Potential clinical applications of TMS in pediatrics

Aaron Boes, MD, PhD
Sidney R. Baer Clinical Neuroscience Fellow, BIDMC
Pediatric Neurologist, MGH
Disclosure: Off-label uses of TMS will be discussed
Topics

Highlight of a few areas in which TMS may find clinical applications in the pediatric population in the near future.

- Depression
- Rehabilitation
- Epilepsy
- Autism
- ADHD
- Tourrettes
Please interrupt, ask questions.
Challenges and opportunities in pediatrics

Neurodevelopmental disorders are common. 1 in 6 (Boyle, 2011)

Neuropsychiatric disease = #1 worldwide cause of disability age 10-24 and overall (Lancet, 2011 & 2013)

Current therapies are inadequate
Current knowledge *gap* in clinical neurology and psychiatry…

Brain disorders currently conceptualized of in terms of dysfunctional networks (Bianchi, 2012)

Diagnoses are based on behavior and subjective symptoms, not network dysfunction.

Therapy does not target dysfunctional networks.
Bridging the gap – Diagnosis and therapy targeting dysfunctional networks
Why Pediatrics – Why now?

All neurodevelopmental disorders and almost 2/3 of neuropsychiatric disorders manifest in the pediatric population

(Kessler, 2005)

Prevention or early diagnosis \ intervention leads to better outcomes.

Research on adults may not apply to pediatric patients
Interventions in younger people = better return on investment

- Pediatric depression is common, 11% (nimh.nih.gov)
- 30% of adolescents have complete remission with therapy

• Clinical problem:

- Pediatric depression is common, 11% (nimh.nih.gov)
- 30% of adolescents have complete remission with therapy

- rTMS works for adult depression
- Younger age may be a predictor of treatment response
  (Gershon, 2003; Janicak, 2002, Avery, 2008)
Use of TMS in treating pediatric depression

Adjunctive Use of Repetitive Transcranial Magnetic Stimulation in Depressed Adolescents: A Prospective, Open Pilot Study

Christopher A. Wall, MD; Paul E. Croarkin, DO; Leslie A. Sim, PhD; Mustafa M. Husain, MD; Philip G. Janicak, MD; F. Andrew Kozel, MD, MSCR; Graham J. Emslie, MD; Sheila M. Dowd, PhD; and Shirlene M. Sampson, MD
TMS in depressed adolescents

Prospective, open multicenter trial of rTMS in adolescents that have not responded to two prior antidepressant agents. Age 14 – 17.
TMS in depressed adolescents

Results:
7 of 8 tolerated procedure.
1 dropped out after first 5 minutes, scalp discomfort.
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.
Larger trial ongoing

**rTMS for Depressed Teens: A Sham-Controlled Trial, Part 1**

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2014 by Mayo Clinic

**Sponsor:**
Paul E. Croarkin

**Information provided by (Responsible Party):**
Paul E. Croarkin, Mayo Clinic

ClinicalTrials.gov Identifier: NCT01804270
First received: March 1, 2013
Last updated: August 13, 2014
Last verified: August 2014

Randomized, double-blinded, sham-controlled trial.

N = 50, projected completion 12/2016
Age range 12-21

Sites: Rochester MN, Charleston, South Carolina
Rehabilitation
• **Clinical problem:**

- Pediatric stroke and cerebral palsy are relatively common and rehabilitation often does not restore function

Adam Kirton, Calgary

Warren Lo, Ohio State

Bernadette Gillick, U. Of Minnesota
Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical paediatric stroke: a randomised trial

Adam Kirton, Robert Chen, Sharon Friefeld, Carolyn Gunraj, Anne-Marie Pontigon, Gabrielle deVeber

2008, Lancet Neurology

N = 10, 9-13 yo, 1 Hz contralesional, 100% MT, 1200 pulses, 20 minutes x8 days
Spastic cerebral palsy

Low and high-frequency repetitive transcranial magnetic stimulation for the treatment of spasticity

Angela C Valle PhD;
Karen Dionisio, Department of Pathology,
University of Sao Paulo, Sao Paulo, Brazil.
Naomi Bass Pitskel;
Alvaro Pascual-Leone MD PhD, Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA.
Fernanda Orsati;
Merari J L Ferreira;
Paulo S Boggio PhD, Mackenzie University, Sao Paulo;
Moises C Lima MD;
Sergio P Rigonatti MD PhD, Department of Psychiatry,
University of Sao Paulo, Sao Paulo, Brazil.
Felipe Fregni* MD PhD, Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA.

N = 17, All with CP
Randomized, sham controlled
6 sham, 6 1 Hz, 5 5 Hz
5 sessions; 90% MT
Increased range of motion for 5 Hz
Noninvasive Brain Stimulation: The Potential for Use in the Rehabilitation of Pediatric Acquired Brain Injury

Melissa G. Chung, MD, Warren D. Lo, MD
Epilepsy
Sample case:

15 year old boy was getting dressed this morning when his father heard a loud thud. A few minutes later the father checked on him and he was sleepy, confused and had bit his tongue. The confusion improved over 20 minutes. He has one similar episode, but nobody observed either.
Differential diagnosis...

- Seizure
-Syncope (fainting)
-School avoidance (geometry exam)
A single routine EEG is only ~66% sensitive.

Sleep deprivation, hyperventilation and strobe light slightly improve sensitivity.
Could TMS increase the sensitivity of EEG, moving from a passive test to actively probing for abnormalities?
Late EEG responses triggered by transcranial magnetic stimulation (TMS) in the evaluation of focal epilepsy

*†Antonio Valentin, †Ramamurthy Arunachalam, *Arvin Mesquita-Rodrigues, ‡Jorge J. Garcia Seoane, *Mark P. Richardson, †Kerry R. Mills, and †Gonzalo Alarcon

*Department of Clinical Neuroscience, Institute of Psychiatry, King's College London, United Kingdom; †Department of Clinical Neurophysiology, King's College Hospital, London, United Kingdom; and ‡Departamento de Fisiología, Facultad de Medicina, Universidad Complutense, Madrid, Spain
Study Design:

- Comparing standard EEG to EEG + TMS (single pulse directed at each electrode site, looking for abnormal discharges).

- 15 controls and 15 patients with focal-onset epilepsy

http://www.neuroconn.de/diagnose_en/
Study Results:

- TMS+EEG had no false positive results in controls.
- Sensitivity of standard EEG: 80%
- Sensitivity of standard EEG + EEG\TMS: 100%
Sample case:
15 year old boy with possible seizure.

- EEG: Abnormal
- Which medicine to start?
Could motor cortex neurophysiology, as assessed with TMS, guide medication selection?
TMS neurophysiology measures relate to neurotransmitter systems (e.g. SICI:GABA$_A$ LICI – GABA$_B$ ICF – glutamate)

Seizure medicines work differentially on neurotransmitter systems

We’re beginning to understand how specific medicines impact TMS-measured neurophysiology (e.g. Lang, 2013)

________________

It is possible we could select medicines to correct specific abnormalities in an individual patient.
Sample case:

- EEG: Abnormal
- Which medicine to start?
- Now on keppra
After starting our patient on 1 gram of keppra twice a day the mother asks “how do we know that the medicine is working?”
After starting our patient on 1 gram of keppra twice a day the mother asks “how do we know that the medicine is working?”

Could TMS measures of motor cortex neurophysiology give us a clue as to whether the medication is effective?
Predicting Seizure Control: Cortical Excitability and Antiepileptic Medication

Radwa A. B. Badawy, MB, BCH, MSc, 1,2
Richard A. L. Macdonell, MD, FRACP, FAFRM, 1−3
Samuel F. Berkovic, MD, FRACP, FRS, 1,2
Mark R. Newton, MD, FRACP, 1,2 and
Graeme D. Jackson, MD, FRACP 1−3

ANN NEUROL 2010;67:64−73
Design

- 99 drug naïve patients about to start a seizure medicine had TMS-based neurophysiological testing.
- They had repeat testing 4-16 weeks later.
- They were followed up one year later.
Results

• At one year 69 of 99 were seizure free.
Effective treatment associated with rise in motor threshold
Conclusion

Increased motor threshold and increased intracortical inhibition after starting a seizure medicine may predict its effectiveness.
Sample case:

Now, fast forward 2 years. Our patient has tried multiple medications and seizures persist. An MRI has revealed a focal cortical dysplasia that is the source of the seizures.
Sample case:

fMRI and TMS mapping reveal the dysplasia is immediately adjacent to motor cortex hand and face area. Surgery would risk causing hemiparesis.
TMS for the treatment of epilepsy

Focal epilepsy often does not respond to medication and surgery often is not a viable option.

Low frequency TMS is able to decrease excitability of underlying cortex.

Can 1 Hz rTMS to the seizure focus be used to treat the epilepsy?
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
Design

- 64 patients with medically refractory focal epilepsy
- Group randomly split into treatment and sham groups, defined by strength of TMS pulse (90% vs. 20% motor threshold)
- Daily TMS x14 days.
- Outcome measures: Seizure frequency + epileptiform discharges on EEG
Results

• Significant seizure reduction and improved interictal EEG pattern in treatment group.
• Only 2 patients in treatment group at medial temporal lobe epilepsy and they did not respond
What about therapeutic rTMS with deep seizure foci?
Medial temporal lobe \ hippocampal sclerosis
Ongoing trial, Alex Rotenberg – deep TMS for medial temporal lobe epilepsy.
Bernard Chuang and Mo Shafi
Annals of Neurology, 2015
Epilepsy - Summary

- Increase sensitivity of EEG
- Guide selection of seizure medicine (?)
- Determine efficacy of medication selected
- Presurgical motor and language mapping
- Treat focal epilepsy with low frequency TMS
Epilepsy – Further Reading

- 2014 Review, Current Opinion in Neurology

Transcranial magnetic stimulation for the diagnosis and treatment of epilepsy

Vasilios K. Kimiskidis, Antonio Valentín, and Reetta Kälviäinen

- 2014 Review, Current Opinion in Neurology
Autism Spectrum Disorders
• Clinical problem:

There are no biomarkers or diagnostic tests available to support the diagnosis of autism spectrum disorders.
Abnormal modulation of corticospinal excitability in adults with Asperger’s syndrome

Lindsay Oberman,¹ Mark Eldaief,¹ Shirley Fecteau,¹,² Fritz Ifert-Miller,¹ Jose Maria Tormos³ and Alvaro Pascual-Leone¹,³,⁴

¹Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
Study Design:

- Assessing the brain's response to TMS-induced plasticity.
- 35 patients, 35 controls
Fig. 2. Baseline-corrected MEP amplitude following cTBS and iTBS. Average baseline-corrected MEP amplitude for the control group (in blue) and AS group (in red) at 11 timepoints from 5 to 120 min post-cTBS. Error bars indicate SEM for each timepoint. Values are represented as proportion of baseline amplitude with a line at 1.0 (representing baseline amplitude). The box at the 50-min timepoint represents the criterion determined by the ROC curve to be the point of maximal sensitivity and selectivity between the groups.
TMS use in the diagnosis of autism spectrum disorders

- 93% Sensitive, 80% Specific at 50 minutes
- Is this result specific to autism spectrum or would it be seen in other neuropsychiatric conditions?
- Could this be used as a biomarker of response to therapy?
TMS use in the diagnosis of autism spectrum disorders

Larger trial ongoing.
Therapeutic TMS in Autism Spectrum

- Low frequency DLPFC stimulation given once per week for 12 weeks improved irritability and repetitive behaviors, N=16 (Baruth, 2010) and attention shifting (Sokhadze, 2012)
Use of Transcranial Magnetic Stimulation in Autism Spectrum Disorders

Lindsay M. Oberman¹, ², Alexander Rotenberg¹, ² and Alvaro Pascual-Leone¹
Interesting anecdote – soon to be in press
Switched On: A Memoir of Brain Change
ADHD
Clinical Problem:

ADHD is common and heterogeneous. There are no diagnostic tests for ADHD and up to a third of children with ADHD do not respond to stimulants.

Could TMS be used to aid in diagnosis or therapy?
Short interval intracortical inhibition (SICI) in ADHD Diagnosis

Hyperactivity is inversely correlated to SICI

(Buchmann, 2007; Moll, 2000, Gilbert, 2004)
Therapeutic rTMS for ADHD

Pilot trial supporting safety of 10 Hz Rt DLPFC stimulation – no efficacy over sham, N = 9
Tic Disorder
Clinical Problem:

Tourette’s is often medication unresponsive or medications have harmful side effects (e.g. Haldol).

Could TMS be used to decrease tic frequency?
1-Hz low frequency repetitive transcranial magnetic stimulation in children with Tourette’s syndrome

Ho Jang Kwon\textsuperscript{a}, Won Seok Lim\textsuperscript{b}, Myung Ho Lim\textsuperscript{b,*}, Seong Jae Lee\textsuperscript{c}, Jung Keun Hyun\textsuperscript{c,d}, Jeong-Ho Chae\textsuperscript{e}, Ki Chung Paik\textsuperscript{b}

- 10 subjects – no sham comparison.
- 2 weeks of daily therapy, 10 days
- 1 Hz stimulation applied to supplementary motor area
- Significant reduction in tic frequency
Clinical Study

Transcranial magnetic stimulation at 1 Hertz improves clinical symptoms in children with Tourette syndrome for at least 6 months

Kai Le, Ling Liu, Manli Sun, Ling Hu, Nong Xiao *

Ministry of Education Key Laboratory of Child Development and Disorders, and Chongqing Key Laboratory of Translational Medical Research in Cognitive Development and Learning and Memory Disorders, and Rehabilitation Centre, Children's Hospital, Chongqing Medical University, NO. 136 Zhongshan2nd Road, Yuzhong District, Chongqing 400014, China

• 25 subjects – no sham comparison.
• 4 weeks of daily therapy, 20 days
• 1 Hz, 110% MT to SMA
Summary

• There are promising, albeit small studies supporting the use of rTMS in pediatric patients

• I mentioned a small fraction of the potential uses here…

• We have not discussed pain, schizophrenia, OCD, TBI, etc…

• Large, multicenter, randomized, sham-controlled trials are needed
Recent review – TMS in Pediatrics

Non-invasive brain stimulation for the treatment of brain diseases in childhood and adolescence: state of the art, current limits and future challenges

Carmelo M. Vicario¹* and Michael A. Nitsche²

¹ School of Psychology, The University of Queensland, St. Lucia, QLD, Australia
² Clinic for Clinical Neurophysiology, University Medical Center, Göttingen, Germany
Welcome to Clinical TMS Society

A professional association dedicated to optimizing clinical practice, awareness, and affordability of Transcranial Magnetic Stimulation therapy.