Magnetic Seizure Therapy in Treatment Resistant Depression

Zafiris ‘Jeff’ Daskalakis, MD, PhD
Chair, Department of Psychiatry
UC San Diego
Major Depressive Disorder Disease Burden

- Millions across the globe are affected annually
- Functional impairment equal to or surpassing that of chronic medical conditions
- Leading cause of disease burden world-wide
- Economic burden on society: 200 billion dollars per year


Some Statistics on Resistant Depression

• 40-50% patients with depression do not respond (i.e., <50% reduction) to medication (Triverdi et al 2006)

• Remission was about 33 percent in STAR*D (Trivedi et. al 2006)

• These patients are twice as likely to be hospitalized

• Receive up to 3 times more psychiatric medications

• 19 times the mean total medical costs of non-treatment-resistant depression

• For remitters up to 40% relapse at 2 years (Bolland and Keller, 2009)
Major Depressive Disorder
Suicide

- Mental illness can cut 10 to 20 years from a person’s life expectancy.
- Nearly 40,000 Americans die by suicide each year – an average of more than 100 suicides a day.
- More than half of suicides involve people 45 and older.
- The World Health Organization (WHO) reports that: In the last 45 years suicide rates have increased by 60% worldwide.
- After accidents, suicide is the second leading cause of death among those aged 15-34 (male and female).
Predictors of change in listlessness, psychic paresis, and loss of interest; significantly associated with number of suicide attempts:

- OR = 0.18 (p > 0.01)
- Δ = 0.29 (p > 0.001)
- Δ = 0.26 (p > 0.001)

**Scale for Suicide Ideation**

- Absent
- Feels life is not worth living
- Wishes he/she were dead or any thoughts of suicide
- Denies being ill at all

**Total Score:** [29]

This scale is in the public domain.
One of the most effective treatments in medicine........

- Remission (i.e., no Depression): 60-80 percent
- Remission i.e., no suicidality: >80 percent

Controversies

• Common Side effects: disorientation, retrograde and anterograde amnesia

• Uncommon: cardiac arrest, stroke, aspiration, prolonged seizures, fractures, malignant hyperthermia, death (1/10,000)

Only 1% of patients with resistant depression receive ECT—fear, stigma, cognitive side effects
Magnetic Seizure Therapy (MST)

- ECT side effects: shunting of electrical activity and higher energies
- MST involves no shunting: minimal involvement of brain structures related to memory
- Pulse width of MST is closer physiologically to activate neurons

Figure 1. This figure demonstrates that (A) MST produces a seizure with much lower e-field strength (cooler colors) compared to (B) right unilateral ECT or (C) bilateral ECT which requires much higher e-field strength (hot colors) to produce an adequate seizure. Additionally, the skull shunts the electrical field making the electrical field from ECT largely non-focal. It is postulated that more focality and lower e-field strength contributes to the preservation of cognitive performance of MST compared to ECT. Modified from Fig 3, Deng et al. 2011.
### ECT vs MST

<table>
<thead>
<tr>
<th></th>
<th>ECT</th>
<th>MST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse Duration</strong></td>
<td>Ultra-brief (i.e., 0.3-0.4 msec), standard (1 msec)</td>
<td>Ultra-brief (0.3 msec)</td>
</tr>
<tr>
<td><strong>Method of seizure induction</strong></td>
<td>Electric</td>
<td>Magnetic</td>
</tr>
<tr>
<td><strong>Target location</strong></td>
<td>Bifrontal, bitemporal, right unilateral</td>
<td>Frontal, vertex</td>
</tr>
<tr>
<td><strong>Localization</strong></td>
<td>Non-focal due to skull shunting and volume conduction</td>
<td>Focal</td>
</tr>
</tbody>
</table>

Fig. 2. (a) Descriptive statistics of E-field magnitude relative to neural activation threshold at current of 800 mA for BL, BF, and RUL ECT, 612 mA for FEAST, 500 mA for FM ECT, and 100% stimulator output for CIRC MST coil configuration. Boxes indicate the interquartile range (25th to 75th percentile) with the median marked by a horizontal black line. Whiskers delimit approximately the 99.3 percentile of the E-field distribution. Outliers beyond this range are plotted in green. (b) Percentage brain volume stimulated above neural activation threshold ($E \geq E_a$).

Lee et al. 2014 IEEE
CAMH Study

- Pilot study of Frontal MST at 3 different stimulation frequencies
  - 100 Hz, 60Hz, 50 Hz and 25 Hz
  - Treatment studies in humans have used 100 Hz, in primates 22 Hz shown to be associated with optimal seizure production

- Patients treated in an open label manner
  - Primary DVs of interest included remission and response rates:
    - In pts completing more than 3 treatments
    - In completers (i.e., completed the protocol with target of either remission or 24 treatments)
  - Cognition evaluated at baseline an at the end of treatment
  - Neurophysiology used as a predictor of treatment response

- Neurophysiology included TMS combined with EEG to measure cortical inhibition from the DLPFC in patients with TRD
Assessed for eligibility 
(n = 140)

Enrolled (n = 108)

Allocated to 100 Hz MST 
(n = 26)

Allocated to 50/60 Hz MST 
(n = 37)

Allocated to 25 Hz MST 
(n = 45)

Excluded (n = 32)

• Did not meet inclusion/exclusion criteria (n = 24)
• Declined to participate/Withdraw prior to first treatment (n = 6)
• Device malfunction (n = 2)

Withdrew (n = 15)

• Could not tolerate (n = 8)
• Physical/health concerns (n = 2)
• Anxiety (n = 2)
• No benefit perceived (n = 3)
  Discontinued (n = 7)
• Physical/health concerns (n = 2)
• Non-compliance (n = 4)
• Device malfunction (n = 1)

Discontinued (n = 7)

• Physical/health concerns (n = 2)
• Non-compliance (n = 4)
• Device malfunction (n = 1)

Completed (n = 19)
Withdraw (n = 10)
Discontinued (n = 7)

Adequate trial of 25 Hz MST 
(n = 36)

Adequate trial of 50/60 Hz MST 
(n = 26)

Adequate trial of 100 Hz MST 
(n = 24)

Completed (n = 16)
Withdraw (n = 8)
Discontinued (n = 0)

Completed (n = 13)
Withdraw (n = 11)
Discontinued (n = 2)

Reasons withdrew/discontinued:
Could not tolerate (n = 3)
Anxiety (n = 1)
No benefit perceived (n = 3)
Health concerns (n = 1)

Reasons withdrew/discontinued:
Could not tolerate (n = 0)
Anxiety (n = 5)
No benefit perceived (n = 4)
Non-compliance (n = 2)
Health concerns (n = 1)
Other (n = 1)

Reasons withdrew/discontinued:
Could not tolerate (n = 0)
Anxiety (n = 0)
No benefit perceived (n = 10)
Non-compliance (n = 1)
Device malfunction (n = 3)
Health Concerns (n = 3)
MST TRD Remission

Daskalakis et al. 2020 NPP
# Cognitive Outcomes

*Means and SD Across Groups for Neurocognitive Measures among patients who have completed an adequate trial of MST (≥ eight treatments) or per protocol.*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adequate Trial</th>
<th>Per Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>MoCA</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>AMI - SF</td>
<td>51.42 (6.89)</td>
<td>51.16 (7.4)</td>
</tr>
<tr>
<td>Trails A</td>
<td>40 (33.3)</td>
<td>40.4 (31.52)</td>
</tr>
<tr>
<td>Trails B</td>
<td>95.11 (67.89)</td>
<td>90.64 (56.14)</td>
</tr>
<tr>
<td>Symbol Coding</td>
<td>50.68 (13.6)</td>
<td>49.05 (12.26)</td>
</tr>
<tr>
<td>HVLT-R Total</td>
<td>25.26 (6.29)</td>
<td>24.32 (5.5)</td>
</tr>
<tr>
<td>HVLT-R Recall</td>
<td>8.78 (2.93)</td>
<td>8.34 (3.33)</td>
</tr>
<tr>
<td>HVLT-R Recognition Index</td>
<td>10.53 (1.93)</td>
<td>10.57 (1.82)</td>
</tr>
<tr>
<td>Spatial Span Forward</td>
<td>8.47 (2)</td>
<td>8.41 (1.92)</td>
</tr>
<tr>
<td>Spatial Span Back</td>
<td>7.78 (2.06)</td>
<td>7.41 (1.93)</td>
</tr>
<tr>
<td>Spatial Span Total</td>
<td>16.24 (3.64)</td>
<td>15.82 (3.45)</td>
</tr>
<tr>
<td>LNS Total</td>
<td>15 (3.85)</td>
<td>14.77 (4.09)</td>
</tr>
<tr>
<td>Mazes Total Score</td>
<td>14.33 (7.91)</td>
<td>13.02 (8.26)</td>
</tr>
<tr>
<td>BVMT-R Total</td>
<td>21.8 (8.78)</td>
<td>22.6 (8.29)</td>
</tr>
<tr>
<td>BVMT-R Learning</td>
<td>3.94 (2.16)</td>
<td>3.84 (2.26)</td>
</tr>
<tr>
<td>BVMT-R Recall</td>
<td>8.4 (3.05)</td>
<td>8.65 (2.84)</td>
</tr>
<tr>
<td>BVMT-R Recognition Index</td>
<td>5.58 (0.81)</td>
<td>5.58 (0.73)</td>
</tr>
<tr>
<td>COWAT Total</td>
<td>39.06 (14.55)</td>
<td>37.1 (15.49)</td>
</tr>
<tr>
<td>Categories Total</td>
<td>54.63 (19.4)</td>
<td>55.35 (20.89)</td>
</tr>
<tr>
<td>Stroop Color-Word Score</td>
<td>95.19 (22.25)</td>
<td>94.63 (22.92)</td>
</tr>
<tr>
<td>Stroop Color-Word Time (sec)</td>
<td>113.62 (16.23)</td>
<td>115.8 (17.3)</td>
</tr>
</tbody>
</table>

* p < 0.005

*Note. MoCA = Montreal Cognitive Assessment; AMI – SF = Autobiographical Memory Interview-Short Form; Trails A/B = Trail Making Test, Part A or B; HVLT-R = Hopkins Verbal Learning Test-Revised; LNS = Letter Number Span; BVMT-R = Brief Visuospatial Memory Test-Revised; COWAT = Controlled Oral Word Association Test; Categories = Category Fluency Test.*
SSI Efficacy Rates

- Modified Intent-to-Treat (ITT) sample: minimum 8 treatments completed

SSI Remission\(^1\) Rate

Chi – square tests revealed the following significant differences:
50 Hz > 100 Hz: \(\chi(1) = 7.80, \ p = .005\)
50 Hz > 60 Hz: \(\chi(1) = 6.81, \ p = .009\)

\(^1\)Remission = score of 0 at post-treatment SSI (i.e. no suicidal ideation reported)

Weissman et al. 2020 JAMA Open
Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy of Depression (CREST – MST)

- 5 year NIMH funded multi-center trial at UT Southwestern and the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada
- Target $n = 260$
- Target population = severe and/or treatment-resistant MDD (unipolar, w/o psychotic features)
- Design = randomized, double blind, parallel-group clinical trial with two treatment arms: Magnetic Seizure Therapy (MST) or right unilateral ultrabrief pulse electroconvulsive therapy (RUL-UB-ECT)
Magnetic seizure therapy in treatment resistant schizophrenia: A pilot study

Victor M. Tang1,2, Daniel M. Blumberger1,2,3,4, Shawn M. McClintock5,6, Tyler S. Kaster1,2, Tarek K. Rajji1,2,3,4, Jonathan Downar1,4,7,8, Paul B. Fitzgerald9 and Zafiris J. Daskalakis1,2,3,4*

1Psychiatry, University of Toronto, Canada
2Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Canada
3Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Canada
4Institute of Medical Science, University of Toronto, Canada
5Psychiatry, University of Texas Southwestern Medical Center, United States
6Psychiatry and Behavioral Sciences, School of Medicine, Duke University, United States
7Krembil Research Institute, University Health Network, Canada
8MRI-Guided rTMS Clinic, University Health Network, Canada
9Monash Alfred Psychiatry Research Centre, Central Clinical School, Monash University, Australia

The full-text will be published soon.
BPRS: All Subjects

[Bar chart showing BPRS scores before and after treatment. The pre-treatment score is significantly higher than the post-treatment score, indicated by an asterisk. Error bars are shown to indicate standard error.]
Autobiographical Memory AMI

![Graph showing AMI scores pre and post treatment](image)
Cognition - MoCA

![Bar chart showing MoCA scores before and after treatment. The chart indicates a decrease in scores post-treatment.](image-url)
Magnetic Seizure Therapy for Schizophrenia (MAST)-Trial

- 5 year CIHR funded multi-center trial at CAMH, UBC and LHSC
- Target $n=160$
- Target population = severe and/or treatment-resistant SCZ (unipolar, w/o psychotic features)
- Design = randomized, double blind, parallel-group clinical trial with two treatment arms: Magnetic Seizure Therapy (MST) or bilateral electroconvulsive therapy
Neurophysiology

Demonstrated inhibition/plasticity in DLPFC in healthy subjects
DLPFC: Combined Baseline N100 and LICI Predicts SSI Remission

**Classifier:**
Baseline N100 and LICI Value

**Model:** Subjects with baseline N100 less than cutoff or LICI greater than cutoff are classified as remitters

**Binary Outcome:**
Post SSI = 0 → Remitter
Post SSI > 0 → Non-Remitter

**Accuracy for optimal cutoff:** 89%

90% sensitivity and 89% specificity

Sun et al. JAMA Psychiatry 2016
MST-Induced Potentiation of Neural Plasticity

Sun et al. Translational Psychiatry, 2018 Nov 23;8(1):253
MST-induced decreased SGC Hyperactivity

Brain Source Image (Post-Pre T-score)
50-500ms average
P < 0.1 Threshold

SGC Region (SCS Pre vs Post)
50-500ms average
P = 0.03

Concurrent EEG (Post-Pre T-score)
50-500ms average
* Significant electrodes

Hadas et al, Translational Psychiatry
Acknowledgments

Temerty Centre: Daniel Blumberger, Tarek Rajji, Daphne Voineskos, Yinming Sun, Julia Dimitrova, Alanah Throop, Jonathan Lee, Reza Moghaddam, Pantelis Lioumis, Itay Hadas, Mawahib Semeralul, Aiuysh Bansal, Jeanette Hui, Jennifer Bennie et al.

Co-Investigators: Mustafa M. Husain, Shawn McClintock, Paul B. Fitzgerald, Robert Chen, Aristotle Voineskos, Stephanie Ameis, Paul Ritvo, Paul Croarkin, Sidney Kennedy, Jonathan Downar, Fidel Vila-Rodriguez, Nir Lipsman, Andres Lozano, Peter Giacobbe, Faranak Farzan

Funding Agencies: CIHR, OMHF, NARSAD, NIMH, CAMH Foundation, CAMH, Temerty Family Foundation, Grant Family, Carlo Fidani Foundation