Transcranial Magnetic Stimulation and Electroencephalography Markers of Adolescent Depression and Suicidality

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Dr. Lewis
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Dr. Doruk Camsari
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Will discuss a non-FDA-approved use of repetitive transcranial magnetic stimulation (rTMS) for treatment of adolescents

Learning Objectives

• Understand how transcranial magnetic stimulation (TMS) can be used for both neurophysiologic research and as a neuromodulatory treatment
• Identify what has been learned from TMS research about brain physiology in adolescent depression and suicidality
• Review available evidence for TMS as a treatment for adolescent depression
• Learn about quantitative EEG (QEEG) and its potential applications in understanding the pathophysiology of adolescent depression and suicidality, as well as in guiding future treatments
Transcranial Magnetic Stimulation (TMS): Investigational Tool of Cortical Physiology and Neuromodulatory Treatment

What is Transcranial Magnetic Stimulation?

- High-intensity magnetic field induces electrical current in conductive material, including neural tissue
- Geometry of electromagnetic coil permits focusing magnetic field to a limited area
- Stimulation results in action potentials in neurons of stimulated area
- Effects of stimulation propagated through neural circuits connected to stimulated region

Image from Klomjai et al, 2015

Transcranial Magnetic Stimulation (TMS): Brain Physiology in Adolescent Depression and Suicidality

Image from: Chervyakov et al., Front Hum Neurosci, 2015.
TMS as a Neurophysiologic Probe

- Single or paired pulses can induce distinct and replicable effects on neural circuits by varying intensity, intervals between stimuli
- Can be measured by established objective methods (EMG, EEG)

TMS-EMG Measures of Cortical Excitability and Inhibition

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pulse</th>
<th>Interstimulus Interval</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor threshold (RMT/AMT)</td>
<td>single</td>
<td>(n/a)</td>
<td>NMDA, AMPA, voltage-gated Na+ channels</td>
</tr>
<tr>
<td>Cortical silent period (CSP)</td>
<td>single</td>
<td>(n/a)</td>
<td>GABA_A, GABA_B</td>
</tr>
<tr>
<td>Short-interval intracortical inhibition (SICI)</td>
<td>paired</td>
<td>2-4 ms</td>
<td>GABA_A</td>
</tr>
<tr>
<td>Intracortical facilitation (ICF)</td>
<td>paired</td>
<td>7-20 ms</td>
<td>NMDA</td>
</tr>
<tr>
<td>Long-interval intracortical inhibition (LICI)</td>
<td>paired</td>
<td>50-200 ms</td>
<td>GABA_B</td>
</tr>
</tbody>
</table>


TMS-EMG Measures of Cortical Excitability and Inhibition

TMS-induced Motor Evoked Potential (MEP)

Image adapted from Lewis et al. Front Neural Circuits, 2016.
TMS-EMG Measures of Cortical Excitability and Inhibition

Short-Interval Intracortical Inhibition (SICI)

Intracortical Facilitation (ICF)

Long-Interval Intracortical Inhibition (LICI)
Cortical Excitability and Inhibition

in Major Depressive Disorder

- Impaired cortical inhibition in adult MDD studies
  - Reduced CSP duration (Bajbouj et al., 2006; Lefaucheur et al., 2008); vs. increased (Steele et al., 2000)
  - Reduced SICI (Bajbouj et al., 2006; Lefaucheur et al., 2008)
  - Levinson et al. (2010): three MDD groups exhibited reduced CSP duration (vs. controls); treatment-resistant MDD group also showed reduced SICI amplitude
- Meta-analysis of adult MDD studies (Radhu et al., 2013)
  - Shortened CSP ($g=1.232$, 95% CI -1.530 to -0.933, $p=0.000$)
  - Impaired SICI ($g=0.641$, 95% CI 0.384 to 0.898, $p=0.000$)

Cortical Excitability and Inhibition

in Adolescents

- GABA and glutamate systems are dynamic in youth
  - Subunit composition of receptors shifts throughout development, affecting functions
  - GABA receptors have excitatory effect in early life
  - Receptor density changes into young adulthood; rates vary across brain structures, with cortex among the last to develop into adult patterns
- Excitatory and inhibitory TMS measures (RMT, LICI) show developmental effects in depressed adolescents (Croarkin et al., 2014)
Cortical Excitability in Adolescent MDD

- Medication-naïve adolescents with MDD (n=24) vs. healthy control adolescents (n=22)
- Increased cortical facilitation (10 ms, 15 ms) in both left and right hemispheres in MDD group

<table>
<thead>
<tr>
<th>TMS Measure</th>
<th>MDD Patients (n=24)</th>
<th>Healthy Controls (n=22)</th>
<th>p value (pFDR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICF-10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>1.98 (0.28)</td>
<td>1.84 (0.28)</td>
<td>.01 (0.05)</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>1.90 (0.28)</td>
<td>1.76 (0.27)</td>
<td>.01 (0.05)</td>
</tr>
<tr>
<td>ICF-15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>2.44 (0.26)</td>
<td>2.01 (0.26)</td>
<td>&lt;.001 (0.005)</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>2.03 (0.27)</td>
<td>1.68 (0.26)</td>
<td>.001 (0.007)</td>
</tr>
</tbody>
</table>

Least Squares Mean (SE)

Impaired Cortical Inhibition in Adolescents with Lifetime Suicidal Behavior

- ROC analysis of LICI for discriminating Depressed from Depressed+SB youth
Cortical Inhibition in Adolescent Suicidality

- Does impaired inhibition correspond to chronic risk (i.e., “suicidal trait”) vs. fluctuating, state-dependent risk?
  - Partial correlation (controlling for change in depression severity) between change in LICI-100 and change in suicidal ideation intensity: $\rho = .746$, $df = 7$, $p = .021$ (Lewis et al. 2019)
  - Need for longitudinal studies tracking cortical inhibition and suicidal risk and behaviors over time

- How does impaired LICI correspond to higher-level behavioral characteristics of suicidal youth (e.g., impulse control, affect regulation, emotional salience processing)?
- How does motor cortex inhibition correspond to inhibition in other regions and networks?
  - LICI can be measured by TMS-EEG (Daskalakis et al., 2008; Farzan et al., 2010, 2016)
  - LICI correlates with connectivity measured by resting-state fMRI (Balzekas et al., 2018)

TMS-Measured Cortical Excitability and Inhibition: Potential Clinical Applications

- Need to improve tools for clinical evaluation and interventions
- Risk assessment and stratification
- Prediction of treatment response
  - TMS-EEG-measured cortical inhibition predicted reduction of suicidal ideation with MST (Sun et al., 2016)
- Individualize targeting and dosing of neuromodulatory interventions
Transcranial Magnetic Stimulation (TMS): Neuromodulatory Treatment for Depression

TMS: Therapeutic Applications

- Repeated stimulation can modulate excitatory and inhibitory functions of neural circuits, including areas distant to stimulation site
- Considerations:
  - Frequency (high vs. low)
  - Patterned pulses (e.g., theta burst stimulation)
  - Placement of coil
  - Intensity of magnetic stimuli
  - Number of pulses
  - Scheduling of rTMS sessions

rTMS
- <5 Hz: inhibitory
- >5 Hz: excitatory
- TBS (50 Hz)
- cTBS: inhibitory
- iTBS: excitatory

rTMS in Adolescent Depression
Case Series and Open-Label Trials

| Study | Sample Size | Age Range | Treatment Details | Baseline | Improvement at End of Treatment | Improvement at 6 Months | Summary
|-------|-------------|-----------|-------------------|----------|---------------------------------|------------------------|--------|
| Wall et al. (2012) | 10 treatments | 16-20 years | 3600 train sessions at 10 Hz, 10 min, 70% of MT | Y/N | Y | Y | Y
| Mayer (2008) | 10 treatments | 16-20 years | 4000 train sessions at 10 Hz, 90% of MT | Y/N | Y | Y | Y
| Wall et al. (2014) | 15 treatments | 15-19 years | 3600 train sessions at 10 Hz, 10 min, 70% of MT | Y/N | Y | Y | Y

Study 1: Mean Depression Severity Scores
Treatment Completers (n = 7)

Study 2: Mean Depression Severity Scores
Treatment Completers (n = 7)

Adapted from Lewis et al., forthcoming

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11/15/2018
Adverse Effects of rTMS in Children and Adolescents

- Systematic review (Krishnan et al., 2015) of 35 rTMS studies in a total of 322 children/adolescents with a variety of neuropsychiatric conditions:
  - Headache (11.5%)  
  - Scalp discomfort (2.5%)  
  - Muscle twitching (1.2%)  
  - Mood changes (1.2%)  
  - Fatigue (0.9%)  
  - Tinnitus (0.6%)  
  - Seizure (0.6%, n=2)  
  - Syncope (0.6%, n=2)


FDA Regulatory Approvals

- 2008:  
  - First rTMS device approved for marketing by the U.S. FDA for the treatment of major depression (adults)  
  - Other devices have subsequently obtained FDA clearance for MDD indication
- 2018:  
  - Deep TMS approved for treatment of obsessive compulsive disorder  
  - First approval of theta burst stimulation device for MDD

- No devices currently cleared for treatment of MDD in adolescents

rTMS in Children and Adolescents: Ongoing and Future Research

- Multisite RCT  
  - 10 Hz rTMS, 6 weeks (30 sessions), n=100
- Mayo Clinic (PI: Paul Croarkin)  
  - Biomarker-stratified (ICF)  
  - Phase I (6 weeks): 1 Hz vs. 10 Hz rTMS, left DLPFC  
  - Phase II (2 weeks): cTBS vs. iTBS, left DLPFC

- Weekly TMS neurophysiology and clinical measures  
- 7T magnetic resonance spectroscopy
rTMS in Children and Adolescents: Ongoing and Future Research

- Future intervention for suicidal ideation/behavior?
  - Odds of suicidal ideation decreased over 6-week course of rTMS in open-label study of 19 adolescents (Croarkin et al., 2018)
  - Magnitude of decrease nonsignificant adjusting for illness severity
  - Need for studies designed specifically to target brain structures/networks implicated in suicidality
  - Need for measures and outcomes specifically designed to assess suicidal ideation/behavior and underlying constructs

Quantitative EEG (QEEG) and its potential applications in understanding the pathophysiology of adolescent depression and suicidality
EEG

- Based on volume conduction of ionic currents generated by nerve cells through the extracellular space.
- Recorded EEG potentials arise from extracellular current flow from summated EPSPs and IPSPs.
- The EEG does not record activity from single neurons but is dependent on the summation of thousands to millions of postsynaptic potentials.
- Thalamocortical pathways along with cortical circuitry are the main neuroanatomical structures involved in EEG generation.

Advantages

- Lower hardware cost
- Higher temporal resolution - ms
- Silent - better for auditory stimulus
- Relatively tolerant to movement
- No IV ligands
- No claustrophobia
- More flexible

Disadvantages

- Lower spatial resolution
- Poor recording for layers below cortex
- Can be time consuming
- Poor signal to noise ratio- more sophisticated analysis and large number of subject is needed
Quantitative EEG

Quantitative EEG (QEEG) is the mathematical processing of digitally recorded EEG in order to highlight specific waveform components, transform the EEG into a format or domain that elucidates relevant information, or associate numerical results with the EEG data for subsequent review or comparison.


Power Analysis

Event Related Potentials

Source Localization
Low resolution electromagnetic tomography

QEEG in Psychiatry
- Depression
- ADHD, learning disabilities
- Dementia
- Schizophrenia
- Cognition

QEEG in Psychiatry
QEEG is useful for research purposes and rarely in a clinical context. No QEEG method has as yet become accepted as providing reliable, independent markers for psychiatric disease or treatment response.

Diagnostic?
Discriminative?
Treatment outcome?
Suicide

- Suicide is the second leading cause of death among young people (WHO 2014).
- Multiple risk factors: environmental factors, affective processes, cognitive processes, social factors and biological correlates (Cha et al., 2018)


Suicide

- One-third of those who experience suicidal ideations proceed with suicide attempt or plan within one year of the onset of ideations (Nock et al., 2013; Glenn et al., 2017)
- Depends on subjective reports which could be concealed due to multiple reasons such as fear of stigma, avoiding involuntary treatment, lack of insight and transient nature of suicidal thoughts.
- It has been estimated that 78% of suicide completers deny any suicidal thoughts before they die (Bush et al., 2003).

Glenn et al. Depress Anxiety, 2017.

Correlates of suicidality in adolescents

EEG
- Increased fronto-central theta power
- P300 amplitude
- Frontal and Posterior alpha asymmetry

TMS Neurophysiologic Measures
- LICI and other measures of cortical inhibition (CSP, SICI)

Neuroimaging (Resting-State fMRI)
- Attempters could be discriminated from non-attempters by their brain activity in the left superior medial frontal area, medial frontal/anterior cingulate and the right middle temporal area

Implicit Association Test
- Implicit associations between self and death/suicide had approximately six-fold increase in the odds of making a suicide attempt at 6-month follow-up (Nock 2010)

Psychosocial factors
- Internalizing and externalizing symptoms, maternal depression, socioeconomic status, trauma history

Psychosocial factors
- Internalizing and externalizing symptoms, maternal depression, socioeconomic status, trauma history
Quantitative EEG correlates of suicidality in adolescents

30 participants between ages 13-18 years old with suicidal behaviors (suicide attempt, suicidal ideations, intent, plan, and non-suicidal self-injurious behaviors) and 30 age- and gender- matched healthy controls will be recruited in this case-control study.

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