Transcranial Direct Current Stimulation (tDCS)

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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

Predictors: Treatment resistance, tDCS “dose”

<table>
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<tr>
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<th>OR</th>
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<td>1.38-4.32</td>
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### tDCS meta-analysis, Brunoni et al, 2016, N=289

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

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<td>12.3%</td>
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<td>9</td>
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<tr>
<td>Remission</td>
<td>14.2%</td>
<td>5.5%</td>
<td></td>
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### TMS NIMH multicentre trial, George et al, 2010, N=190

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<tbody>
<tr>
<td>Response</td>
<td>15%</td>
<td>5%</td>
<td>4.6</td>
<td>1.47-14.42</td>
<td>12</td>
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<tr>
<td>Remission</td>
<td>14.1%</td>
<td>5.1%</td>
<td>4.2</td>
<td>1.32-13.24</td>
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</table>

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**

**Active Treatment phase**
- 4-8 weeks
  - Randomly Assigned
  - Active
  - Sham

**Blind**
- 4 weeks (every weekday)
- If MADRS $\geq 10$
- If MADRS $< 10$
  - Open label
    - 4 weeks (every weekday)
  - Use Unique subject code
  - Use open active code “999999”

**Taper phase**
- Once per week
- 4 weeks
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
Machine

Blinding
- Individual subject code. Multi digit – differ by \( \geq 2 \) 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
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

SyNC  Sydney Neurostimulation Centre
Bifrontal  Fronto-Occipital  Fronto-Cerebellar  

Ho et al, 2014  
N=15 depressed  
Pilot clinical trial  
Fronto-occipital or fronto-cerebellar  

Unit: V  

≥ 0.2  

MADRS Scores  

Baseline  Post 8  Post 15  Post 20  

Time
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
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Stimulation parameters/ sessions</th>
<th>Mean Δ depression scores</th>
<th>% Response</th>
<th>% Remitters</th>
</tr>
</thead>
</table>
| Fregni et al, 2006    | 10 | 1mA, 20 mins, 5 sessions/ 1.5 weeks | Active: 59%  
Sham: 13% | 80         | ?                        |
| Boggio et al, 2008    | 40 | 2mA, 20 mins, 10 sessions/ 2 weeks | Active: 40%  
Sham: 10% | 40         | 25                       |
| Loo et al, 2010       | 40 | 1 mA, 20 mins, 5 sessions/ 1.5 weeks | Active:20%  
Sham: 19% | 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                        |
| 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          | 0                        |
| Brunoni et al, 2013   | 120| 2mA, 30 mins  
10 sessions/2 weeks  
Taper: 2 sessions/4 weeks | Active:40%  
Sham: 18% | 9 [13]  
6 [4]                       |
| Multicentre Trial     | 120| 2.5 mA, 30 mins, 20 sessions/4 weeks  
Taper Phase | | | |
Dose – Stimulus Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Equation/Calculation</th>
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<tbody>
<tr>
<td>Intensity (mA)</td>
<td>Intensity x duration = charge</td>
</tr>
<tr>
<td>Duration (mins)</td>
<td></td>
</tr>
<tr>
<td>Electrode size (cm²)</td>
<td>Charge/electrode area = charge density</td>
</tr>
<tr>
<td>Number sessions</td>
<td>Intensity x duration x # sessions = total charge</td>
</tr>
<tr>
<td>Spacing of sessions</td>
<td>Total charge/electrode area = total charge density</td>
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</tbody>
</table>
Stimulation Duration

≥ 26 min?

Anodal tDCS
Nitsche & Paulus, 2001
**Session spacing**

*Baseline MEPs*
- Single Pulse TMS
  - 0.25 Hz
  - 1mV

*Current Stimulation*
- Repeated Anodal tDCS
  - 0.25 Hz
  - 1mA

*Post tDCS MEPs*
- Single Pulse TMS
  - 0.25 Hz
  - 1mV

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**Stimulation Parameters**

- **Experiment 1**
  - **No intervals**
  - **Short intervals**
  - **Long intervals**

- **Experiment 2**
  - **BASELINE 1**
  - **BASELINE 2**
  - **BASELINE 3**

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**Time after tDCS (minutes)**

- **13-0-0 protocol**
  - 13 min tDCS
  - 13 min tDCS

- **13-0-13 protocol**
  - 13 min tDCS
  - 13 min tDCS

- **13-3-13 protocol**
  - 13 min tDCS
  - 3 min break
  - 13 min tDCS

- **13-20-13 protocol**
  - 13 min tDCS
  - 20 min break
  - 13 min tDCS

- **13-3h-13 protocol**
  - 13 min tDCS
  - 3 hours break
  - 13 min tDCS

- **13-24h-13 protocol**
  - 13 min tDCS
  - 24 hours break
  - 13 min tDCS

- **13-0-13 protocol**
  - 13 min tDCS
  - 13 min tDCS

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**Breakdown**

- **SAME EVENING**
  - Baseline 1
  - Baseline 2
  - Baseline 3

- **NEXT MORNING**
  - Baseline 1
  - Baseline 2
  - Baseline 3

- **NEXT AFTERNOON**
  - Baseline 1
  - Baseline 2
  - Baseline 3

- **NEXT EVENING**
  - Baseline 1
  - Baseline 2
  - Baseline 3
Session spacing

Short Interval

Long Interval

MEP amplitude normalized by pre-tDCS baseline

- 13.3min.13
- 13.20min.13

- 13.3h.13
- 13.24h.13
Strategies to Enhance Efficacy II
Daily vs 2\textsuperscript{nd} Daily tDCS: Alonzo et al, 2011

N=12, healthy
Crossover trial
Motor cortex

Random Allocation

Daily tDCS

Second Daily tDCS

Minimum 2 week washout period

Second Daily tDCS

Daily tDCS

Procedure for each session

2mA tDCS
20 mins

Baseline

0 5 10 15 20 25 30 60 90 120

Time (mins) after tDCS
Daily vs 2nd Daily tDCS: Alonzo et al, 2011

MEP amplitude (relative to baseline)

- • daily
- ○ second daily

Pre Post Pre Post Pre Post Pre Post Pre Post
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

SyNC  Sydney Neurostimulation Centre
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

Role of white matter

Bai et al. 2014

Suh et al. 2012

SyNC Sydney Neurostimulation Centre
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
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