Modulation of the Neural Circuitry Underlying Neuropsychiatric Disorders

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Objectives

• Introduce the Concept of Modulating Psychiatric Symptoms at the Level of the Circuit

• Discuss Some of the Currently Utilized Approaches

• Discuss Some of the Emerging Interventional Techniques
Beyond Neural Cubism: Promoting a Multidimensional View of Brain Disorders by Enhancing the Integration of Neurology and Psychiatry in Education

Joseph J. Taylor, Nolan R. Williams, MD, and Mark S. George, MD

2014
The Way in Which We Conceptualize Psychiatric Disorders Dictates the Treatment Advances
Neuropsychiatric Disorders are Disorders of Distributed Neural Networks

Neurology:
• Parkinson’s Disease
• Tourette’s syndrome

Psychiatry:
• Obsessive-Compulsive Disorder
• Depression
• BPAD
Brain Interventions Start In Neurology and Transition to Psychiatry

NON-INVASIVE MAGNETIC STIMULATION OF HUMAN MOTOR CORTEX

SIR,—This note describes a novel method of directly stimulating the human motor cortex by a contactless and non-invasive technique using a pulsed magnetic field. Merton et al.1 have drawn attention to the electrical stimulation of human brain and spinal cord using external electrodes on the skin. Interesting results have been reported on the cortical threshold in Parkinson’s disease,2 on pyramidal conduction velocity in multiple sclerosis,3 and on pelvic neuropathy related to faecal incontinence.4

Proceedings of the Meeting of the American Society for Stereotactic and Functional Neurosurgery, Montreal 1987

Combined (Thalamotomy and Stimulation) Stereotactic Surgery of the VIM Thalamic Nucleus for Bilateral Parkinson Disease

A.L. Benabid a, P. Pollak b, A. Louveau a, S. Henry a, J. de Rougemont b
Interventional Tools
Deep Brain Stimulation (DBS)

• Video
Motor Disorders Can Be Observed

• Video
Brain Circuits Can Be Modulated Effectively with Neurotechnology

- Video
Psychiatric Symptoms Can Be Recorded in the Brain

- Video
Stimulation-Induced Mood Change

Haq, 2011
Mood Can Be Turned Up Exogenously

- Video
EpCS for TRD
Hot Off the Press

Brain Stimulation

Five-Year Follow-Up of Bilateral Epidural Prefrontal Cortical Stimulation for Treatment-Resistant Depression

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# Sample Demographics

<table>
<thead>
<tr>
<th>Sample demographics.</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>4 F/1 M</td>
</tr>
<tr>
<td>Diagnosis recurrent</td>
<td>MDD</td>
<td>BPAD depressed</td>
<td>BPAD depressed</td>
<td>Recurrent MDD</td>
<td>Recurrent MDD</td>
<td>3 MDD/2 BPAD</td>
</tr>
<tr>
<td>Current age</td>
<td>42</td>
<td>57</td>
<td>47</td>
<td>31</td>
<td>45</td>
<td>44.4 (±9.7)</td>
</tr>
<tr>
<td>Length of illness (years)</td>
<td>17</td>
<td>32</td>
<td>31</td>
<td>16</td>
<td>32</td>
<td>25.6 (±8.3)</td>
</tr>
<tr>
<td>Current depressive episode (months)</td>
<td>N/A</td>
<td>N/A</td>
<td>84</td>
<td>8</td>
<td>N/A</td>
<td>46 (±53.7)</td>
</tr>
<tr>
<td>HRSD score (24 item)</td>
<td>23</td>
<td>33</td>
<td>33</td>
<td>29</td>
<td>24</td>
<td>28.4 (±8)</td>
</tr>
<tr>
<td>Previous brain stimulation therapies</td>
<td>ECT, VNS, TMS</td>
<td>ECT, VNS, TMS</td>
<td>ECT</td>
<td>VNS, TMS</td>
<td>None</td>
<td>4 yes/1 no</td>
</tr>
<tr>
<td>Past psychotherapy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>All</td>
</tr>
<tr>
<td>Family history of depression</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>4 yes/1 no</td>
</tr>
<tr>
<td>Number of psychiatric treatments in current depressive episode</td>
<td>12</td>
<td>18</td>
<td>6</td>
<td>8</td>
<td>5</td>
<td>9.8 (±5.3)</td>
</tr>
<tr>
<td>Current ATHF</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5.8 (±2.05)</td>
</tr>
<tr>
<td>Number of psychotropics at baseline</td>
<td>9</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>7</td>
<td>6 (±2.23)</td>
</tr>
<tr>
<td>Number of psychotropics at 5 years</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4.4 (±1.34)</td>
</tr>
</tbody>
</table>

ATHF, Antidepressant History Treatment Form; BPAD, bipolar affective disorder; ECT, electroconvulsive therapy; F, female; HRSD, Hamilton Rating Scale for Depression; M, male; MDD, major depressive disorder; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation.

\(^a\) Excluding psychotherapy.

\(^b\) Mean (±SD).
EpCS: Two Cortical Stimulation Sites

- The frontopolar (FP-BA 10) and dorsolateral (DL-BA 9/46) prefrontal cortices (PFC) play distinct, yet complementary roles in the integration of emotional and cognitive experiences (Nahas 2010).

- One or both of these two cortical areas appear to be central to the efficacy of deep targets (Williams 2014).

- Our study utilized bilateral dorsolateral prefrontal and the frontopolar cortex as stimulation sites (Nahas 2010).
EpCS: Dorsolateral Prefrontal Cortex

- Established cortical stimulation site for non-invasive brain stimulation (transcranial magnetic stimulation) (George 2010).
- In TRD, L DLPFC hypoactivity is associated with negative emotional judgment and right DLPFC hyperactivity is linked to attentional modulation (Grimm 2008).
- DLPFC has been demonstrated to be anti-correlated with subcallosal cingulate (SCC) (Fox 2012).
EpCS: Frontopolar Cortex

• The medial prefrontal cortex has been implicated in animal (Covington 2010) and human studies (Downar 2013) as playing a central role in the pathogenesis of depression as well as in its recovery.

• There is a consistent finding of increased resting-state activity in the frontopolar cortex (FPC) in patients with depression (Fitzgerald 2008).

• Effective SCC DBS requires functional connection to the FPC (Riva Posse 2014).
Modified Mayberg Target
Epidural Prefrontal Cortical Stimulation

• We implanted five adults with four stimulation paddles over dura (between dura and skull) covering FP and DLPFC.

• These five individuals had failed an average of 5.8 antidepressants prior to implant with three who had failed VNS and four who had failed or were unable to tolerate ECT.

• All subjects received ongoing clinical assessments at baseline, seven-month (7mo), one-year (1yr), two-year (2yr), and five-year (5yr) time points.
Epidural Prefrontal Cortical Stimulation

- All patients have continued to tolerate the therapy.
- There were five serious adverse events: one paddle infection and four device malfunctions, all resulting in suicidal ideation and/or hospitalization with three involving the battery (2-drain, 1-turned off) and one involving connectors.
- Three of five (60%) subjects continued to be in remission at 5yr.
- One of the non-responders converted to a responder (80%) once a technical error was discovered.
Average HAMD Scores

![Bar chart showing average HAMD scores at different time points: Base, 7 months, 1 year, 2 years, and 5 years. The chart indicates a decrease in scores over time.]
Average HAMD Scores

<table>
<thead>
<tr>
<th>Time</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative baseline</td>
<td>23</td>
<td>33</td>
<td>33</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Week of EpCS activation</td>
<td>22</td>
<td>32</td>
<td>38</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>2 weeks post-EpCS activation</td>
<td>14</td>
<td>36</td>
<td>38</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>4 months</td>
<td>2</td>
<td>33</td>
<td>23</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>7 months</td>
<td>4</td>
<td>3</td>
<td>19</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>5 years</td>
<td>7</td>
<td>1</td>
<td>38</td>
<td>27</td>
<td>8</td>
</tr>
</tbody>
</table>

EpCS, epidural prefrontal cortical electrical stimulation.
The First Circuit-Level Intervention for a Neuropsychiatric Disorder
Transcranial Magnetic Stimulation

- Transcranial magnetic stimulation (TMS) is a non-invasive procedure that uses magnetic fields to stimulate cortical neurons.

- In 2008, the FDA approved rTMS as a treatment for adults with MDD who “have not responded to a single antidepressant medication in the current episode.”
Transcranial Stimulation

• Video
rTMS Effects on Brain Circuits

A) BOLD Signal following Dorsolateral PFC stimulation (F3)
Importance of Accelerating and Compressing rTMS Treatment

![Graph showing the comparison between traditional rTMS and accelerated rTMS in terms of treatment duration. The graph indicates that accelerated rTMS has a shorter length of treatment.]

Courtesy of J Pannu
aTBS Piloted in 2 Patients

![Graph showing HRSD-6 Score vs Days from first treatment for Patient 1 and Patient 2.](image)

Courtesy of J Pannu
Accelerated TMS Effects on SCC
Δ in HDRS to Δ in SCC Activity

Figure 4. Scatter plot of the ranked order effect size in the % change of HDRS scores (Y) in combination with the ranked order of % of sgACC CMRglc (X), calculated between T₀ and T₂. The line represents the least squares fit to the data.
Acknowledgements

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Contact:
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References

References


References


