Using Transcranial magnetic stimulation to improve our understanding of Transverse Myelitis

Kathy Zackowski, PhD, OTR
Kennedy Krieger Institute
Johns Hopkins University School of Medicine
- TMS (transcranial magnetic stimulation)
  - Definition
  - Applications
    - Diagnostic tool
    - Therapeutic intervention
- Studying brain and spinal cord function in Transverse Myelitis
In the last 3 decades our view of the CNS has changed.

Formerly believed to be a rigid structure, not plausible of changing, now believed to be plastic and dynamic, constantly changing.

The change in dogma resulted from technological advancement in all levels.

Human studies => PET, fMRI, TMS, MEG
Transcranial magnetic stimulation is a tool used to study:

- **connectivity** of neuronal pathways
- **cortical plasticity** and its **mechanisms**
- **behavioral** consequences of noninvasive transient inactivation of specific cortical sites.

Electrophysiological results could indicate the underlying systems or pathways effected and, provide useful insight into the mechanism of action.
An electric pulse induces a rapidly changing magnetic field with lines of flux that runs perpendicular to the coil.

Courtesy of Pablo Celnik
TMS activates excitatory and inhibitory presynaptic fibers to the pyramidal upper motor neuron

Courtesy of Pablo Celnik
Motor Evoked Potential
MEP
(Measurement of cortical excitability)

Courtesy of Pablo Celnik
Similar to peripheral nerve studies, conduction time is measured from different stimulation sites (i.e. Motor cortex, brainstem, cervical roots)
1. Diagnostic tool
   a) Central conduction time
   b) Measuring cortical excitability
      • Motor Threshold
      • Recruitment Curves
      • Intracortical Inhibition (ICI)
      • Intracortical Facilitation (ICF)
      • Interhemispheric inhibition (IHI)
   c) Probing cortical function

2. Therapeutic intervention
   a) To induce plasticity
   b) To modulate behavior
Motor Threshold (MT)

- Lowest stimulus intensity that evoke MEP of 50 mV in 5 of 10 trials in a target muscle during 2% reductions in intensity from above threshold (Rossini 1994)
- Drugs that block voltage-gated sodium channels elevate motor threshold (Ziemann 1996)
Recruitment Curve (RC)

Determines the slope of the input-output curve by increasing the stimulus intensity (input) while measuring the resultant MEP amplitude (output) change (Cohen 1998).

*Provides information regarding the level of excitability of the entire network investigated.*
Intracortical Excitability

- Short Intracortical Inhibition (sICI)
- Short intracortical Facilitation (sICF)
Intracortical Excitability

- Short Intracortical Inhibition (sICI)
- Short intracortical Facilitation (sICF)
What studies have been done involving transverse myelitis?
Motor cortex excitability changes following a lesion in the posterior columns of the cervical spinal cord

Raffaele Nardone a,*, Stefan Golaszewski c, Jürgen Bergmann c, Alessandro Venturi b, Igor Prünster d, Arianna Bratti a, Günther Ladurner c, Frediano Tezzon a

an isolated lesion in the posterior white columns of the spinal cord may lead to long-term changes in motor cortex. Can sensory training help?
Motor recovery paralleled MEP improvements
Motor recovery paralleled MEP changes. Sample size small!
• TMS can be used to understand brain processes (diagnostic tool) or to induce plastic changes (therapeutic tool) like excitability changes or modulation of behavior.

• Understanding the basic physiology mechanisms associated to motor behavior has permitted the development of novel strategies to enhance recovery processes in patients with CNS lesions.
How can we use this technique to provide additional information about TM?

Evaluate the effectiveness of a known pharmacologic therapy
New Study
Efficacy of Sustained Release Oral Dalfampridine in Transverse Myelitis

Site
Johns Hopkins University, Transverse Myelitis Center

Study Investigators
Michael Levy
Carlos Pardo
Daniel Becker
Kathleen Zackowski
Fampridine (4-aminopyridine)
- Amplified conductivity in demyelinated peripheral nerves
- Limited therapeutic window due to stimulation of seizure activity

What is Oral Dalfamridine (Ampyra)?
What do we know about dalfampridine’s effects?

Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial

Andrew D Goodman, Theodore R Brown, Lauren B Krupp, Randall T Schapiro, Steven R Schwid*, Ron Cohen, Lawrence N Marinucci, Andrew R Blight, on behalf of the Fampridine MS-F203 Investigators†
Results:

Figure 3: Percent change in walking speed at each visit after randomisation
The fampridine-treated timed walk responders showed a sustained improvement during the treatment period that was completely reversed at 2-week and 4-week follow-up visits. The fampridine-treated timed walk non-responders showed a significant improvement compared with the placebo group only for visit 3 (2 weeks after randomisation). TW = timed walk. *Means fampridine TW responders are greater than placebo and fampridine TW non-responders (p<0.001). †Means fampridine TW non-responders are greater than placebo only (p<0.001).

(Goodman et al., 2009)
Dalfampridine, a sustained-release potassium channel blocker that has been shown to be effective in improving gait and other neurologic functions in people with MS.

Dalfampridine has the potential to improve gait and neurologic function in patients with TM because it shares a similar pathogenic process with MD.

We hypothesize that Dalfampridine will improve gait and neurologic function in patients with TM, and that TMS will improve our understanding of what the characteristics are for “responders”.
Study Protocol for TM:

- **0**: 2-week Placebo Run-in
- **2**: Dalfampradine
- **4**: Dalfampradine
- **6**: Placebo
- **8**: Placebo
- **10**: Dalfampradine
- **12**: Dalfampradine
- **14**: Placebo
- **16**: Placebo
- **18**: 2-week Follow-up
- **20**: 2-week Follow-up

8-week cross over treatment period
Inclusion criteria for this study include:

• Diagnosis of idiopathic transverse myelitis confirmed by MRI

• Gait impairment defined by a timed 25-foot walk

• Age 18-70 yrs

We are happy to answer questions about this study. Email Maureen Mealy at mmealy1@jhmi.edu if you are interested in participating.
Thank you for your support!