Brain Neuromodulation in Child and Adolescent Psychiatry: Present and Future

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Psychiatric neuromodulation IS

• Any intervention intended to alter nervous system function

• Using energy fields such as electricity, magnetism, or both.

• With the goal to improve psychiatric symptoms or related conditions.

• Brain Plasticity
Treatment & Theory

• Psychotherapy
• Psychopharmacology
• Brain modulation
Transient Acute Depression with DBS
Neuromodulation
Invasive or Noninvasive

Vagal nerve stimulation VNS epilepsy >4y
Adult depression

Invasive = continuous
= localized

Deep brain stimulation – dystonia
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Neuropsychiatric diseases included in neuromodulation trials in children and adolescents</th>
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<tbody>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td>rtTMS</td>
<td>X</td>
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<tr>
<td>TBS</td>
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<tr>
<td>tDCS</td>
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<tr>
<td>ECT</td>
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<tr>
<td>MST</td>
<td>X</td>
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<tr>
<td>eTNS</td>
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Abbreviations: ECT, electroconvulsive therapy; eTNS, external trigeminal nerve stimulation; MST, magnetic seizure therapy; OCD, obsessive-compulsive disorder; rtTMS, repetitive transcranial magnetic stimulation; TBS, theta burst stimulation; tDCS, transcranial direct current stimulation.
Non-surgical brain stimulation
Comparative efficacy and acceptability for the acute treatment of major depressive episodes in adults

Summary
The findings provide evidence to consider non-surgical brain stimulation techniques as alternative or add-on treatments.

Data sources
- 113 RCTs
- 6750 Adults with major depressive disorder or bipolar depression

Overall risk of bias:
- High: 17%
- Low: 34%
- Unclear: 50%

Results
Active vs sham treatment comparisons

<table>
<thead>
<tr>
<th>ECT</th>
<th>Electroconvulsive therapy</th>
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<tbody>
<tr>
<td>Bitemporal</td>
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<tr>
<td>High dose right unilateral</td>
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<tr>
<td>Bifrontal</td>
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<tr>
<td>Low-moderate dose right unilateral</td>
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<td>Bilateral repetitive</td>
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<td>Low frequency repetitive (right)</td>
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<td>High frequency repetitive (left)</td>
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<td>TBS</td>
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<tr>
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<tr>
<td>Other</td>
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<tr>
<td>Magnetic seizure therapy</td>
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Response rates and Discontinuation

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Indications For ECT in Adolescents

- MDD and BPAD
- Catatonia and self injurious behaviour
- NMS
- Psychosis (Schizophrenia)
Pros and Cons of the use of ECT in treating Adolescents

**Pros**: 
- High efficacy 50-90%
- Anti suicidal >60%
- Quick response few weeks
- Safety

**Cons**: 
- Need for maintenance
- Memory disturbances
- Stigma
- Ethics and legislation
- Other side effects
ECT in Adolescents - Reasons for referral

- Adults-resistant depression
- Adolescents-severe and immediate risk-No choice
Dura exposure
Dislocation of the jaw
What is the right prescription

Mandatory
• Clinical evaluation
• Proper ethical and legal procedure
• Anesthesia and Muscle relaxation
• Placement and Energy
• Wave characteristics
• Duration and monitor

Wrong!
• No place for old machines,
  – sine wave
  – Wide width wave 0.5 msec<
• No place for low dose (less then X4 times threshold) rt unilateral
• No wait and see
Potentials of Noninvasive brain modulation in C&A psychiatry

Brain Plasticity

High safety
Safety of Noninvasive Brain Stimulation in Children and Adolescents

Brain Stimul. 2015 Jan-Feb; 8(1): 76–87.
Transcranial Direct Current Stimulation

• Variable tDCS montages with anodal (excitatory) and cathodal (inhibitory) stimulation produce divergent neurophysiological effects.
• In general, prior research suggests that stimulation with tDCS modifies neuronal resting membrane potential and excitability with resultant alterations in GABAergic and glutamatergic synapses.
Transcranial Direct Current Stimulation

- low cost, accessibility, tolerability, and presumed safety.
- Possible continuous therapy
- Comparatively simple device complex science and clinical science
- Probably more sales then research

Very high potential in C&A psychiatry
Transcranial magnetic stimulation
Location

- Precentral gyrus (motor strip)
- TMS treatment location
- Dorsolateral prefrontal cortex
- Thumb motor area
What are the parameters?

- 1 Hz rTMS or less-low frequency inhibitory
- Above 1 Hz rTMS (5 Hz) usually 10Hz; 20 Hz excitatory
- In rTMS, a longer lasting effect using thousands of pulses.
- Similar long term potentiation (LTP), or depression (LTD) at the neuronal level.
Prescription:

• High frequency Left or
• Low frequency Right

• theta burst

Coil
Bloch et al. 2008 JECT

9 severely depressed adolescents,
3 adolescents - significant improvement
JECT Mayer et al. 2012
3 years later-
no hospitalization
7 of 8 much improved
Figure 1. Mean CDRS-R and QIDS-A17 Scores of Adolescents (n=7) With MDD During Adjunctive rTMS Treatment and at 6-Month Follow-Up

Abbreviations: CDRS-R = Children's Depression Rating Scale-Revised, MDD = major depressive disorder, QIDS-A17 = Quick Inventory of Depressive Symptomatology-Adolescent Version, rTMS = repetitive transcranial magnetic stimulation.
Zhang T, 2019 rTMS probably better for adolescents than for adults, naturalistic
Croarkin, 2018 JAD repetitive TMS for suicidal ideation in adolescents open label 19
Working on a double blind placebo controlled rTMS study to treat adolescent depression

1. 14-18y old
2. Treatment resistant Depression (not schizo, ASD)
3. 20 working days to come to Shalvata for an hour.

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I understood that to study brain modulation in Children & Adolescents:

- Severe disorders
- Adults first
- Better robust “powerful” stimulation
- Learn from FDA


*Positive effects of repetitive transcranial magnetic stimulation on attention in ADHD Subjects. World J Biol Psychiatry. 2010

*Randomised sham-controlled study of high-frequency bilateral deep transcranial magnetic stimulation (dTMS) to treat adult (ADHD): Negative results. World J Biol Psychiatry. 2018
For Immediate Release:

April 19, 2019

The U.S. Food and Drug Administration today permitted marketing of the first medical device to treat attention deficit hyperactivity disorder (ADHD). The prescription-only device, called the Monarch external Trigeminal Nerve Stimulation (eTNS) System, is indicated for patients ages 7 to 12 years old who are not currently taking prescription ADHD medication and is the first non-drug treatment for ADHD granted marketing authorization by the FDA.
Trigeminal nerve stimulation (TNS)

- Approved in Canada and Europe for adult treatment of resistant depression
- TNS uses a small stimulator worn during sleep, low-level current. Thin wires extend from the TNS device to an adhesive electrode worn across the forehead over branch V1 of the trigeminal nerve.
Trigeminal nerve stimulation (TNS)
Bottom up technique based on VNS

- Sensory inputs from the skin, muscles, and skull
- To the locus coeruleus, reticular activating system, and nucleus tractus solitaries
- Regions involved in selective maintenance of attention
Double-Blind, Sham-Controlled, Trigeminal Nerve Stimulation for ADHD

- Sixty-two children 8 to 12 years old, ADHD
- 4 weeks of nightly treatment with active or sham TNS, 1 week without intervention.
- Clinician-administered ADHD Rating Scales (ADHD-RS) and Clinical Global Impression (CGI) scales and quantitative
- EEG at baseline and at week 4.
Double-Blind, Sham-Controlled, Trigeminal Nerve Stimulation for ADHD

Figure 1: Attention-Deficit/Hyperactivity Disorder Rating Scale Total Scores Over 4-Week Blinded Trial: Active Versus Sham Trigeminal Nerve Stimulation
Treatment-Related Change in EEG Spectral Power at F4 Electrode

A

Eyes open resting state power - F4 electrode

B

Treatment change by group

C

F4 gamma (40-50 Hz) power
## Side effects

**Increased pulse**

**Gained 1 KG**

<table>
<thead>
<tr>
<th>Side Effect (% Reporting)</th>
<th>Active (n = 32)</th>
<th>Sham (n = 30)</th>
<th>Side Effect (% Reporting)</th>
<th>Active (n = 32)</th>
<th>Sham (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trouble sleeping</td>
<td>19</td>
<td>17</td>
<td>Rapid heartbeat</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Nightmares</td>
<td>6</td>
<td>0</td>
<td>Out of breath</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Drowsy</td>
<td>22</td>
<td>13</td>
<td>Nausea</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Hyperactive</td>
<td>41</td>
<td>63</td>
<td>Stomachache</td>
<td>6</td>
<td>3</td>
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<tr>
<td>Fatigue</td>
<td>13</td>
<td>3</td>
<td>Constipation</td>
<td>9</td>
<td>7</td>
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<tr>
<td>Feels strange</td>
<td>0</td>
<td>7</td>
<td>Frequent urination</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Tingling</td>
<td>3</td>
<td>0</td>
<td>Frequent sweating</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>0</td>
<td>Decreased appetite</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Stuffy nose</td>
<td>16</td>
<td>20</td>
<td>Increased appetite</td>
<td>19</td>
<td>7</td>
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<tr>
<td>Muscle cramps</td>
<td>3</td>
<td>3</td>
<td>Skin rash</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Muscle twitch</td>
<td>0</td>
<td>7</td>
<td>Finding words</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
<td>3</td>
<td>Apathy</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Slurred speech</td>
<td>0</td>
<td>3</td>
<td>Clenching teeth</td>
<td>13</td>
<td>7</td>
</tr>
</tbody>
</table>
To sum up the present clinical use of brain modulation in the field:

1. ECT
   1. Severe treatment resistant/life threatening depression
   2. Proper usage
2. rTMS
   1. Approved in adult depression
   2. Current research protocol
3. TNS
   1. FDA approval in children
4. tDCS
   1. Near future? Need for studies
Some thoughts about the Future

1. Localizing
   - Rt unilateral ECT
   - TMS

2. Less energy
   - Ultra-brief and brief pulse ECT

3. Continuous
   - TNS; VNS; DBS;
   - Pharmacotherapy
   - Psychotherapy
Some thoughts about the Future

• 1. Combining techniques.
  – Clinical practice
• 2. Clinical & biomarker monitor
  – EEG
• 3. Loop adjustments
  – Parkinson DBS
• 4. New approaches (never say never)
  – Auricular neuromodulation strategies
Thank you for listening
(green=vagus; blue =trigeminal)