TMS in Special Populations

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Conflict of Interest Disclosure

Alexander Rotenberg

Current:
- Neuro’motion Inc. (co-founder, consultant)
- NeuroRex Inc. (consultant, medical advisory board)
- Brainsway Inc. (research support)
- Soterix Medical Inc. (research support)
- Neuroelectrics Inc. (research support)
- Sage Therapeutics Inc. (research support)
- Wuhan Yirude Medical Equipment New Technology Co., Ltd. (research support)
- Assimon Family Fund (research support)
- NIH NIMH, NIH NINDS, DoD, CIMIT, ERF, TRP, MassLife, Assimon Family, Autism Speaks (research grants)

Past:
NBS in Children

Boston Children’s Hospital Neuromodulation Program
Neuronetics Trial

N=164; 23 centers; triple blind

L DLPF 10 Hz rTMS
120% MT
4 sec trains
26 sec ITI
3000 pulses/day
2-3 weeks

Lisanby et al., 2008
Glutamate Alterations Associated With Transcranial Magnetic Stimulation in Youth Depression
A Case Series

Xiao-Ru Yang, BSc,* Adam Kirton, MD,†‡ Thomas Christopher Wilkes, MD,*† Sarah Pradañan,*
Irene Liu, MSc,§ Natalia Jaworska, PhD,* Omar Damji, MSc,†‡ Jamie Kees, BSc,†‡
Lisa Marie Langevin, PhD,* Thilinie Rajapakse, MD,†‡ Robert Marc Lebel, PhD,*† Mariko Sembo, BSc,*
Marilyn Fife, RN,* and Frank P. MacMaster, PhD†‡

Hamilton Depression Rating Scale

Beck Depression Inventory

Baseline
Post-TMS
RESPONDER
NON-RESPONDER

Journal of ECT • Volume 30, Number 3, September 2014
Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: A controlled clinical study


Departments of *Neurology and †Functional Neurosurgery, Xuan Wu Hospital, Capital Medical University, Beijing, China

N=64 (32: 90% RMT; 32: 20% RMT)
0.5 Hz rTMS over seizure focus
Clinical trials: gaps in knowledge

- Limited TMS data in pediatrics
- Few clinical trials segmented by developmental stage
- Fragmented pediatric data available from inclusive prospective trials

Fregni et al., 2005
...but, conventional TMS does not reach the temporal lobe

Electrical current distribution
(phantom model)

Roth and Zangen
1 Hz rTMS in temporal lobe epilepsy trial in progress

Epilepsy Therapy Project (PI: Rotenberg)

Deep TMS H-Coil System

Boston Children’s Hospital Neuromodulation Program
Figure 1

A

First treatment block

B

Second treatment block

C

Third treatment block

Gersner et al., 2016
Stimulation protocols

Presurgical motor mapping by TMS
Motor cortex TMS in children
Motor TMS example
Right hand (APB) map
Right foot (TA) map
Transcranial Magnetic and Direct Current Stimulation in Children

Mustafa Q. Hameed, Sameer C. Dhamne, Roman Gersner, Harper L. Kaye, Lindsay M. Oberman, Alvaro Pascual-Leone, Alexander Rotenberg
Motor map relative to lesion (hand; FDI)
Motor map relative to lesion (foot; TA)
Map identifies surgical access
Presurgical motor mapping by TMS
Development and Plasticity of the Corticospinal System in Man

J.A. Eyre

A. Normal

B. Stroke

Non–infarcted Infarcted

Dashed: contra
Solid: ipsi

AGE
newborn

3 months

6 months

12 months

24 months

200 μV

20 ms
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

Healthy 12yF
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
Right (ipsilesional) Hemisphere Stimulation
Left (ipsilesional) Hemisphere APB Stimulation
Right (ipsilesional) Hemisphere Stimulation
Color Coded Left and right Tibialis Anterior Map
Special considerations in pediatric TMS

- 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
Physiology is reflected in disease … and maybe in neurostimulation risks

Status epilepticus by age

DeLorenzo et al., 1992
Motor threshold

A  Motor evoked potentials
   Young
   90%
   95%
   100%
   105%
   110%
   115%
   120%
   125%
   130%
   TMS onset

   Old
   90%
   95%
   100%
   105%
   110%
   115%
   120%
   125%
   130%
   TMS onset

B  Stimulus-response curves
   Old
   $R^2 = 0.99$

   Young
   $R^2 = 0.96$

Smith et al., 2011
Motor Threshold v. Age

$R^2 = 0.4442$
$p < 0.001$
Motor threshold and age

Cluster 2
<15 years

\[ y = -8.8598x + 237.05 \]
\[ R^2 = 0.2337 \]
\[ p < .01 \]

Cluster 2
>15 years

\[ y = 11.126x - 89.615 \]
\[ R^2 = 0.1696 \]
\[ p = 0.1 \]
Neuronal Receptor Expression vs Age

GABA (excitatory)
- Yellow line
GABA (inhibitory)
- Black line
NMDA
- Blue line
AMPA
- Orange line
Kainate
- Green line

EXCITATION

INHIBITION

% Adult Function

Rodent
- P0
- P5
- P10
- P15
- P20
- P25
- P30
- Adult

Human
- preterm
- term
- 1-2y
- >10y
- Adult

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

Ben-Ari 2002
NKCC1 and KCC2 expression in autism, as compared to epilepsy and controls.

**NKCC1**

![Graph showing NKCC1 expression with fold change and % of control.]

**KCC2**

![Graph showing KCC2 expression with fold change and % of control.]

**NKCC1:KCC2**

![Graph showing NKCC1:KCC2 ratio with min and max GABA inhibition.]

Salah and Talos, in preparation.
Measures of Cortical Excitability by Paired-Pulse TMS (ppTMS)

Rotenberg and Pascual-Leone, 2010
GABAergic cortical inhibition measures by paired-pulse TMS (ppTMS)

Rotenberg and Pascual-Leone, 2010
Motor cortex inhibition
A marker of ADHD behavior and motor development in children

D.L. Gilbert, MD, MS
K.M. Isaacs, BA
M. Augusta, BA
L.K. MacNeil, BA
S.H. Mostofsky, MD

Figure 1: Transcranial magnetic stimulation (TMS) data from one typically developing child

Figure 2: Short interval cortical inhibition (SICI) is significantly reduced in children with attention-deficit/hyperactivity disorder (ADHD) vs typical children

\[ p < .0001 \]
Transcranial Magnetic Stimulation-Evoked Cortical Inhibition: A Consistent Marker of Attention-Deficit/Hyperactivity Disorder Scores in Tourette Syndrome

Donald L. Gilbert, Floyd R. Sallee, Jie Zhang, Tara D. Lipps, and Eric M. Wassermann
Neurochemical Effects of Theta Burst Stimulation as Assessed by Magnetic Resonance Spectroscopy

**Fig. 3.**

A: Typical γ-aminobutyric acid (GABA)–optimized spectrum acquired. Insets show representative GABA and N-acetylaspartate (NAA) peaks before and after stimulation in the same subject. Glx, composite measure of glutamate and glutamine.

B: Percentage change in GABA:NAA ratio from baseline. Verum stimulation leads to a significant increase in GABA:NAA ratio, compared with control.

C: Percentage change in creatine signal for baseline. There is no significant change with either stimulation condition.

Stagg et al., *J Neurophysiol*, 2009
Theta burst stimulation and synaptic plasticity

Hyperplasticity in Autism Spectrum Disorders

Oberman et al. 2009 & in press
Maturation of motor plasticity
Transcranial Magnetic and Direct Current Stimulation in Children

Mustafa Q. Hameed, Sameer C. Dhamne, Roman Gersner, Harper L. Kaye, Lindsay M. Oberman, Alvaro Pascual-Leone, Alexander Rotenberg
Paradoxical facilitation in children with ASD

Oberman et al., 2014
Why is this interesting?

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 Lemonnier\textsuperscript{1,2}, C Degrez\textsuperscript{1}, M Phelep\textsuperscript{1}, R Tygio\textsuperscript{3}, F Josse\textsuperscript{1}, M Grandgeorge\textsuperscript{1,2}, N Hadjikhani\textsuperscript{4,5} and Y Ben-Ari\textsuperscript{3}

\textbf{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).
Threshold: TMS safety in pediatrics

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disorder, number of children studied</th>
<th>Significant adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyre 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>Pietrek et al. (2000)</td>
<td>48 Normal children</td>
<td>None reported</td>
</tr>
<tr>
<td>Aguglia et al. (2000)</td>
<td>23 Patients with epilepsy including 2 adolescents</td>
<td>No seizures, headaches, or any other adverse effects (personal communication, U. Aguglia, 6/6/2001)</td>
</tr>
<tr>
<td>Moll et al. (1999)</td>
<td>3 Children with tic disorders vs. 3 healthy controls</td>
<td>None except mild transient headache in a few patients</td>
</tr>
<tr>
<td>Karak 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>59 Normal children vs. 11 adults</td>
<td>No seizures or any other adverse effects</td>
</tr>
<tr>
<td>Heiron 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>Noza et al. (1999)</td>
<td>20 Normal children ages 2–13 years vs. 5 normal adults at ages 26 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Noza et al. (1998a)</td>
<td>Three children ages 9–12 years with Perlszts-Merzbacher Disease</td>
<td>None reported</td>
</tr>
<tr>
<td>Noza et al. (1998b)</td>
<td>Three children with Rett Syndrome</td>
<td>None reported</td>
</tr>
<tr>
<td>Muller et al. (1997)</td>
<td>Seven normal children ages 4–6 vs. 7 adults</td>
<td>None reported</td>
</tr>
<tr>
<td>Norra et al. (1997a)</td>
<td>50 Normal children ages 3–14 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Norra et al. (1997b)</td>
<td>13 Children with benign Rolandic epilepsy vs. 10 normal children</td>
<td>“TMS produced no remarkable side effects in any subjects”</td>
</tr>
<tr>
<td>Norra et al. (1997b)</td>
<td>46 Normal children vs. 10 adults</td>
<td>None reported</td>
</tr>
<tr>
<td>Udias et al. (1996)</td>
<td>15 Children with ADHD vs. 23 normal children</td>
<td>None reported</td>
</tr>
<tr>
<td>Masar 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>Brooower 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 Aceitones (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 0–26 years</td>
<td>None reported</td>
</tr>
</tbody>
</table>
- 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).
more enjoyable than “a long car ride”
Heart Rate Stability During nTMS
Right deltoid sample
Right Deltoid sample (stim in CSF)
Right deltoid map
Case Report

Neurophysiological evidence of preserved connectivity in tuber tissue

Kaye HL\textsuperscript{a,b,c,1}, Peters JM\textsuperscript{a,c,1}, Gersner R\textsuperscript{a,b}, Chamberland M\textsuperscript{d,c}, Sansevere A\textsuperscript{b}, Rothenberg A\textsuperscript{a,b,c,3}
Left deltoid and tibialis anterior Motor Maps
Diffusion Tractography Imaging
corticospinal connectivity within the tuber tissue

Kaye et al., Epilepsy & Behav. Case Reports 2016
- 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.

Hsieh et al., Clin Neurophys 2011
THANKS!