IC 9: NON-INVASIVE BRAIN STIMULATION TRIALS IN HEMIPARETIC CEREBRAL PALSY: MAKING A DIFFERENCE?
AACPDM 2016 HOLLYWOOD, FL
Thursday, September 22, 2016
4:00 PM – 6:00 PM
Disclosure Information
AACPD 70th Annual Meeting | September 20-24, 2016

• **Speaker Name:** Bernadette Gillick, PhD, MSPT, PT, Kathleen Friel, Andrew Gordon, PhD, Yannick Bleyenheuft, PhD, Jason Carmel, MD, PhD

**Disclosure of Relevant Financial Relationships**

We have no financial relationships to disclose.

**Disclosure of Off-Label and/or investigative uses:**

We will discuss the following off label use and/or investigational use in our presentation:

Soterix tDCS LTE, Magstim rTMS Rapid2
Hemiparetic cerebral palsy can affect movement in individuals throughout their lifespan. Current interventions have limited impact on motor function during childhood and across the lifespan. Non-Invasive Brain Stimulation (NIBS) has been used both to assess the excitability of the brain and as an intervention to neuromodulate, or influence, brain activity. In adult and (more recently) pediatric hemiparesis brain stimulation studies, significant improvements in reducing severity and improving motor function have been found. These novel intervention findings are however limited in study design and numbers of individuals studied. Moreover, consensus on optimal dosing has not been established. In this Instructional Course, attendees will discover the current challenges and benefits of applications in non-invasive brain stimulation to discover, are we truly making a difference with these interventions?
recognize the varying forms of non-invasive brain stimulation
familiarize with the variable outcomes associated with non-invasive brain stimulation
describe stimulation-related adverse events in case studies and clinical trials
identify concurrent or complementary therapies and neuroimaging assessments related to stimulation trials

This course will present the current forms of non-invasive brain stimulation researched in children with hemiparetic cerebral palsy, current trials findings, challenges and limitations and a discussion regarding dosing consensus by investigators performing active clinical trials in this field. Additionally, an explanation of adjuvant therapies (e.g.-constraint-induced movement therapy) and investigational tools (e.g.-neuroimaging), and their role in brain stimulation trials, will be explored through a broader panel discussion with related co-investigators on these teams. Such a course provides the opportunity for an audience participant to become familiar with the current state of the art of brain stimulation as a neuromodulatory assessment and intervention tool as relates to cerebral palsy across the lifespan.
4:00-4:20PM: Discussion regarding non-invasive brain stimulation (NIBS) types and mechanisms of action (BTG)

4:20-4:30PM: Audience Interaction with Video Review of Children in NIBS trials (KF)

4:30-4:50PM: Safety and adverse events review. Audience Participation in review of safety surveys for child tolerance to NIBS (BTG)

4:50-5:15PM: Audience Review of 5 Case Reports in current active pediatric NIBS laboratories and trials (KF)

5:15-5:50PM: Audience Interaction with Panel: Investigator's Perspectives, Adjuvant Therapies and Assessment Techniques (AG, YB, JC)

5:50-6:00PM Question and Answer Session (ALL)
Non-invasive brain stimulation (NIBS): types and mechanisms of action
Brain Stimulation

A: Transcranial Electrical
B: Transcranial Magnetic
C: Invasive Leads (also Vagus, Spinal...)

Figure from Marom Bikson
Non-Invasive Brain Stimulation

- Transcranial Magnetic Stimulation (TMS and rTMS)
- Transcranial Direct Current Stimulation (tDCS)
Non-Invasive Brain Stimulation

Investigate Brain Physiology (TMS)

Modify Physiology and Performance (rTMS and tDCS)

Gillick and Zirpel, 2012

Gillick Lab, tDCS and CIMT
clinicaltrials.gov # NCT02250092
Neuromodulation as a Research Intervention

Repetitive Transcranial Magnetic Stimulation

Transcranial Direct Current Stimulation
Neurobiological Effects of Non-Invasive Brain Stimulation

• Influence firing of the neuron
• Modulate gene expression
• Modify the release of neurotransmitters

Lefaucheur, 2008, Medina and Tunez 2013
Animal Studies

Fig. 1. Electrode montage used for transcranial DC stimulation in the rat. (a) The epicranial electrode (contact area = 3.5 mm²) is fixed onto the skull unilaterally above the frontal cortex (1.5 mm right and 2 mm anterior to bregma) using dental cement. (b) Before DC stimulation the epicranial electrode is filled with saline solution. A large rubber plate mounted on the chest serves as the counter electrode (b).

Safety limits of cathodal transcranial direct current stimulation in rats

David Liebetanz, Reinhard Koch, Susanne Mayenfels, Fatima König, Walter Paulus, Michael A. Nitsche

Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016

Exogenous Stimulation Restores Motor Skill

Friel et al.
Stimulation or Training Strengthen and Reroute Corticospinal Projections

Stim, Training restore connections to motor laminae of spinal cord

Salimi, Friel, Martin 2008
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

Figure 2: Grip strength of the affected hand: mean differences from baseline
Bars indicate SE. Differences between the rTMS and sham groups were significant at day 10 (p=0.009) and day 17 (p=0.01), 1 week after cessation of treatment.

Figure 3: MAUEF scores: mean differences from baseline
Bars indicate SE. Differences between the rTMS and sham groups were significant at day 10 (p=0.002) but, unlike the difference in grip strength, the difference in MAUEF was not sustained after 1 week of no treatment (day 17).
Primed low-frequency repetitive transcranial magnetic stimulation and constraint-induced movement therapy in pediatric hemiparesis: a randomized controlled trial

BERNADETTE T GILICK1 | LINDA E KRACH1 | TIM FEYMA2 | TONYA L RICH3 | KELLI MOBERG3 |
WILLIAM THOMAS4 | JESSICA M CASSIDY1 | JEREMIAH MENK5 | JAMES R CAREY1
"Addition of rTMS or CIMT doubled the chances of significant improvement with additive effect."

"The effect of the camp itself was large with most children showing sustained functional gains at 6 months."
Synergistic effect of combined transcranial direct current stimulation/constraint-induced movement therapy in children and young adults with hemiparesis: study protocol

Bernadette Gillick1, Jeremiah Menk2, Briyon Mueller3, Gregg Meekins4, Linda E. Krach5, Timothy Feyma6 and Kyle Rudser7
Making a Difference?

• Types
• Mechanisms
Video Review of Children in NIBS trials
Making a Difference?

- Participant Feedback
- Caregiver Feedback
Safety and adverse events review for child tolerance to NIBS
243 reported/322 total

95 reported/191 total
Therapeutic Brain Stimulation Trials in Children With Cerebral Palsy

B.T. Gillick
University of Minnesota, Minneapolis, MN, United States

K.M. Friel
Burke-Cornell Medical Research Institute, White Plains, NY, United States; Weill Cornell Medical College, New York, NY, United States

J. Menk, K. Rudser
University of Minnesota, Minneapolis, MN, United States
Reported Adverse Events

"All patients were able to tolerate the TMS treatments, with no incidence of seizures"

"No serious adverse events reported. Two patients had single episodes of neurocardiogenic syncope with their initial exposure to TMS, two patients reported mild headache, one nausea and neck stiffness"

"No serious adverse event were reported; the most common minor adverse events were self-limiting headache, which resolved within 24 h after rTMS, and cast irritation."

Reported Adverse Events

Statements “One child complained of discomfort and withdrew from study.” “One child was comfortable after the experimenters reduced the stimulator current.”

One drop out, one child with rash and mild skin burn which resolved in 3 days

Redness (n = 3), tingling (n = 18)

Statement “No adverse effects were found”

No serious adverse events reported. Report of “discomfort” in three participants which abided after adjusted intensity.

Redness and tingling (n = 3) in experimental group

No serious adverse events reported. Tingling for “most patients”. Two cases Reduced stimulation to 1.5 due to skin discomfort, mild headache, n = 1

Statement “No child experienced any serious adverse event throughout the study. Four children reported mild tingling with anodal tDCS”

None mentioned.

Statement “No serious adverse events, including seizure, occurred.” Most common side effects itchiness, burning, sleepiness, difficulty concentrating.
Cerebral Palsy

• In 19 recent studies investigating NIBS in a combined 291 children with CP:
  – 11 (58%) incorporated, at minimum, a statement regarding adverse events
  – Of the percentage who did report adverse events, statements varied from “no adverse events were reported” to “no adverse events occurred.” All of those studies, however, reported details regarding the adverse events, and in some cases detailed the duration of the complaint and the amelioration techniques.
  – Of the 291 total children with CP receiving TMS or rTMS in these combined 19 studies, only 6 (2%) reportedly withdrew from the studies due to discomfort or related adverse event.

Gillick, Gordon, Bleyenheuft, Carmel, Rich, Friel, in preparation
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

**Figure 2:** Grip strength of the affected hand: mean differences from baseline. Bars indicate SE. Differences between the rTMS and sham groups were significant at day 10 (p=0.009) and day 17 (p=0.01), 1 week after cessation of treatment.

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Neurocardiogenic Syncope Complicating Pediatric Transcranial Magnetic Stimulation

Adam Kirton, MD, MSc*, Gabrielle deVeber, MD, MHSc†, Carolyn Gunraj, MSc‡, and Robert Chen, MBBCChir, MSc‡
<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Real rTMS Plus mCIMT Group (N=10)</th>
<th>Sham TMS Plus mCIMT Group (N=9)</th>
<th>Comparing the No. of Children With Complaints Between Groups (P)</th>
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<tbody>
<tr>
<td>No. of Children With Complaints</td>
<td>Total Overall No. of Complaints</td>
<td>No. of Children With Complaints</td>
<td>Total Overall No. of Complaints</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Cast irritation</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Tingling</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Mood changes</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Concentration</td>
<td>2</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Abnormal muscle contractions</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Stomachache</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>1</td>
<td>1</td>
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Safety of Primed Repetitive Transcranial Magnetic Stimulation and Modified Constraint-Induced Movement Therapy in a Randomized Controlled Trial in Pediatric Hemiparesis

Bernadette T. Gillick, PhD, MSPT, PT, Linda E. Krach, MD, Tim Feyma, MD, Tonya L. Rich, OTL/R, Kelli Moberg, OTL/R, Jeremiah Menk, MS, Jessica Cassidy, DPT, Teresa Kimberley, PhD, PT, James R. Carey, PhD, PT
<table>
<thead>
<tr>
<th>Group</th>
<th>REAL rTMS/CIT</th>
<th>SHAM rTMS/CIT</th>
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<tbody>
<tr>
<td>Satisfaction (0-10)</td>
<td>7.2 ± 2</td>
<td>8.9 ± 2</td>
</tr>
<tr>
<td>Re-enrollment? (%)</td>
<td>88</td>
<td>86</td>
</tr>
<tr>
<td>Recommendation? (%)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**Safety of Primed Repetitive Transcranial Magnetic Stimulation and Modified Constraint-Induced Movement Therapy in a Randomized Controlled Trial in Pediatric Hemiparesis**

Bernadette T. Gillick, PhD, MSPT, PT, a Linda E. Krach, MD, a,b Tim Feyma, MD, b Tonya L. Rich, OTL/R, b Kelli Moberg, OTL/R, b Jeremiah Menk, MS, c Jessica Cassidy, DPT, a Teresa Kimberley, PhD, PT, a James R. Carey, PhD, PT a
Replicative Transcranial Magnetic Stimulation/Behavioral Intervention Clinical Trial:
Long-Term Follow-Up of Outcomes in Congenital Hemiparesis

Tonya L. Rich, MA, OTR/L1 Jeremiah Menk, MS2 Linda E. Krach, MD3 Timothy Feyma, MD4 and Bernadette T. Gillick, PhD, MSPT, PT5
Synergistic effect of combined transcranial direct current stimulation/constraint-induced movement therapy in children and young adults with hemiparesis: study protocol

Bernadette Gillick, Jeremiah Menk, Byron Mueller, Gregg Werking, Linda E. Krach, Timothy Feyma and Kyle Ruther
Perinatal Stroke: Understanding Brain Reorganization through Infant Neuroimaging and Neuromodulation

Neuroimaging- MRI, DTI, Resting-State fMRI
General Movement Assessment
Cortical Excitability and Organization- TMS
Making a Difference?

• Adverse Events Identification
• Adverse Events Management
Case Reports in current active pediatric NIBS laboratories and trials

Transcranial Magnetic Stimulation

Repetitive Transcranial Magnetic Stimulation

Transcranial Direct Current Stimulation
Panel: Investigator's Perspectives, Adjuvant Therapies and Assessment Techniques

Selective Manipulation of Neural Circuits

Hong Geun Park1, Jason B. Carmel1,2

Hand and Arm Bimanual Intensive Therapy Including Lower Extremity (HABIT-ILE) in Children With Unilateral Spastic Cerebral Palsy: A Randomized Trial

Yannick Bleyenheuft, PhD1, Carlyne Arnould, PhD2, Marina B. Brandao, PhD3, Corrine Bleyenheuft, MD1,4, and Andrew M. Gordon, PhD5

Skilled Bimanual Training Drives Motor Cortex Plasticity in Children With Unilateral Cerebral Palsy

Kathleen M. Friel, PhD1,2, Hsing-Ching Kuo, MS2, Jason Fuller, PhD1,4, Claudio L. Ferre, PhD2, Marina Brandão, PhD2, Jason B. Carmel, MD, PhD1,2, Yannick Bleyenheuft, PhD2, Jaimie L. Gowatsky, MA1, Arielle D. Stanford, MD2, Stefan B. Rowny, MD1, Bruce Luber, PhD1, Bruce Bassi, MD1, David L. K. Murphy1, Sarah H. Lisanby, MD1, and Andrew M. Gordon, PhD1,3

Pediatric Issues in Neuromodulation: Safety, Tolerability and Ethical Considerations

K.M. Friel
Burke-Cornell Medical Research Institute, White Plains, NY, United States; Weill Cornell Medical College, New York, NY, United States

A.M. Gordon
Teachers College of Columbia University, New York, NY, United States; Columbia University Medical Center, New York, NY, United States

J.B. Carmel
Burke-Cornell Medical Research Institute, White Plains, NY, United States; Weill Cornell Medical College, New York, NY, United States

A. Kirton
University of Calgary, Calgary, AB, Canada

B.T. Gillick
University of Minnesota, Minneapolis, MN, United States
Making a Difference?

- Mechanisms
- Outcomes
- Adverse Events
- Interventions
Question and Answer Session

Bernadette T. Gillick, PhD, MSPT, PT
University of Minnesota

Kathleen Friel, PhD
Burke Rehabilitation Center and Weill Cornell Medical College

Andrew Gordon, PhD
Teachers College Columbia University

Yannick Bleyenheuft, PhD PT
Université catholique de Louvain

Jason Carmel, MD, PhD
Weill Cornell Medical College
Blythedale Children’s Hospital