Non-invasive Stimulation of the CNS: Application in Neuropsychiatric Disorders

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Deputy Director, MAPrc
Why new approaches for Neuropsychiatric Disorders?

- Neuropsychiatric disorders are:
  - Common
  - Highly disabling
  - Costly to treat
  - Frequently unable to be treated or respond poorly to treatment
**STAR*D**

- Citalopram then one of 4 levels of other treatments
- >2800 patients
- ~40% responded at level 1
- > 30% patients failed to respond across multiple levels
Drug Development in Psychiatry

• "This is hardly a rich pipeline,"

• "It suggests a sad dearth of ideas and involves lots of attempts at patent extensions and new indications for old drugs."

• Steven Hyman, former NIMH director, Provost Harvard
Developing biological treatments in psychiatry

<table>
<thead>
<tr>
<th>Non convulsive</th>
<th>Convulsive</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>tDCS</td>
<td>MST</td>
<td>Vagal nerve stimulation (VNS)</td>
</tr>
<tr>
<td>TMS</td>
<td>ECT</td>
<td>Deep brain stimulation (DBS)</td>
</tr>
<tr>
<td>Deep TMS</td>
<td></td>
<td>Novel neurosurgeries (e.g. Cortical Stimulation)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
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</tbody>
</table>

Other – optogenetics, ultrasound stim

Less invasive  More invasive
Developing biological treatments in psychiatry

- Circuit based model of psychiatric illnesses
- Stimulation at one point in circuit will modify activity at other points in circuit
  - Modify distant regions by activation through direct stimulation of projecting neurones
  - Modify distant regions by altered functional inputs
  - Modify the strength of connections between regions
- Need to identify if there are optimal target points
Depression Circuitry

Limbic-Cortical Dysregulation Model

- Attention-cognition-context
  - CORTEX
  - Placebo
  - SUBCTX
  - Drug
  - LIMBIC

- Mood state
  - CBT
  - Surgery

- Reward
  - mOF11

- Salience
  - mF9-10
  - rCg24

- Autonomic-circadian internal milieu
  - Cg25
  - Hth
  - Hc
  - a-ins
  - amyg
  - p-ins

Depression Circuitry: Putative Targets

- Epidural cortical stimulation
- Magnetic and electrical stimulation
- Deep brain stimulation
- Vagal nerve stimulation

Brain regions: PFC, Cg25, NAc, LC, VTA, Hippoc, Hypoth
Transcranial Magnetic Stimulation
rTMS as a Therapeutic Tool in Depression

• Initial case reports in early 1990’s: vertex then Left DLPFC stimulation
• First controlled studies mid 90’s [Pascual-Leone, 1996] [George, 1997]
• Initial studies for 1 week, cross over designs
• Gradually longer duration and increased pulse number
• Predominant focus on Left DLPFC
Evidence for Efficacy of Left PFC rTMS in adults

- 30+ clinical trials
- Numerous meta-analyses
  - >1000 patients
  - Effect sizes 0.39 – 0.71
- Greater effects in more recent studies
  - Longer duration of treatment
  - Increased intensity
  - Increased pulse number

Schutter et al 09
Left and Right Sided rTMS in Depression

60 patients, 4 weeks: High freq left versus low freq right versus placebo

Response to rTMS


Fitzgerald et al. Archives Gen Psych 2003
A randomized controlled trial of sequential bilateral rTMS for treatment resistant depression

50 patients, 6 weeks: Sequential Bilateral rTMS versus placebo

<table>
<thead>
<tr>
<th>Response: MADRS (HAMD)</th>
<th>Response</th>
<th>Remission</th>
<th>Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>11* (13)</td>
<td>9**</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>2* (2)</td>
<td>0**</td>
<td>2</td>
</tr>
</tbody>
</table>

Fitzgerald et al American J Psychiatry, 2006
Does targeting matter?

Herwig et al. 2001
Enhanced response to rTMS with improved treatment targeting

Change in MADRS Score

Sign time vs group

p<0.05
DTI before and after rTMS for MDD

rTMS treatment responders
- Broad regions of increased cortical – subcortical connectivity
rTMS and Auditory Hallucinations

- Left T-P cortical focus
- 1 Hz – reduce local ‘over active’ cortical activity

Hoffman et al 2003
- Reduced self-report social symptoms in active (p<.05) but not sham (n.s.) (RAADS; Ritvo et al., 2008)
rTMS Status

• FDA approved US 2008
• Clinical programs developing rapidly internationally
• First public clinic in Australia to be established at the Alfred, late 2011
• Unanswered questions:
  – Is the superficial PFC the optimal site of stimulation
  – Use in maintenance treatment
  – Individualisation of treatment
  – Clinical predictors of likely response
  – Optimal characteristics of equipment
Developing biological treatments in psychiatry

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Convulsive
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- ECT

Surgical
- Vagal nerve stimulation (VNS)
- Deep brain stimulation (DBS)
- Novel neurosurgeries (e.g. Cortical Stimulation)

Less invasive

More invasive

Medication

Brain Stimulation in Psychiatry

- Medication
- Novel neurosurgeries (e.g. Cortical Stimulation)
- Convulsive and less invasive
- Deep brain stimulation (DBS)
- More invasive
MST Background

• Electroconvulsive Therapy (ECT)
  – Is commonly used
    (e.g. 17,414 treatments (1706 pts) in Victoria in 2006)
  – Is highly effective BUT

  – Can result in substantial cognitive side effects and has considerable stigma
MST

• Seizure induction via high frequency magnetic stimulation
  – no skull resistance → better control over the site of seizure onset
  – No direct spread of current to subcortical brain regions
MST

• First generation studies (40-60 Hz stimulation)
  – Demonstrated safety in primates
    • Histological analysis
    • Cognitive performance
  – Established feasibility of seizure induction in humans and antidepressant potential
    • However, limits in stimulator capacity
Second Generation MST (100 Hz)

- Increased stimulator capacity to 100 Hz
  - Enhanced capacity for seizure induction
  - Possibility of dose titration
- Demonstrated to date
  - Safety and cognitive benefits over ECT
  - Antidepressant effects
Clinical Response to 100 Hz MST (n=10)

Kayser et al 2008
MST at MAPrc

- Pilot study – 13 patients
  - clear antidepressant effects
  - no cognitive side effects

<table>
<thead>
<tr>
<th>Clinical Scales</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS Pre Treatment</td>
<td>38.2</td>
<td>6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADRS Post Treatment</td>
<td>26.4</td>
<td>13.6</td>
<td>3.3</td>
<td>0.007</td>
</tr>
<tr>
<td>HAMD Pre Treatment</td>
<td>26.7</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMD Post Treatment</td>
<td>19.2</td>
<td>7.5</td>
<td>3.3</td>
<td>0.008</td>
</tr>
<tr>
<td>BDI Pre Treatment</td>
<td>35.8</td>
<td>11.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI Post Treatment</td>
<td>26.7</td>
<td>12.9</td>
<td>3.0</td>
<td>0.012</td>
</tr>
<tr>
<td>BPRS Pre Treatment</td>
<td>20.7</td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS Post Treatment</td>
<td>13.6</td>
<td>7.0</td>
<td>2.8</td>
<td>0.019</td>
</tr>
</tbody>
</table>

- Current – randomised ECT – MST trial
Developing biological treatments in psychiatry

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- Deep TMS

Convulsive
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- ECT

Surgical
- Vagal nerve stimulation (VNS)
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- Novel neurosurgeries (e.g. Cortical Stimulation)

Less invasive

More invasive
Transcranial Direct Current Stimulation

- tDCS involves the application of a weak electrical current (1-2mA) to the scalp via two surface electrodes, an anode and a cathode.
- tDCS does not induce neuronal action potentials – it polarises the underlying neuronal tissue.
- Causing modification of spontaneous neuronal activity by a tonic de- or hyper-polarisation of resting membrane potentials.
  - Anode = hyperpolarisation leading to increases in neuronal activity.
  - Cathode = depolarisation leading to decreases in neuronal activity.
Depression
• 5 sham controlled trials to date of tDCS to the DLPFC; all but one demonstrated significant therapeutic benefits of tDCS.

Schizophrenia
• Preliminary evidence of capacity to reduce auditory hallucinations

Cognitive Function
• Prefrontal tDCS enhances working memory
Developing biological treatments in psychiatry

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Medication

Less invasive

More invasive
DBS (Deep Brain Stimulation)
Brain Stimulation in Psychiatry

- Putamen
- Internal capsule
- Nucleus accumbens
DBS
Subcaudate DBS (n=20)

Mayberg et al 2008
Ventral Capsule / Ventral Striatal DBS (n=15)

Table 4. Summary of SAEs

<table>
<thead>
<tr>
<th>Event</th>
<th>No. Patients (%)</th>
<th>No. SAEs (%)</th>
<th>Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical and Procedural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain or discomfort at incision/implant sites</td>
<td>1 (6.7)</td>
<td>1 (4.0)</td>
<td>Yes</td>
</tr>
<tr>
<td>Device</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead fracture</td>
<td>1 (6.7)</td>
<td>1 (4.0)</td>
<td>Yes</td>
</tr>
<tr>
<td>Mood and Anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidality</td>
<td>1 (6.7)</td>
<td>1 (4.0)</td>
<td>No</td>
</tr>
<tr>
<td>Suicidality/Increased depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomania</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed bipolar state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope (medication or DBS)</td>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Syncope (activity/dehydration)</td>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>1 (6.7)</td>
<td>1 (4.0)</td>
<td>No</td>
</tr>
<tr>
<td>Lung calcification</td>
<td>1 (6.7)</td>
<td>1 (4.0)</td>
<td>No</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1 (6.7)</td>
<td>1 (4.0)</td>
<td>No</td>
</tr>
<tr>
<td>Total</td>
<td>6 (40.0%)</td>
<td>25 (100%)</td>
<td>—</td>
</tr>
</tbody>
</table>

SAEs, serious adverse events; DBS, deep brain stimulation.

Malone et al 2008
Long Term Responses

- Patient 1: partial responder
- Patient 2: clear responder: full remission of symptoms, sustained for ~24 months
Long Term Responses

• Patient 3: Partial response
• Patient 4: Partial early response, adjustment ongoing
  – “I am no longer feeling suicidal for the first time since I was eleven”
  – “I do feel better in myself and have cleaned both the kitchen and bathroom entirely for the first time in a long time.”

• Patient 5: undergoing programming
Funding sources
NHMRC
Australia Research Council
NARSAD
Stanley Medical Research Institute
Beyond Blue
Victorian Neurotrauma Initiative
Alfred Foundation
Monash University