Combining non-invasive brain stimulation with motor training programs

......sounds a good idea, but is there evidence to support it?

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Non-Invasive brain stimulation

- Potential to modulate cortical excitability and plasticity
- Promote improvement in motor performance through LTP and possibly offline learning
- Uncertainty around stimulation parameters and which patients might benefit
- Evidence from systematic reviews
- Examples of clinical trials with robot therapy, motor training and CIMT
- Future directions
Motor training

- Robot therapy
- CIMT
- Graded Repetitive Arm Supplementary Programme (GRASP) [http://neurorehab.med.ubc.ca/grasp/](http://neurorehab.med.ubc.ca/grasp/)
- Motor learning principles - neuroplasticity
Donald Hebb (1904 – 1985) strengthening connections

“When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that B’s efficiency, as one of the cells firing A, is increased”

‘Fire together wire together’
Growing new dendrites – connections between cells

Pyramidal cells of a mouse
New post-synaptic dendrite spines appearing one hour after stimulation – accompanying synaptic efficiency

Engert & Bonhoeffer, Nature. 1999
Testing Hebb’s rule

- Each time a particular synaptic connection is active, see if the receiving cell also becomes active.
- If so, the connection contributed to the success (firing) of the receiving cell synapse and it should be strengthened.
- If the receiving cell was not active the synapse did not contribute.
- And the synapse will be weakened.
Hebb’s Rule; neurons that fire together wire together

- First of all it’s a chemical change that enables calcium ions to flow more freely and so make the synapse more likely to fire
- Subsequently there is a structural change which makes the connections more permanent
And eventually areas of the brain can change the connections they make with the rest of the body.

And that is neuroplasticity.

And it underpins our ability to learn.

And people who have had a stroke or a spinal cord or head injury to recover.
Representation of the hand in the motor cortex of the squirrel monkey

Nudo et al., 1997
Motor map of a rat before and after training to do a skilled task involving the hand but not the whole arm.

Digit and wrist representations (green) can be seen to expand into elbow/shoulder representations (blue). (Figure adapted from Monfils et al., 2005).
What happens in the brain when someone has a stroke?

Red: tracts descending from M1 that were **uninjured**
Yellow: tracts descending from M1 that were **injured**
Green: area affected by the stroke

A. This person had 40% of the M1 tract injured by stroke – good recovery
B. This person had 93.4% of the M1 tract injured by stroke - very little recovery.
Functional MRI scans of the brain....

Showing brain activity during movement of the left or right hand in a healthy control and a stroke patient with a left sided lesion

A. In patients, movements of the paretic (right) hand is associated with activation in the non-damaged motor area of the brain

But not in healthy controls

AND

B. when moving the unaffected (left) hand activity is mainly in the Right (unaffected) cortex in both patients and healthy controls

Nerves from one side of the brain connect with the opposite side of the body
Imbalance of excitation and inhibition between the two sides of the brain following stroke causes further problems...

The unaffected cortex has a greater inhibitory effect on the affected cortex than vice-versa.

Can we re-balance the activity?

By up-regulating the damaged side?

Or by down-regulating the undamaged side?

Figure taken from Nowak et al., 2009).
Using electricity to restore a normal balance!

tDCS

TMS
Changing cortical excitability

- Anode over the **affected** motor cortex – attracts electrons which depolarize the nerve cells thus increasing their excitability

- Cathode over the **unaffected** motor cortex attracts cations (+ve charged ions) thus decreases excitability
Transcranial Direct Current Stimulation (tDCS)

- ↑Calcium- and sodium-dependant membrane channels
- ↑Strength of N-methyl-D-aspartic acid glutamate receptors
- Altering cortical excitatory/inhibitory pathways
- Demonstrated by changes in TMS MEPs

(Liebetanz et al., 2002, Nitsche et al., 2008, Stagg et al., 2009)
Testing cortical excitability using Transcranial Magnetic stimulation (TMS)
Changes in the muscle response to TMS

A  ANODAL TDCS

B  CATHODAL TDCS

C  SHAM TDCS

Baseline  Immediate  30 Minutes  60 Minutes
Learning

• Increasing cortical excitability may accelerate neuroplasticity

• But for useful changes in connectivity to be made the person must practice

• This is some of the research that has been done to find ways of enabling people to practice
• At six months post-stroke, 33% to 66% of people with stroke do not present with recovery of upper limb function (Kwakkel and Kollen, 2013)

• As a result, lack of movement can be a determinant of participation restriction (Chau et al., 2009)
Cortical and short term behavioural effects of tDCS

- Three stimulation paradigms anodal, cathodal and sham
- > 6 months post stroke
- N=11 Single sessions / short term response
- fMRI and behavioural (Response Time – wrist flexion holding joystick in response to cue and grip strength
- Anodal (statistically significant) and cathodal (minimal) but not sham led to improved response times
- Increased motor related cortical activity on fMRI
- Correlation between increased response times and increased cortical activity

*Stagg et al. Cortical Activation changes underlying stimulation – induced behavioural gains in chronic stroke. Brain 2012*
Systematic Review of clinical trials of tDCS & motor training

Effect of real tDCS versus sham tDCS for UE motor impairments measured by FMA at immediate post-intervention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Real tDCS + Rehab</th>
<th>Sham tDCS/No stim + Rehab</th>
<th>Std. Mean Difference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Kim et al., 2010</td>
<td>48.9</td>
<td>15.2</td>
<td>11</td>
</tr>
<tr>
<td>Lindenberg et al., 2010</td>
<td>43.8</td>
<td>12.3</td>
<td>10</td>
</tr>
<tr>
<td>Hesse et al., 2011</td>
<td>19</td>
<td>12.45</td>
<td>64</td>
</tr>
<tr>
<td>Bolognini et al., 2011</td>
<td>31.7</td>
<td>31.1</td>
<td>7</td>
</tr>
<tr>
<td>Nair et al., 2011</td>
<td>33.7</td>
<td>12.9</td>
<td>7</td>
</tr>
<tr>
<td>Viana et al., 2014</td>
<td>50.6</td>
<td>13.4</td>
<td>10</td>
</tr>
<tr>
<td>Lee et al., 2014</td>
<td>47.7</td>
<td>21.3</td>
<td>20</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>129</td>
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</tbody>
</table>

Heterogeneity: Chi² = 0.89, df = 6 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.44)

Small but non-significant effect on UL Impairments and ADL
Wide range of tDCS parameters and patients

(Tedesco Triccas, Burridge et al., 2015, Clinical Neurophysiology)
tDCS and motor training using GRASP – double-blind RCT

• N=24 >6 months post-stroke Range of Baseline FMA score = 13-62
• 1 hour/day on 9 consecutive working days
• tDCS x 20 mins (1mA Anodal to affected cortex) OR Sham simultaneous with training following by 40 mins additional training
• Improvements in both groups on all functional outcomes – not statistically significant
• Lower functioning patients in tDCS group made bigger gains

1Allman C et al. Anodal tDCS enhances the positive functional effects of motor rehabilitation and increases the recruitment of ipsilesional motor areas in chronic stroke: a randomised controlled trial with neuroimaging measures. submitted.
tDCS combined with Robot training (Bi-ManuTrack) Double-blind RCT¹

- N=96 3-8 weeks post-stroke severe flaccid UL impairment and FMA<18
- 30 sessions x 20 mins over 6 weeks
- Three groups, all received conventional rehabilitation 45 minutes/day:
  - tDCS x 20 mins 1mA Anodal to affected cortex
  - tDCS x 20 mins 1mA Cathodal to unaffected cortex
  - OR Sham simultaneous with repetitive motor training
- Outcome measures included FMA and Box&Blocks
- No effect of tDCS either Cathodal or Anodal
- But pure subcortical strokes improved significantly more than those with cortical involvement

tDCS and mCIMT

- Pilot study in chronic stroke n=21 - double-blind RCT
- Three groups: Anodal tDCS; Cathodal tDCS; Sham
- Outcome measures: FMA and MAL
- Intervention: mCIMT + tDCS
- tDCS: 12 sessions 1mA for 13 mins (Anodal) and 9 mins (Cathodal)
- mCIMT immobilisation of whole arm for 6 hours/day for 7 days/week for 4 weeks. Intensive training for 1 hour 3-days/week
- Assessment: Before, Post treatment and follow-up @ 1 month

Rocha et al. Disability and Rehab 2015
tDCS + mCIMT Results

• Post treatment both Anodal and Cathodal groups had statistically significant improvement on FMA but not Sham (repeated measures ANOVA)

• At 1 month only the Anodal group had statistically significant improvement

• No difference between groups on MAL

• Only the Anodal group post treatment had a MCID in FMA of 5.25 compared with Sham

• Very small sample to conduct statistical tests but

• MCID is important - larger study justified
What is the effect of transcranial direct current stimulation and robot therapy for the impaired upper limb in sub-acute and chronic stroke?

Tedesco Triccas L (PhD), Burridge JH (PhD), Hughes AM (PhD), Verheyden G (PhD), Desikan M (MD), Rothwell JR (PhD)
Armeo
Aims of the study

• To examine the effectiveness of additional tDCS to RT for the impaired upper limb in stroke

• To understand the views and experiences of tDCS and RT of people with sub-acute and chronic stroke
Methods

Group A: 1 hr RT and 20 min 1mA Anodal tDCS

Baseline Assessment

18 sessions

Group B: 1 hr RT and 20 min sham tDCS

Post-Intervention Assessment

Three-month follow-up

Semi-structured interview
tDCS and Robot therapy double-blind RCT N=22

- Robot therapy 18 x 60 minutes sessions with breaks after each 20 mins
- Sham or Anodal tDCS 1mA x 20 mins during robot therapy
- FMA (UL) and ARAT
- Pre-post treatment and at 3-month follow-up
- Post-treatment Interviews
Results

- One participant dropped out of the trial due to hypersensitive skin.

- 22 participants (12 sub-acute mean age: 67.2 [SD=11.4] and (10 chronic mean age: 59.4 [SD=11.7]) completed the trial.

- No significant difference in Fugl-Meyer Assessment between the real and sham groups (p=0.123).

- Combined data revealed a significant stage (sub-acute or chronic) x time (baseline and post-treatment) interaction (p=0.016).
# Sub-Acute Vs Chronic (FMA)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD) Baseline (B)</th>
<th>Mean (SD) Post-intervention (P)</th>
<th>Mean (SD) Follow-up (F)</th>
<th>Change (P-B) (%)</th>
<th>Change (F-B) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sub-Acute</strong></td>
<td>36.67 (18.36)</td>
<td>46.92 (17.78)</td>
<td>47.3 (18.00)</td>
<td>+10.25 (15.53%)</td>
<td>+10.58 (16.03%)</td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td>24.20 (8.60)</td>
<td>30.00 (10.23)</td>
<td>27.20 (11.01)</td>
<td>+5.80 (8.78%)</td>
<td>+3.00 (4.55%)</td>
</tr>
</tbody>
</table>

MCID = 10% - 6.6
## Sub-Acute Vs Chronic (ARAT)

<table>
<thead>
<tr>
<th></th>
<th>Median (min,max) Baseline</th>
<th>Median (min,max) Post-intervention</th>
<th>Median (min,max) Follow-Up</th>
<th>Change</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sub-Acute Group</strong></td>
<td></td>
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<tr>
<td></td>
<td>(B)</td>
<td>(P)</td>
<td>(F)</td>
<td>(P-B) (%)</td>
<td>(F-B) (%)</td>
</tr>
<tr>
<td></td>
<td>33.50 (0,56)</td>
<td>48.50 (0,57)</td>
<td>50.00 (0,57)</td>
<td>+15.00 (26.32%)</td>
<td>+16.50 (28.95%)</td>
</tr>
<tr>
<td><strong>Chronic Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(B)</td>
<td>(P)</td>
<td>(F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.00 (0,16)</td>
<td>8.00 (0,18)</td>
<td>8.00 (0,13)</td>
<td>+2.00 (3.51%)</td>
<td>+2.00 (3.51%)</td>
</tr>
</tbody>
</table>

MCID = 5
How is motor training best delivered

- Evidence from experimental studies shows an increase in excitability following tDCS that lasts for about one hour
- Which is enhanced with motor training concurrent or immediately post-stimulation motor training
- And consolidation of motor learning continues offline
- Positive feedback during training improves retention, whereas negative feedback impairs retention
- Randomised training of different skills increases offline learning more than block training – supported by fMRI studies

\(^1\)Wessel et al 2015
Summary

• Despite good experimental evidence, clinical trials have not generated strong evidence

• No large scale trials

• Many questions remain to be answered:
  – How and when tDCS should be delivered
  – Type and delivery of motor training
  – When during recovery
  – Which patients are most likely to respond

• Without answering these questions large clinical trials are unlikely to demonstrate positive effects
Thank you

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