Transcranial Magnetic Stimulation & Transcranial Direct Current Stimulation: Investigative and Therapeutic Applications

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Brain Stimulation/ Neuromodulation Treatments

**Convulsive Treatments:**
- ECT
- Magnetic Seizure Therapy (MST)
- Focal Electrically Assisted Seizure Therapy (FEAST)

**Non Convulsive Stimulation:**
- Repetitive Transcranial magnetic stimulation (rTMS)
- Deep rTMS
- Transcranial Direct current stimulation (tDCS)
- Caloric Vestibular stimulation (CVS)

**Surgically invasive techniques:**
- Vagus nerve stimulation (VNS)
- Direct cortical stimulation (DCS)
- Deep brain stimulation (DBS)
Potential of Brain Stimulation as a Treatment

- Treatment to specific brain sites
- Different & specific effects at different sites:
  - ↑ activity
  - ↓ activity
- Individual tuning (by adjusting stimulus parameters)
- Treatment can be specific in time eg. intermittent, as needed

Transcranial Magnetic Stimulation (TMS)
<table>
<thead>
<tr>
<th><strong>MAGNETIC STIMULATION</strong></th>
<th><strong>ELECTRICAL STIMULATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp and skull are transparent to magnetic stimulation</td>
<td>Only 5-15% current reaches brain cortex</td>
</tr>
<tr>
<td>Ratio of induced current in scalp to cortex is 2:1</td>
<td>Ratio of induced current in scalp to cortex is 10:1</td>
</tr>
<tr>
<td>Stimulation is more focused (5-22mm resolution)</td>
<td>Stimulation is more diffuse in the brain</td>
</tr>
<tr>
<td>Ability to stimulate deeper structures is limited as magnetic fields attenuate rapidly</td>
<td>Deeper structures are stimulated but such stimulation is diffuse rather than being focused</td>
</tr>
<tr>
<td>Induced current in brain is smaller (about 19 mA/cm² with an fig-8 coil)</td>
<td>A typical ECT pulse induces a current of about 75 mA/cm² in the brain</td>
</tr>
<tr>
<td>A typical TMS session delivers a charge of 10-20 mC</td>
<td>A typical ECT delivers a charge of 100mC to 1 C</td>
</tr>
</tbody>
</table>
TMS Parameters

- Frequency: pulses/second (Hz)
- Train duration
- Intertrain interval
- Repetitive TMS “rTMS”
- Intensity

**sTMS**
Single TMS pulse

**Train duration**

**Intertrain interval**

**Repetitive TMS “rTMS”**
Eg Typical parameters used in depression trials:
10 Hz, 30 x 5s train, 25s intertrain interval, 100% motor threshold
Assessing cortical effects of TMS – Motor Cortex Experiments

- Transcranial magnetic stimulation (TMS) can be combined with EMG to measure cortical excitability
TMS – Effects of stimulus frequency

- TMS to motor cortex (single/ repeated pulses)
- EMG recording from peripheral muscle

High frequency rTMS increases excitability
- 10 Hz rTMS

Low frequency rTMS reduces excitability
- 1 Hz rTMS
TMS - an investigative tool

- Only stimulates outer 1-2 cm cortex
- Temporal resolution: milliseconds
- Spatial resolution: depends on coil shape and size e.g. 0.5 – 2 cm
- Depolarise neurons, disrupt or enhance brain functions
- Combine with EMG, EEG, neuropsychological tasks, SPECT, fMRI etc
Spatial Mapping: Motor and Speech Areas
Spatial (and Temporal) Mapping: Assessing Motor Cortex Plasticity in Braille Readers

Pascual-Leone et al, 1995
Spatial & Temporal Mapping: Virtual lesion: High frequency rTMS to Dorsolateral PFC during Working Memory Task

High frequency tTMS
Investigative study of Psychiatric Disorder
eg Psychomotor Retardation in Depression

Previous research:
Stimulus → Processing → Response

Motivation /effort of subject?
UNSW Psychomotor Retardation Study:

• Compare:
  1. Depressed retarded
  2. Depressed non-retarded
  3. Healthy Control

• Involuntary activation with TMS
• Test motor pathways

Loo, Taylor et al, 2008
TMS – Clinical Application of Investigative Use

- Speech arrest (spontaneous, read aloud) – TMS to L facial motor cx. (writing, singing, comprehension, repetition, naming spared)
- Singing – loss of melody (n=2/8) – TMS to R facial motor cx
- Cf. Wada test
Therapeutic Applications of rTMS in Psychiatric Disorders

- Depression – 2 definitive RCTs:
  - O’Reardon et al, 2007
  - George et al, 2010
Neurostar TMS Trial Design

Randomized, Double-blind, Sham-Controlled

Phase I
Drug-Free Lead-In
7-10 days

Phase II
Acute Treatment Phase
6 weeks

Phase III
Taper Phase
3 weeks

Neurostar TMS Therapy
(N=155)
- 120% MT
- 10 pulses per second
- 4 sec on-time/26 sec off-time
- 3000 pulses/session

Sham (N=146)
- <10% field exposure at cortex

Primary Efficacy @ 4 weeks
Secondary Efficacy @ 6 weeks
Durability of Effect @ 9 weeks

[+ Open-label AD Mono-Rx]

O’Reardon et al, Biological Psychiatry, 2007
Effect on Continuous Outcomes
MADRS and HAMD24 Rating Scales

MADRS Total Score
Baseline to Endpoint Change

Baseline | Week 2 | Week 4 | Week 6
---|---|---|---
Baseline | Week 2 | Week 4 | Week 6

- Neurostar TMS Therapy
- Sham

HAMD24 Total Score
Baseline to Endpoint Change

Baseline | Week 2 | Week 4 | Week 6
---|---|---|---
Baseline | Week 2 | Week 4 | Week 6

- Neurostar TMS Therapy
- Sham

* P < 0.05, LOCF analysis

...P-Values with correction for baseline imbalance in Total MADRS Score
[N=6 patients censored w/Total MADRS < 20 at baseline]

O’Reardon et al, Biological Psychiatry, 2007
Neurostar TMS Therapy Shows a Durable Effect

**MADRS Response and Remission Rates**

**MADRS Response Rates**
(50% Improvement from Baseline)

- (TMS Monotherapy)
- (TMS + Open-label AD Medication)

**MADRS Remission Rates**
(MADRS Total Score <10)

- (TMS Monotherapy)
- (TMS + Open-label AD Medication)

**Neurostar TMS Therapy improves response and remission rates during taper phase compared to sham treatment**

Analyses reported for intent-to-treat evaluable population
Comparative Analysis of Effect Size: NeuroStar TMS Therapy (Study 101--Week 4) vs Meds

Khan, 2000

- NeuroStar TMS Therapy Study 101 (HAMD17)
  - Overall Population (N=301): 0.55
  - 1 AD Failure Subgroup (N=164): 0.83

- Pharmaceutical Antidepressants (HAMD17)
  - Pharmaceuticals (Khan): 0.49
Schutter et al, 2009
Meta-analysis

- 30 double-blind, sham controlled, parallel trials, N= 1164
- High frequency left prefrontal rTMS
- Clearly superior to sham
- Overall effect size 0.39
Slotema et al, 2010
rTMS in depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges' g</th>
<th>P Value</th>
<th>Hedges' g and 95% CI</th>
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<td>Mosimann et al, 2004</td>
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<td>Berman et al, 2000</td>
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<tr>
<td>Weighted effect size, mean</td>
<td>0.545</td>
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Meta-Analysis of rTMS Versus ECT in the Treatment of Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges'g</th>
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<tr>
<td>Eranti et al, 2007</td>
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<td>Pridmore et al, 2000</td>
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<td>Grunhaus et al, 2000</td>
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<td>Grunhaus et al, 2003</td>
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<td>Janicak et al, 2002</td>
<td>-0.202</td>
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<td>Rosa et al, 2006</td>
<td>-0.102</td>
<td>.760</td>
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<tr>
<td>Weighted effect size, mean</td>
<td>-0.474</td>
<td>.004</td>
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</tbody>
</table>
Safety issues

- Pain / discomfort, headache
- Seizures ! (screening and Mx of risk factors, stim parameter guidelines)
- Hearing – need earplugs
- Neuropsychological – no lasting effects
- Manic upswing
- Precipitate delusions (n=1)
- Pregnancy – case reports safe
- Long term EMF effects ?
- ↑ gray matter ?
Predictors of Response

Neuronetics Trial: Lisanby et al, 2009

- Better response if:
  - Less treatment resistance
  - Shorter duration current episode
  - No anxiety disorder
  - Higher baseline depression score

Other reports – better response in:

- Younger
- Non psychotic depression

? Baseline pattern of cerebral metabolism
TMS & Auditory Hallucinations

Meta-analysis: Tranulis et al, 2008 (Can J Psychiatry)

• 10 RCT (N=232+)
• Low frequency rTMS, L temporoparietal cx
• Effect size 0.5
• rTMS and clozapine = only Rx’s with evidence efficacy for treatment refractory psychotic sx’s

• See also Meta-review of rTMS in schizophrenia, Matheson et al, 2010
Role of TMS in Neuropsychiatric Disorders

- RANZCP Position Statement on TMS (Oct 2013)
- FDA, other countries
- Depression
- Schizophrenia
- Other disorders (OCD, PTSD, conversion disorder, pain, tinnitus, migraine, neurorehabilitation, mild cognitive impairment)
Strategies to Enhance Efficacy

Eg Depression - mostly L PFC high frequency, R PFC low frequency

- Other stimulation sites – eg parietal, temporal, deep?
- Stimulus parameters – intensity, frequency (Hz), waveform
- Vary stimulus parameters over session/course
- Frequency of treatment sessions
- Priming
- Adjunctive to other treatments eg meds, psychological Rx
- Tailor rTMS to baseline metabolic pattern?

For review of strategies, see Loo et al, 2005
TMS: focal & superficial stimulation

Limbic-Cortical Dysregulation Model

attention-cognition-context

CORTEX

Placebo

SUBCTX

Drug

LIMBIC

Autonomic-circadian internal milieu

CBT

mood state

Self

salience

gating

reward

mOF11

mF9-10

dF9-46

pmF6

par40

aCg24

dOF9-24

vACC24

PCC23

MCC24

C. calosum

VMF10

SCC2425

OF11

AHc

BS

Hc

Hth

Cg25

p-ins

amyg

a-ins

Drug
rTMS works in depression but efficacy may be limited by physics of magnetic field. (Further research into approaches to rTMS)

Other strategies?

- Deep TMS
- Magnetic Seizure Therapy (MST)
- Deep Brain Stimulation
- Transcranial Direct Current Stimulation (tDCS)
FIGURE 1. Sketch of the H1-coil ("Hesed") near a human head. The coil position and orientation shown in the figure is designated for activation of structures in the prefrontal and orbitofrontal cortical and subcortical regions, with left hemispheric preference.

Roth et al, 2007
Magnetic Seizure Therapy

MagPro MST
N=20.
ECT: RUL @ 3 ST, 0.5 ms PW
MST: 6/10 responders, 3/10 remitters
ECT: 4/10 responders and 4/10 remitters
Cognition: slight decrease anterograde memory, verbal fluency, no dif b/w groups
Kayser et al, 2011
Transcranial Direct Current Stimulation: History

- Largus, Pliny, Galen (1-2C) – torpedo electric fish: induce sudden transient stupor
- Galvani, Volt – scientific study of effects of electrical stimulation
- Aldini (nephew of Galvani) 1804 – first report of modern use of electrical stimulation to treat mental disorders

Figure 1. (A) Details from plate V in Aldini J. *Essai théorique et experimental sur le galvanisme*. It illustrates the treatment of Luigi Lanzarini with galvanism applied to the head (figure from Parent 2004). (B) The effect of transcortical DC current on spontaneous activity (top line) and EEG (lower line) in the motor cortex. (a) Control condition. (b) During 1000 µA anodal current. (c) Control condition, 20 seconds after (b). A clear increase in neuronal firing can be seen in (b) during anodal stimulation (adapted from Fig. 1; Creutzfeldt and others 1962). (C) The aftereffects of anodal stimulation on the peak amplitude (mV) of the evoked potential. Between the 12th and 20th minute, a current of 25 µA was passed (figure 4, Bindman and others 1964).
Transcranial Direct Current Stimulation (tDCS)

1-2 mA, 9V

Direct current: anode (+)
cathode (-)

Alternating current (AC)

Direct Current (DC)

DC current applied via pair of electrodes; current induced in conductor
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 – Neuronal Effects

Membrane polarisation:
  • anodal – depolarise (↑ neuronal excitability)
  • cathodal – hyperpolarise (↓ neuronal excitability)

Effects demonstrated:
  • Brain imaging - fMRI, PET-O15
  • Behavioural studies - alter functioning: motor, visual, frontal brain regions
**tDCS Compared with TMS**

- Less focal
- Mild stimulation: polarises membrane but not to extent of inducing action potential
- Both cause lasting changes in cortical excitability

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Sadleir et al, 2010
Applications of tDCS

Therapeutic in neuropsychiatric disorders:

- Depression
- Schizophrenia
- Pain
- Migraine
- Rehabilitation after stroke, traumatic brain injury
- Tinnitus

Cognitive effects

- Cognitive enhancement/modulation – during tDCS
- Cognitive modulation – immediately after tDCS
- Combine with CBT, cognitive training.
- Cumulative effects of repeated sessions?
Meta-analysis of tDCS placebo-controlled trials in depression

Effect size = 0.743

Kalu et al, 2012
Loo et al, 2012
Br J Psychiatry

N=64

Randomly Assigned

Active

Sham

Blind 3 weeks (15 sessions)

Open 3 weeks (15 sessions)

Sham tDCS
Active tDCS
Loo et al
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 et al, 2013 “SELECT” Trial

Phase 1: Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study

- Screening
- Baseline assessment
- Daily stimulation (10 sessions)
- Week 2 assessment + stimulation
- Week 4 assessment + stimulation
- Week 6 assessment + stimulation

= tDCS session
Optimising Stimulation: Combining with Medications
Brunoni et al, 2013 - Depression

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response (6/52)</th>
<th>Remission (6/52)</th>
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<tbody>
<tr>
<td>Sham tDCS + placebo</td>
<td>5%</td>
<td>4%</td>
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<tr>
<td>Sham tDCS + sertraline 50mg</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Active tDCS + placebo</td>
<td>13%</td>
<td>12%</td>
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<tr>
<td>Active tDCS + sertraline 50mg</td>
<td>19%</td>
<td>14%</td>
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## Side Effects
(Loo et al, 2012)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Active Condition (N=33)</th>
<th>Sham Condition (N=31)</th>
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<tbody>
<tr>
<td>Skin redness</td>
<td>30</td>
<td>29</td>
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<tr>
<td>Tingling</td>
<td>26</td>
<td>27</td>
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<tr>
<td>Itching</td>
<td>23</td>
<td>22</td>
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<tr>
<td>Burning/Heating sensation</td>
<td>14</td>
<td>7</td>
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<td>Pulsing sensation</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Headache</td>
<td>12</td>
<td>10</td>
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<td>Dizziness/lightheadedness</td>
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<td>6</td>
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<td>Fatigue</td>
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<td>4</td>
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<td>Nausea</td>
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### 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
- Right ear ache (N=1); ringing in ears (N=1)
- N=0

### Related to neck
- Neck soreness (N=1)
- Stiffness in neck and shoulders (N=1); tingling on neck (N=1)
- N=0

### 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)
tDCS Acutely Enhances Attention And Psychomotor Speed  
Cognitive tests results immediately before and after DCS sessions 1 and 15: sham vs. active

<table>
<thead>
<tr>
<th>Measure</th>
<th>Main effect: group</th>
<th>Main effect: Time</th>
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<td>(F)</td>
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<tr>
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<td>Simple RT (msec)</td>
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<tr>
<td>Choice RT (msec)</td>
<td>0.14</td>
<td>0.71</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Loo et al, 2012
“Maintenance” tDCS

Weekly x 3 months → 84% no relapse
Then fortnightly x 3 months → 51% no relapse

Martin et al, 2013
Brunelin et al, 2012
RCT in Schizophrenia

FIGURE 1. Effect of Active and Sham Transcranial Direct-Current Stimulation (tDCS) on the Severity of Auditory Verbal Hallucinations

N=30
Schizophrenia
2mA, 20 mins
2x daily
5 days
Anode: LDLPFC
Cathode: T3-P3
Strategies to optimise tDCS

- Synergy with pharmacotherapy
- Stimulus parameters
  - Intensity
  - Duration
  - Number & Frequency sessions
  - Alter stimulus over course?
- Electrode number/ size/ type. “High Definition tDCS”
- Electrode placement
- Novel stimulus types eg random noise stimulation, alternating current stimulation
- Priming (next slide)
tDCS Priming of rTMS

Lang et al, 2004
May the flow be with you!

Flow is completely focused motivation. Your emotions are not just channeled, but positive, energized and focused on the task. When you feel joy, rapture, satisfaction, then you are focused.

Want to be the best?
When the US Army train snipers, they use transcranial direct current stimulation. Now you can too.

Accelerated Learning
Start your head!
The first non-military transcranial direct current stimulation headset available to the public.
Conclusions - tDCS

- tDCS: promising therapeutic effects in depression... schizophrenia, other?
- Mild stimulation - excellent safety profile
- Risk hypomania, especially if bipolar? Mood stabilisers prevent manic upswing?
- Risk skin burns – technique important
- Other side effects - minor
- Acute neuropsychological enhancement?
- Well tolerated, portable, practical
- Further strategies to optimise treatment
The Future?

Psychological therapy/ Medications

↓

Transcranial Magnetic Stimulation (TMS)

? Transcranial Direct Current Stimulation (tDCS)

↓

ECT

? Magnetic Seizure Therapy (MST)

↓

? Vagal Nerve Stimulation (VNS)

? Deep Brain Stimulation (DBS)
Resources/Training:

- **STP Registrar position**
  @ Black Dog Institute

- **Advanced ECT course**
  Wesley Hospital, Sydney

- **TMS course**
  28-29 Nov 2014, Sydney

- **RANZCP ECT and Neurostimulation Special Interest Group (ENSIG)**

- **International Society for ECT and Neurostimulation**
  www.isen-ect.org
  Annual Conference 4 May 2014, New York
  Colleen.loo@unsw.edu.au

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**2-Day ECT General Course**
27-28 March 2014

**1 Day ECT Advanced/Refresher**
28 March 2014

Course Director: Professor Colleen Loo
Wesley Hospital, SYDNEY

The Black Dog Institute presents
**1-Day Certificate Course in Transcranial Magnetic Stimulation (TMS) – Sydney**
Save The Dates

Call for Abstracts & Oral Poster Presentations Begins December 2013
Online Registration Opens February 2014

Check our website frequently, as information will be updated as it becomes available: www.isen-ect.org
Questions? Please email: contact@isen-ect.org

May 3rd-5th
Two Thousand Fourteen
NYU Kimmel and Global Centers
Washington Square Park
New York, NY

Black Dog Institute
Psychiatry Registrar
Full time RANZCP STP Accredited Position
Mood Disorders & Neurostimulation
The Black Dog Institute, Randwick, Sydney.