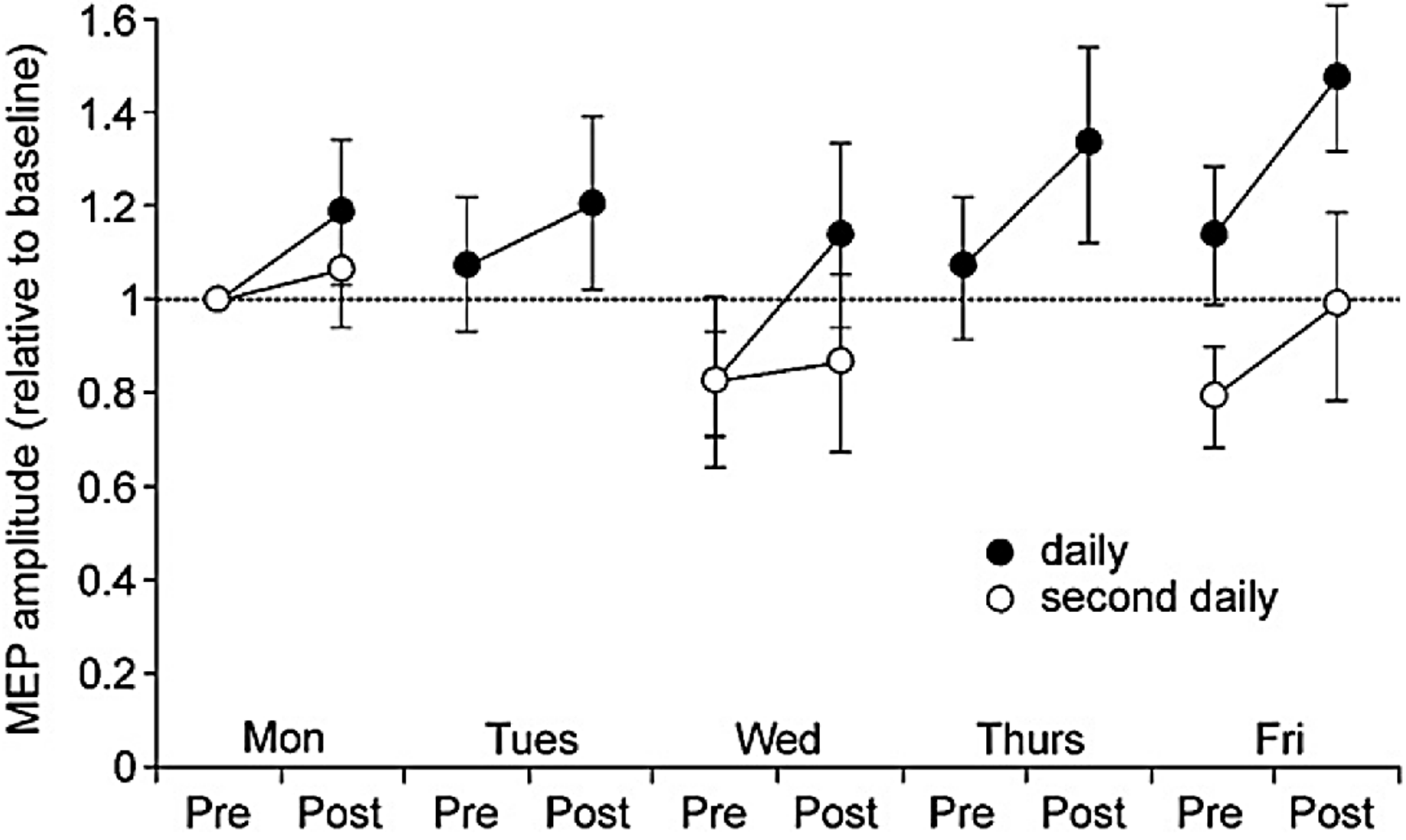
Strategies to Enhance Efficacy II

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

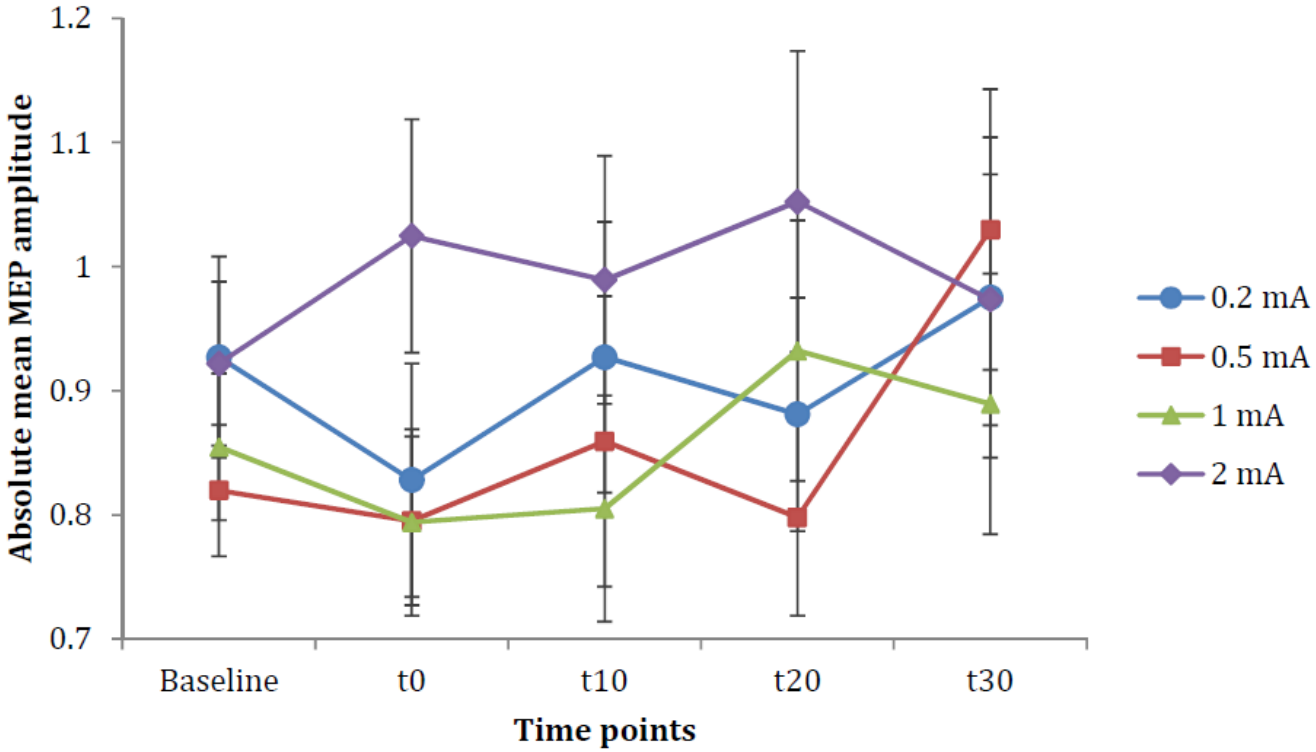
N=12, healthy
Crossover trial
Motor cortex

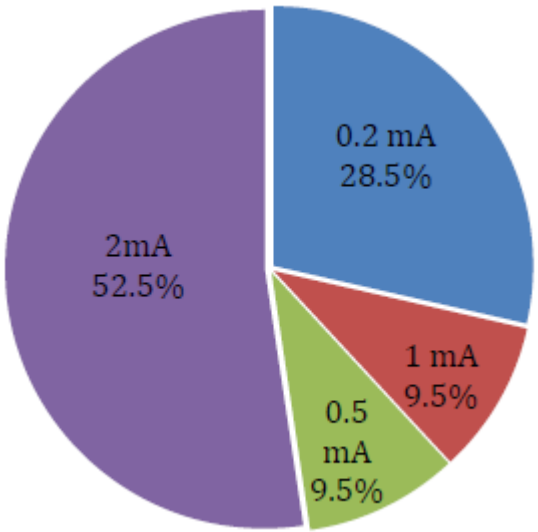


Daily vs 2nd Daily tDCS : Alonzo et al, 2011



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

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

Strategies to Enhance Efficacy : Activation during tDCS

Brunoni et al, 2013. “SELECT” Trial

- N=120
- RCT - 4 groups:

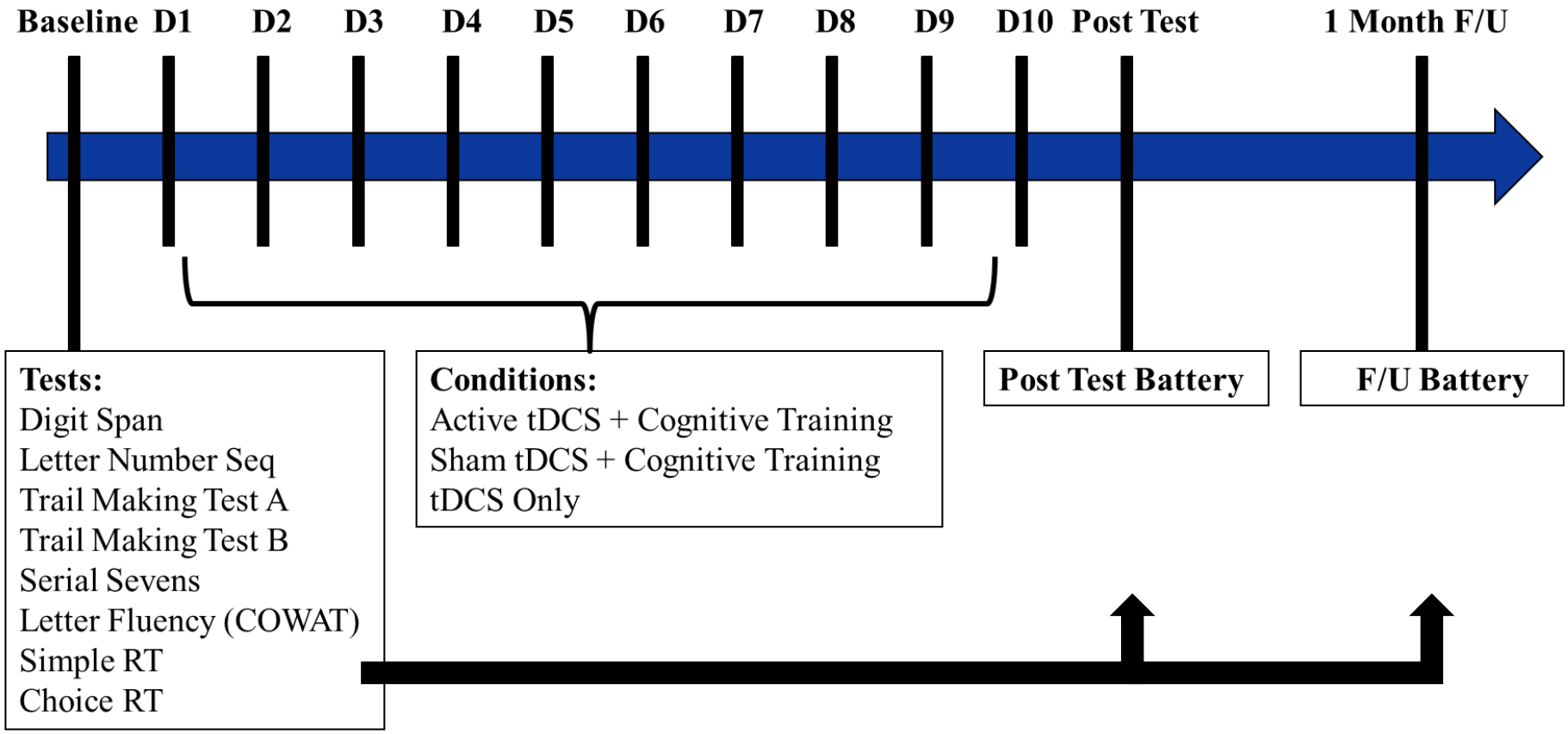
	Active tDCS	**Sham tDCS**
Sertraline 50 mg	Active tDCS + Sertraline	Sham tDCS + Sertraline
Placebo	Active tDCS + Placebo	Sham tDCS + Placebo

Strategies to Enhance Efficacy : Activation during tDCS

Response (& Remission rates)

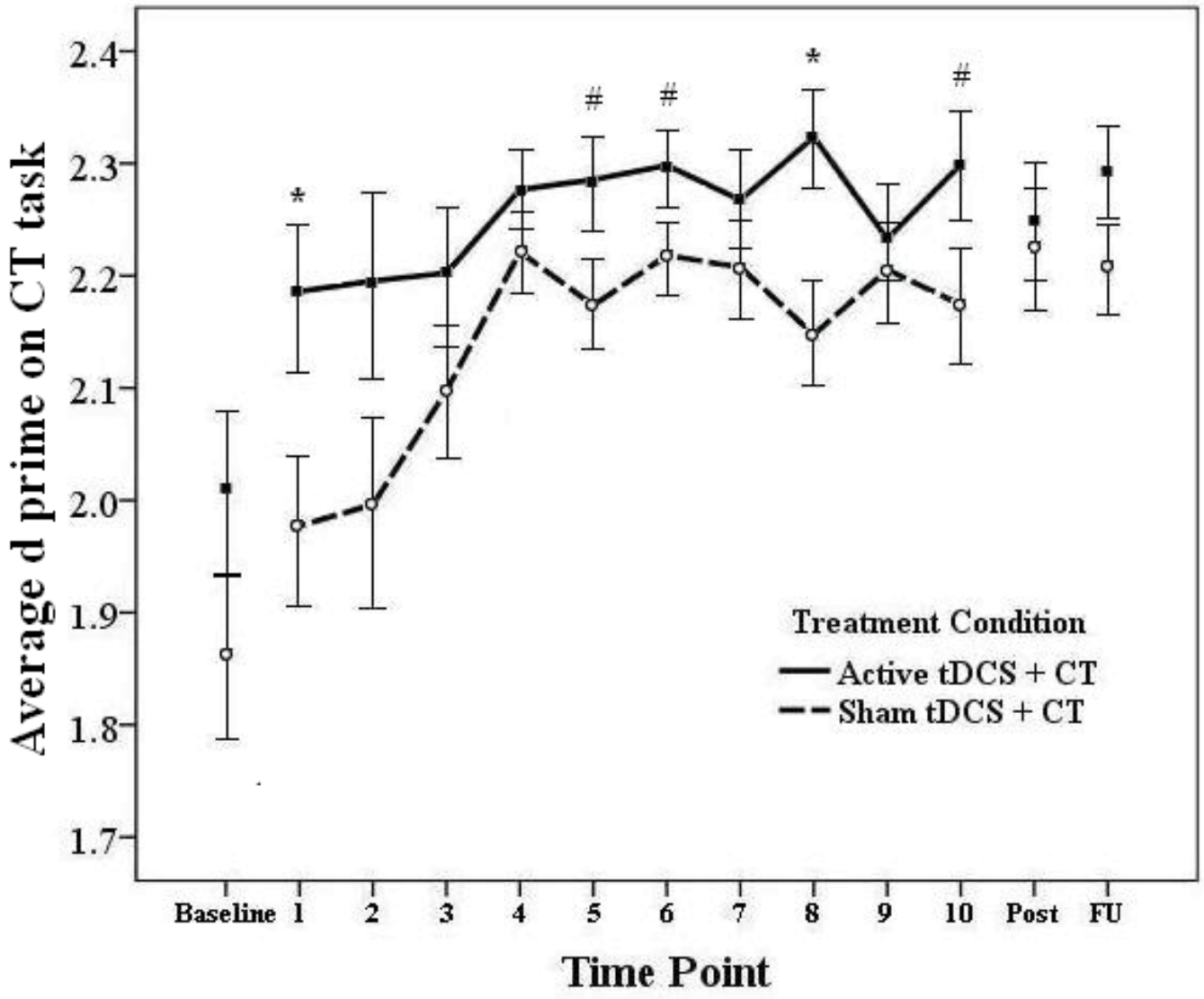
	Active tDCS	**Sham tDCS**
Sertraline 50 mg	19% (14%)	10% (9%)
Placebo	13% (12%)	5% (4%)

tDCS + Cognitive Training – Healthy Volunteers



Martin et al. 2013

tDCS improves accuracy on a Cognitive Training Task (Healthy sample)



Martin et al 2013

tDCS & the Cognitive Control Model of Depression

Directly activate DLPFC

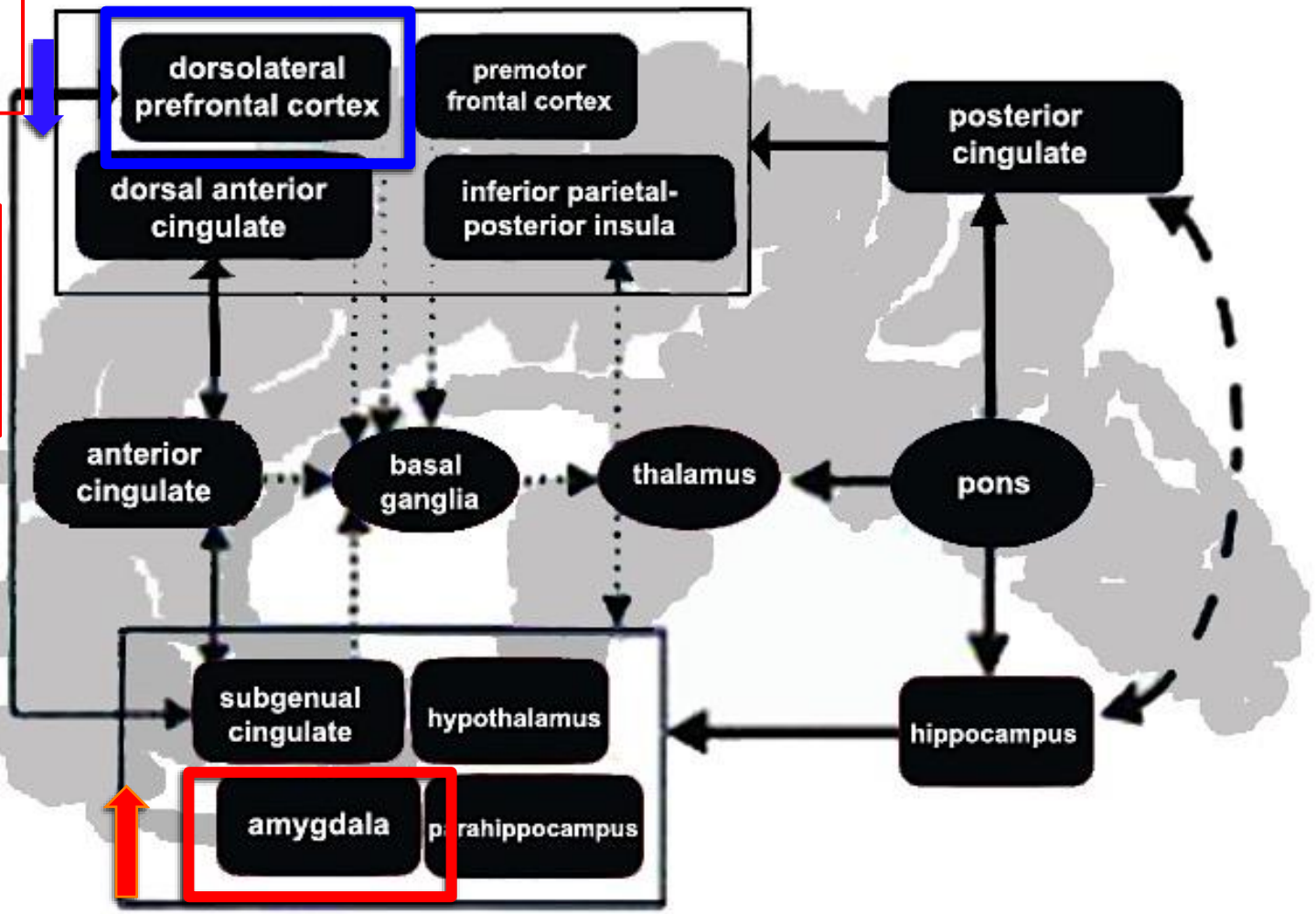
Cortical

Enhance attention for cognitive training

Sub-cortical

Reduce negative attentional bias

Limbic-paralimbic

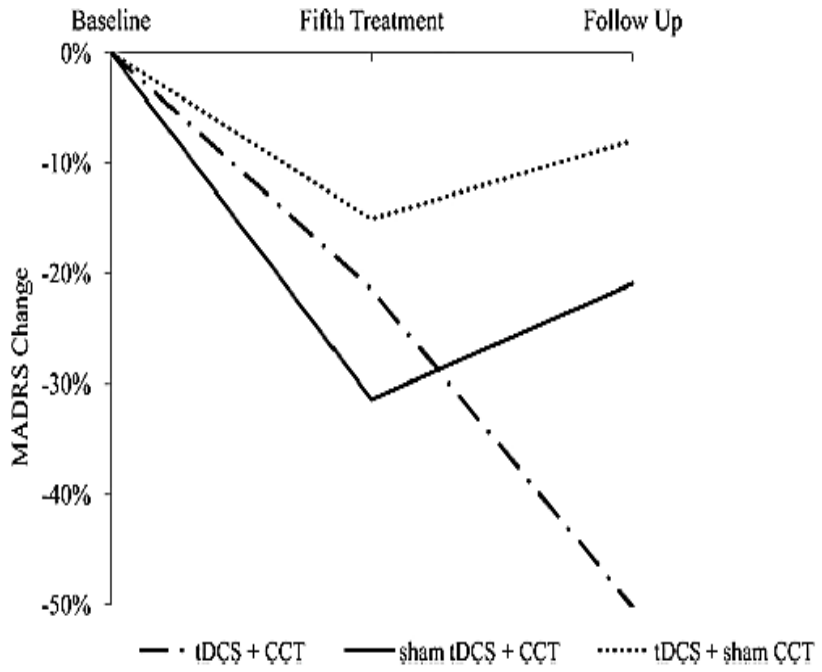


Concurrent Cognitive Control Training Augments the Antidepressant Efficacy of tDCS: A Pilot Study

R.A. Segrave*, S. Arnold, K. Hoy, P.B. Fitzgerald

Brain Stimulation

N=27
3-arm trial:
— · — tDCS + CCT
····· Sham CCT + tDCS
—— CCT + sham tDCS



Cognitive Control Training (CCT) – increases DLPFC activity, but with behavioral methods.

Two computer-based tasks:

- Modified Wells Atention Training (WAT)
- Paced Serial Addition Task (PASAT)

CCT was done concurrently with tDCS

TDCS – 24 min / 2 mA
Anodal over F3 // cathodal over F8
5 days, once a day
FU at 3 weeks

tDCS + Concurrent Intervention

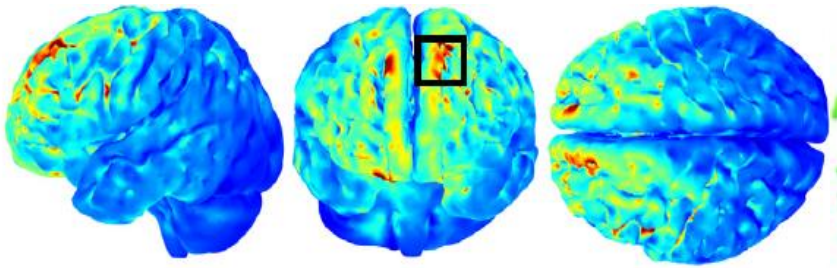
Translational pitfalls

- 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?)

Problem of Inter-individual Variability

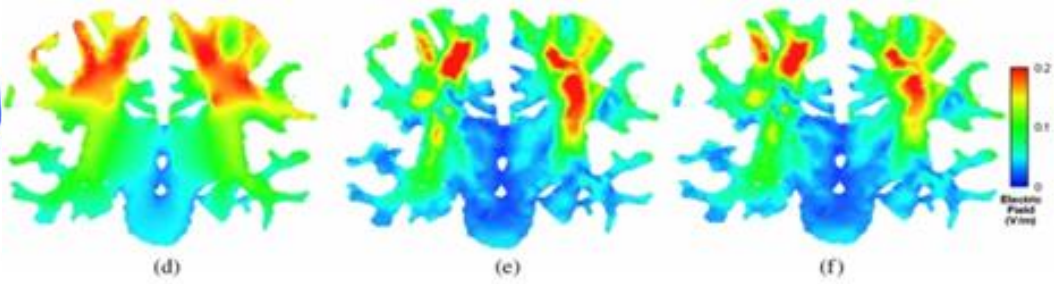
- Identify individual predictors of response to stimulation?
- Eg Pre-treatment letter fluency performance predicts antidepressant response to active tDCS [Martin et al, 2016]. N=104 depressed, pooled from 5 clinical trials: 57 active tDCS, 47 sham tDCS

Stimulated structures



Bai et al. 2014

Role of white matter



Suh et al. 2012

Home-Administered Trial of Direct Current Stimulation (HAT-DCS)

User Instructions

Name: _____

Study Team Contact Information:

	Phone	Email

Reasons for developing home-administered system

- Acute course – number and frequency treatments
- Maintenance treatment
- Treatment costs - staff time
- Travel time and costs - patients
- Access in remote areas
- Patient interest

→ **HAT – DCS trial:**

- Pilot system for home administration, in depressed patients
- Assess feasibility & safety

Considerations for home-administered tDCS in depression

Equipment

- Easy to use
- Foolproof - amount and frequency of stimulation, stimulation site, skin-electrode contact

Patient selection

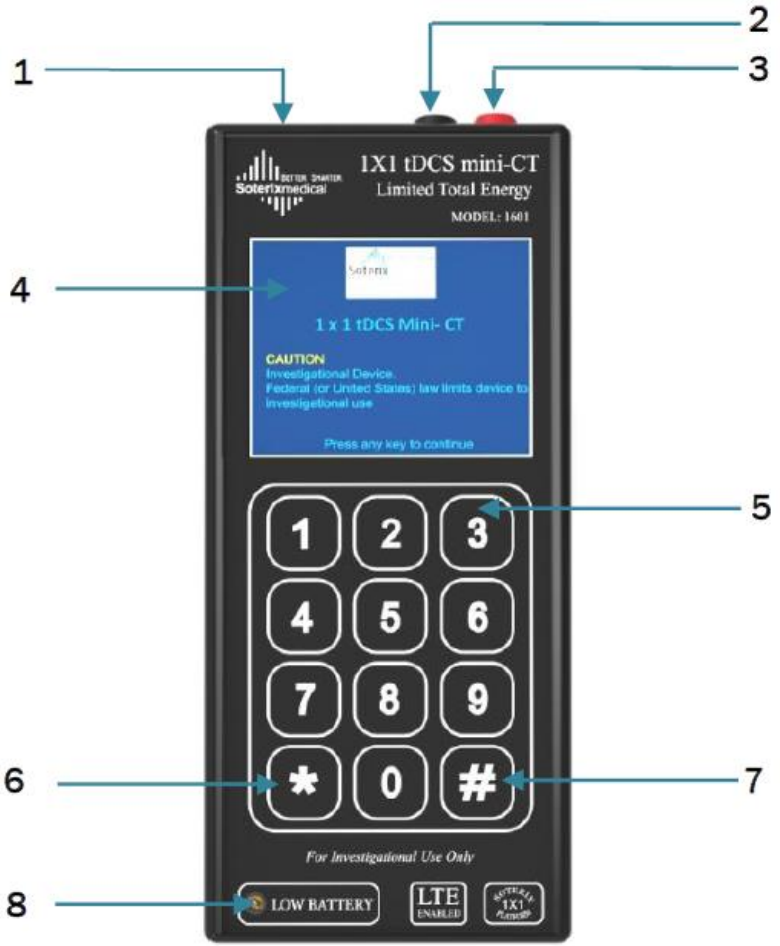
- Suitability – diagnosis, severity, insight, risk, support
- Ability to comply with treatment – time, motivation, skills

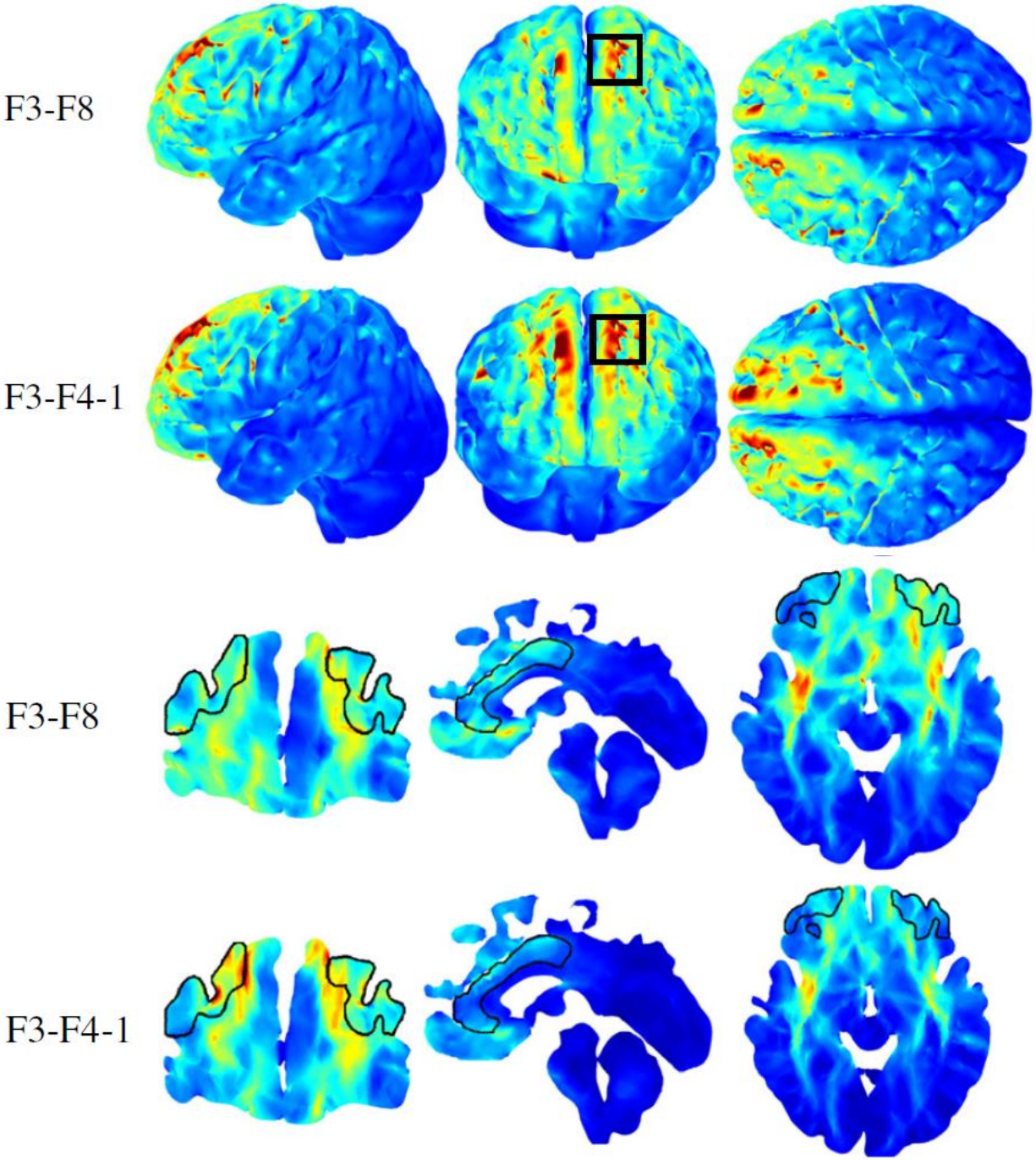
Monitoring

- Compliance
- Efficacy – continue? Change treatment frequency/ dose ?
- Adverse effects
- Safety – worsening, suicide risk

Home-Administered, Remote Supervised tDCS: Device

1. USB jack for charging the device
2. Connector port for cathode cable (black)
3. Connector port for anode cable (red)
4. Display screen
5. Numeric keypad
6. * is used for BACK or backspace
7. # is used for OK
8. When lit up, this indicates low battery





Stimulation Montage

F3-F8

Bai et al, 2014

Process

Training & Credentialling

Treatment diary – mood, side effects

tDCS: Role

Useful in depression:

- Non TRD. Effective in TRD?
- Cognitive enhancement. Enhance neuroplasticity
- Mild stimulation. Excellent safety & tolerability
  NB: DIY tDCS !!
- Home-based, remote supervised capacity – excellent translation potential.
- Maintenance treatment (spaced treatments)