TMS in Special Populations: Part 1

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Conflict of Interest Disclosure

Alexander Rotenberg

Current:
- Neuro’motion Inc. (technology for improving emotional control; co-founder)
- NeuroRex (medical advisor)
- Brainsway Inc. (research support [equipment and personnel])
- Soterix Medical Inc. (research support [equipment])
- Neuroelectrics Inc. (research support [equipment])
- Journal of Central Nervous System Diseases (EIC)
- NIH NIMH, DoD, CIMIT, ERF, TRP (research grants)

Past:
- Neuropace Inc. (research grant and equipment)
- Nexstim Inc. (consultant)
- Sage Therapeutics Inc. (consultant)
- Fisher Family Fund and Fisher-Wallace Inc. (research support [unrestricted gift and equipment])
Why Stimulate in Pediatric Neurology?

• Therapeutic
  – Pharmacoresistance is prevalent in many disorders
    • Epilepsy: ~1/3
    • Major Depression: ~1/3
    • Tourette syndrome: ~1/4
    • Dystonia: most
  – Some patients do not tolerate pharmacotherapy

• Diagnostic
  – Localize function
  – Measure cortical excitability
  – Track a biomarker
Special considerations in pediatric brain stimulation

• Head and brain growth
• Developmental regulation of neuronal excitability
Developing brain is a moving target

- Vulnerability (or resistance) to injury likely varies with age
- Studies restricted to narrow age windows are lacking
- Subdivision of the pediatric age group may be necessary
Potential mechanisms for injury to the developing brain

• Enhanced excitability and vulnerability to seizure in early life
  – Risk for excitotoxicity

• Enhanced synaptic plasticity
  – Risk for interference with learning and memory

• Ongoing neurogenesis, synaptogenesis, myelination, etc.
  – Risk of use-dependent structural change
Neuronal Receptor Expression vs Age

Rakhade and Jensen, *Nature Rev.*, 2010
Chloride homeostasis in the immature brain

Ben-Ari 2002
Physiology is reflected in disease...and maybe in neurostimulation risks

Status epilepticus by age

DeLorenzo et al., 1992
Modulation of corticospinal excitability by transcranial magnetic stimulation in children and adolescents with autism spectrum disorder

Lindsay M. Oberman¹,²,³,⁴ *, Alvaro Pascual-Leone¹ and Alexander Rotenberg¹,² *

Maturation of motor plasticity
Paradoxical facilitation in children with ASD

Oberman et al., 2014
Chloride homeostasis may be dysmature in the ASD brain, and NKCC1 block may rescue the ASD phenotype.
A randomised controlled trial of bumetanide in the treatment of autism in children

E Lemonnier¹,², C Degrez¹, M Phelep¹, R Tyzio³, F Josse¹, M Grandgeorge¹,², N Hadjikhani⁴,⁵ and Y Ben-Ari³

Figure 2  All the values obtained with CARS are depicted. Note the significant differences between placebo and bumetanide treated patients and a partial return to pretreatment values after 1-month wash-out period. The number of items > 3 was also significantly reduced as shown at the right side of the figure (number corresponding to D0, D90 and D120; ***p < 0.005 for D90 and **p < 0.05 for D120).
Ethical Concerns

• Children are a “vulnerable” population
• Consent / assent in healthy volunteers is difficult
• Better in disease state where potential benefit to patient, or to field is more apparent
• Strict local guidelines limit investigations
Gaps in knowledge

• Limited neurostimulation data in pediatrics
• Few clinical trials segmented by developmental stage
• Fragmented pediatric data available from inclusive prospective trials
N = 40  
-Avg age 12y 7mo  
-no serious adverse events  
-Five of 40 children reported mild, self-limited adverse events:  
- a subjective sensation of finger twitching (1)  
- neck stiffness (1)  
- mild headache (3)  
-Total adverse event rate was 11.6%. No emotional changes, as rated with the visual analog mood scale, were identified (p > 0.05).  

Wu et al., Annual Meeting Child Neurology Society, 2011
Development and Plasticity of the Corticospinal System in Man

J.A. Eyre

Dashed: contra
Solid: ipsi
Clinical motor mapping in pediatrics: Sample case
right FDI map
left FDI map
right TA map
left TA map
nTMS for motor mapping:

Spatial resolution approximates fMRI (and DCS)
Verification by subdural electrodes

from Rotenberg, 2012
Motor lateralization in pediatric epilepsy: test of preserved ipsilateral corticospinal connectivity

Lesional and contra-lesional mapping (Rotenberg, unpublished)
Patient with hemispheric malformation, referred for motor mapping
Bilateral hand MEPs with contralesional stimulation of the POSTcentral gyrus
Diffusion Tensor Imaging Study of the Cortical Origin and Course of the Corticospinal Tract in Healthy Children

A. Kumar
C. Juhasz
E. Asano
S.K. Sundaram
M.I. Makki
D.C. Chugani
H.T. Chugani

Absent MEP with lesional stimulation
Same patient as previously: Hand Motor Task - fMRI

R hand

L hand
N=4 boys with hemispheric polymicrogyria

fMRI: ipsilesional BOLD signal in 3 / 4

nTMS: 0 / 4 crossed lesional corticospinal connections

4 / 4 with preserved grasp in paretic hand after hemispherectomy
....other special populations
- No spurious VNS trigger
- Minimal current (200 nA X 1 ms) induced between the leads
rTMS safety after cranial surgery

Rotenberg et al., 2007
Rotenberg and Pascual-Leone 2009
Ex vivo stimulation

Titanium Skull Plates and Gold EEG Electrode
Temperature vs. Time During 1Hz rTMS

Rotenberg et al., Clin Neirophysiol 2007
Ex vivo stimulation (aneurism clip)

Results (15 cm interval):

We found the temperature of clip increased 1.5 °C. However, it could be due to the changes of room temperature. Please note the difference while AC on. Hence, we added the measurement of room temperature in next trials.

\[\Delta T = 7.4^\circ C \text{ (Coil)}\]
\[\Delta T = 1.5^\circ C \text{ (Clip)}\]

Hsieh et al., Clin Neurophys 2011
## Threshold: TMS safety in pediatrics

### Should transcranial magnetic stimulation research in children be considered minimal risk?

**Donald L. Gilbert**, Marjorie A. Garvey, Aloks S. Bansal, Tara Lips, Tao Zhano, Eric M. Wassermann


<table>
<thead>
<tr>
<th>Reference</th>
<th>Disorder, number of children studied</th>
<th>Significant adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyre et al. (2001)</td>
<td>84 Normal children, neonates, children with cerebral palsy</td>
<td>None reported</td>
</tr>
<tr>
<td>Garvey et al. (2001)</td>
<td>20 Children ages with attention deficit hyperactivity disorder (ADHD) vs. 20 normal children. The mean age of the 40 children was 10±10 years</td>
<td>Two subjects discontinued the transcranial magnetic stimulation because they found it uncomfortable</td>
</tr>
<tr>
<td>Moll et al. (2001)</td>
<td>64 Children with ADHD, Tic disorder, both or neither</td>
<td>None except mild transient headache in a few patients</td>
</tr>
<tr>
<td>Moll et al. (2000)</td>
<td>18 ADHD children vs. 18 normal children</td>
<td>None except mild transient headache in a few patients</td>
</tr>
<tr>
<td>Dan et al. (2000)</td>
<td>Two adolescents with multiple sclerosis</td>
<td>None reported</td>
</tr>
<tr>
<td>Fiozzi et al. (2000)</td>
<td>48 Normal children</td>
<td>None reported</td>
</tr>
<tr>
<td>Azzogli et al. (2000)</td>
<td>23 Patients with epilepsy including 4 adolescents</td>
<td>None except mild transient headache in a few patients</td>
</tr>
<tr>
<td>Moll et al. (1999)</td>
<td>21 Children with tic disorders vs. 25 healthy controls</td>
<td>None reported</td>
</tr>
<tr>
<td>Kana et al. (1999)</td>
<td>20 Malnourished children vs. 20 normal children</td>
<td>None reported</td>
</tr>
<tr>
<td>Mayston et al. (1999)</td>
<td>39 Normal children vs. 11 adults</td>
<td>None except mild transient headache in a few patients</td>
</tr>
<tr>
<td>Hein et al. (1999)</td>
<td>10 Adolescents, 4 with cerebral palsy, two with hereditary spastic paraplegia, 4 normal</td>
<td>None reported</td>
</tr>
<tr>
<td>Maegaki et al. (1999)</td>
<td>17 Children ages 10–18 years with cerebral palsy vs. 6 normal children ages 9–14 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Nezu et al. (1999)</td>
<td>20 Normal children ages 2–13 years vs. 6 normal children ages 9–14 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Nezu et al. (1998a)</td>
<td>5 normal adults at ages 26 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Nezu et al. (1998b)</td>
<td>Three children ages 9–12 years with Pekasue Murrheber Disease</td>
<td>None reported</td>
</tr>
<tr>
<td>Nezu et al. (1998)</td>
<td>Three children with Rett Syndrome</td>
<td>None reported</td>
</tr>
<tr>
<td>Hein et al. (1998)</td>
<td>Seven normal children 4–6 vs. 7 adults</td>
<td>None reported</td>
</tr>
<tr>
<td>Muller et al. (1997)</td>
<td>50 Normal children age 5–11 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Nezu et al. (1997a)</td>
<td>13 Children with benign Rolandic epilepsy vs. 10 normal children</td>
<td>None reported</td>
</tr>
<tr>
<td>Nezu et al. (1997b)</td>
<td>46 Normal children vs. 10 adults</td>
<td>None reported</td>
</tr>
<tr>
<td>Ucles et al. (1996)</td>
<td>15 Children with ADHD vs. 10 normal children</td>
<td>None reported</td>
</tr>
<tr>
<td>Masur et al. (1995)</td>
<td>24 Normal children</td>
<td>None reported</td>
</tr>
<tr>
<td>Carr et al. (1993)</td>
<td>33 Subjects at ages 2–26 years with hemiplegic cerebral palsy vs. 17 normal subjects at ages 2–21 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Muller et al. (1992)</td>
<td>20 Children with hemiparesis, 16 children with extrapyramidal disease</td>
<td>None reported</td>
</tr>
<tr>
<td>Brouwer and Ashby (1991)</td>
<td>Six children ages 14–19 years with cerebral palsy</td>
<td>None reported</td>
</tr>
<tr>
<td>Cruz Martinez and Ainciones (1991)</td>
<td>Two children ages 11–13 years with Cockayne’s Syndrome</td>
<td>None reported</td>
</tr>
<tr>
<td>Muller et al. (1991)</td>
<td>86 Normal children ages 12 months to 13 years vs. 10 normal adults at ages 20–35 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Muller et al. (1991)</td>
<td>58 Normal children, ages 2 weeks to 14 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Eyre et al. (1990)</td>
<td>Five children ages 5–8 years with Rett Syndrome vs. 3 normal subjects at ages 9–26 years</td>
<td>None reported</td>
</tr>
</tbody>
</table>
Subjective Reactions of Children to Single-Pulse Transcranial Magnetic Stimulation

Marjorie A. Garvey, MD; Karen J. Kaczynski, BA; Danielle A. Becker, BS; John J. Bartko, PhD

more enjoyable than “a long car ride”
Now on to clinical TMS applications in pediatrics...