Using Cerebellar Stimulation to Study Cerebellar Function
Part 1: Transcranial Magnetic Stimulation

John E. Desmond

Department of Neurology
Johns Hopkins University

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The Johns Hopkins Brain Science Institute
Large Capacitor

http://ohio.com
Capacitor Bank
Capacitor Discharge

Magnusson & Stevens, 1911

http://dipity.com

Sparing & Mottaghy (2008)
*Methods*, 44, 329
Simplified TMS Circuit
Basic Principles

• Capacitors discharge produces strong (10,000A) brief (200 us) rapidly changing current
• This induces a perpendicular magnetic field that easily penetrates the scalp and skull
• The magnetic field induces a current of opposite direction in brain tissue

\[ E \sim \frac{dB}{dt} \]
Induced Voltage from Monophasic Pulse

Max dB/dt

Types of TMS Coils

- Circular
- Figure of 8, or Double Coil
- Double Cone
Magstim Figure Eight Coil Construction

Air-Cooled Double Coil

http://mitcheliryrlivejournal.com
Specificity or Focality of TMS

- Depends on Coil Geometry and stimulation intensity
Effects of Coil Geometry On Region of Stimulation
Fig. 3. Stimulated areas on a hemisphere for relative stimulation intensities ranging from 110 to 200% with three different figure-8 coils: Medtronic, Magstim and an idealized 50 mm coil. The Medtronic coil was calculated with two orientations: (1) ‘normal’ orientation with the wings angled along the convexity of the head, (2) ‘flipped’ with the wings pointing away from the convexity. The idealised coil consists of two single loops with a diameter of 50 mm each. Calculations are based on a sphere with \( r_{\text{Cortex}} = 8 \) cm, coil–cortex distance is \( d = 1.5 \) cm (inset on the right).

Coil Magnetic Field Measurements
Setup For Field Measurements
Induced Current

Fig. 1. Physical and physiological principles of TMS. The current $I(t)$ in the coil generates a magnetic field $B$ that induces an electric field $E$. The lines of $B$ go through the coil; the lines of $E$ form closed circles. The middle drawing in the upper line illustrates schematically a lateral view of the precentral gyrus in the right hemisphere. Two pyramidal axons are shown, together with a typical orientation of the intracranial $E$. The electric field affects the transmembrane potential, which may lead to local membrane depolarization and firing of the neuron. The lower line represents the potential TMS-induced macroscopic responses at the neurophysiological and behavioral level. Adapted from Ruohonen and Ilmoniemi [62].
Standardizing TMS Magnitude

• Most studies find Motor Cortex threshold and set experiment intensity as some percent of that threshold
  – RMT = Resting motor threshold
  – AMT = Active motor threshold (measured during muscle contraction)
    • usually 10-20% lower than RMT
TMS Pulse Types

Monophasic

Biphasic

Optimum Coil Orientation: Motor Cortex Threshold

Obtaining Motor Cortex Threshold

- **Neurophysiological**: Lowest stimulator output that produces EMG response in 5/10 administrations
- **Visualization**: Lowest stimulator output that produces perceptible thumb, wrist, or finger movement in 5/10 administrations
- Pridmore et al *J ECT*, 14 (1998) 25-7, found thresholds to be similar in the 2 methods, with a trend for greater sensitivity (lower threshold) for the visualization method
Motor vs Phosphene Threshold

- Motor cortex threshold (MT) has been used to standardize stimulation amplitude
- However, studies have shown no correlation between phosphene threshold and MT
Greater cortical depth yields a reduction of effective brain stimulation. A: motor threshold (MT) provides a convenient measure of the cortical effect of transcranial magnetic stimulation (TMS). Stimulation applied to the scalp overlying motor cortex (M1) induces overt motor activity in the contralateral hand muscle that can be identified visually (Pridmore et al. 1998) or recorded using an electromyogram (Rossini et al. 1994). MT is defined as the minimum percent of stimulator output required to reliably induce a motor response. B: structural magnetic resonance imaging (MRI) scans reveal substantial variation in the cortical depth of M1 between individuals. The white line indicates the cortical surface of M1. C: effect of individual variations in the depth of M1 was revealed by comparing observed MT with the scalp-cortex distance measured at M1. Each data point represents an individual participant, and the straight line represents a linear regression. As illustrated, individuals with greater scalp-cortex distances tend also to have a higher MT.
FIG. 3. The depth of underlying cortex varies across the surface of the scalp. A: scalp-cortex distance was measured across a range of brain regions. Mean ± SD of the distances between scalp and cortex are shown for each site. Frontal sites (blue): primary motor cortex (M1/BA4: circle), middle frontal gyrus (MFG/BA9: triangle), inferior frontal gyrus (IFG/BA45: diamond). Temporal sites (red): superior temporal gyrus (STG/BA22: triangle), middle temporal gyrus (MTG/BA 21: diamond). Parietal sites (purple): superior parietal lobule (SPL/BA7: triangle) and angular gyrus (AG/BA39: diamond). Occipital lobe sites (green): primary visual cortex (V1/BA17: triangle) and secondary visual cortex (V2/BA18: diamond). [B] Scalp-cortex distances for each voxel representing the scalp surface, shown in the right hemisphere of one participant. Distance is color-coded, with red representing small distances, and blue/purple representing large distances.
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<tr>
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<td>4.0***</td>
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<td>0.38</td>
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Upper entries denote the mean difference in scalp-cortex distance (mm) between sites (x_i-x_j), and lower entries are the respective correlation values. MRI, magnetic resonance imaging; MFG and IFG, middle and inferior frontal gyrus; SPL, superior parietal lobe; AG, angular gyrus; STG and MTG, superior and middle temporal gyrus; V1 and V2, primary and secondary visual cortex. *P < 0.01, **P < 0.001.
Adjusting for Skull Thickness

\[ \text{AdjMT\%} = \text{MT} + m(D_{\text{SiteX}} - D_{M1}) \]

AdjMT\% is adjusted MT in % stimulator output
MT is unadjusted MT in % stimulator output
\(D_{M1}\) is distance from scalp to M1
\(D_{\text{SiteX}}\) is distance from scalp to second cortical region
\(m\) is spatial gradient relating MT to distance (~3)

Types of TMS Studies

- **Sham**: Special coils designed to click but not stimulate the brain
  - Economy version: Tilt coil on its side
- **Single-pulse**: Non-cyclical, seconds between trials
- **Paired pulse**: Short interval (ms range) between successive pulses. Initial “conditioning” pulse can affect ensuing “test” pulse, depending on inter-pulse interval
- **Repetitive (rTMS)**:
  - Low frequency: $\leq 1$ Hz
  - High frequency: $> 1$ Hz
  - Theta burst
    - cTBS: Continuous theta burst
    - iTBS: Intermittent theta burst
Theta Burst

50 Hz

5 Hz

cTBS

20 or 40 sec total
300 or 600 pulses

iTBS

10 sec

2 sec

190 sec total
600 pulses
Special Considerations for Cerebellar TMS

- Depth of Stimulation
- Proximity to neck muscles
Deeper Stimulation

Double Cone Coil

Used in 319 publications:
103 Cerebellum
68 Brainstem
148 Motor/supp motor
(Ugawa: induced current flowing up using monopolar stim)

H-Coil

H-Coil Depth of Stimulation

Fig. 2. Intensity needed for APB stimulation at different heights above the scalp. Resting motor threshold of the APB was measured at different distances above the 'hot spot' when using either the H-coil or the figure-8 coil. The % of stimulator power needed to reach the resting motor threshold vs. the distance of the coil from the 'hot spot' on the skull is plotted. The points represent means and SDs of 6 healthy volunteers.

Depth of Stimulation

Figure of 8 Coil

Neuronal Stimulation ~ 20-60 V/m


Brainstem Stimulation with DCC: Collision Evidence

Motor Cortex  ------------>  Corticospinal tract  <------------>  Spinal Cord

Cortex-Brainstem Interval

-2 ms  -1 ms  0 ms  +1 ms  +2 ms

Cortex alone

Brainstem alone

cortex + brainstem

superimposition

TMS Targeting

- High Tech Expensive Approach: Neuronavigation
- Low Tech Cheap Approach: EEG electrode position
TMS Neuronavigation
The 10-20 Electrode System and Cerebral Location

Richard W. Homan, M.D.

Department of Neurology
University of Texas Southwestern Medical Center
Dallas, Texas
Regional Epilepsy Center
Veterans Administration Medical Center
Dallas, Texas 75216

ABSTRACT. In the three decades since it was introduced, the International 10-20 System of electrode placement has become the standard for locating scalp electrodes in EEG. The technique employs measurements of external cranial landmarks to locate the electrodes on the scalp. This process assumes a consistent correlation between scalp electrode locations and underlying cerebral structures.

KEY WORDS. Cerebral structures, external cranial landmarks, International 10-20 Electrode System, scalp electrodes.

In 1982, Binnie et al. found that the quadrants bounded by the nasion, inion, and preauricular points varied in size by more than 10% in the majority of normal subjects, thus casting some doubt upon the basic assumption of a consistent correlation between scalp locations and cerebral structures. The original data which suggested a consistent relationship was obtained by studying post-operative X-ray of surgical clips placed along the central and sylvian fissures in living subjects on the one hand, and by marking cadaver brains through holes drilled in the skull at electrode sites on the other (Jasper 1958). Blume et al. (1974) found some degree of variability of the cortical landmarks which underlie the scalp electrode positions. They studied infant cadavers and found
The 10-20 System of EEG Electrode Placement
FIG. 2. A and B. Left and right hemispheres showing cortical location of scalp markers placed according to the 10-20 system. Shading represents primary Brodmann area of cortical loci. Numbers indicate subjects with >10% cranial asymmetry, letters indicate subjects with minimal cranial asymmetry.

**Brodmann Areas for EEG 10-20 Electrode Positions**

**TABLE 2.** Primary cortical location of scalp electrodes

<table>
<thead>
<tr>
<th>Electrode Position</th>
<th>Brodmann Location</th>
<th>Cortical Location</th>
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<tbody>
<tr>
<td>Fp1,2</td>
<td>10</td>
<td>Rostral limit of superior frontal gyrus</td>
</tr>
<tr>
<td>F3,4</td>
<td>46</td>
<td>Middle frontal gyrus, near superior frontal sulcus; rostro-caudal location—even</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with temporal pole</td>
</tr>
<tr>
<td>F7,8</td>
<td>F7–45</td>
<td>Inferior frontal gyrus rostral portion of pars triangularis</td>
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<tr>
<td>C3,4</td>
<td>F8–46</td>
<td>Inferior frontal gyrus rostral portion of pars triangularis</td>
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<td></td>
<td>4</td>
<td>Precentral gyrus, shoulder to wrist area, caudal to middle frontal gyrus</td>
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<tr>
<td>P3,4</td>
<td>7</td>
<td>Superior parietal lobule near intraparietal sulcus, superior to posterior portion</td>
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<td></td>
<td></td>
<td>of supramarginal gyrus</td>
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<tr>
<td>TP3,4</td>
<td>40</td>
<td>Inferior parietal lobule, anterior portion of supramarginal gyrus</td>
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<tr>
<td>T1,2</td>
<td>38</td>
<td>Temporal pole overlapping superior temporal sulcus, more in middle than superior</td>
</tr>
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<td></td>
<td></td>
<td>temporal gyrus</td>
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<tr>
<td>T3,4</td>
<td>T3–21</td>
<td>Overlapping middle and superior temporal gyri, rostro-caudal location—posterior to</td>
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<tr>
<td></td>
<td>T4–22</td>
<td>rolandic fissure</td>
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<tr>
<td>T5,6</td>
<td>T5–37</td>
<td>Left-middle temporal gyrus caudal to termination of sylvian fissure</td>
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<td></td>
<td>T6–19,37,39</td>
<td>Right overlapping superior temporal sulcus, with rostro-caudal location even with</td>
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<td></td>
<td></td>
<td>termination of sylvian fissure</td>
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<tr>
<td>O1,2</td>
<td>17</td>
<td>Occipital lobe, lateral and superior to occipital pole, overlapping calcarine</td>
</tr>
<tr>
<td></td>
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<td>fissure</td>
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TMS Administration
Methods

Advantages of TMS in the Study of Cognition

- “Virtual Lesions” under experimental control
  - Test the necessity of regions highlighted by functional activation studies
  - Unlike real lesions, compensatory changes/re-wiring has not had a chance to occur
Verbal Working Memory Deficit from a Cerebellar Lesion

Advantages of TMS in the Study of Cognition

• “Virtual Lesions” under experimental control
  – Test the necessity of regions highlighted by functional activation studies
  – Unlike real lesions, compensatory changes/re-wiring has not had a chance to occur

• Temporal resolution

• Connectivity
Virtual Lesion: Online rTMS

Example: Speech Arrest
Speech Arrest with TMS

Daily Telegraph
http://www.youtube.com/watch?v=XJtNPqCj-iA
Virtual Lesion: Offline rTMS

Two critical findings for doing offline rTMS studies
Frequency Dependence of TMS-induced Effects

- 0.9 Hz TMS to motor cortex for 15 minutes decreased MEP by ~20% for at least 15 minutes after 15 min of stimulation (Chen et al. *Neurology*, 48, 1997, 1398-403)
- Not observed at 0.1 Hz
- 5 Hz has shown opposite effect of increased cortical excitability
Effects of Continuous (cTBS) vs Intermittent (iTBS) Theta Burst Stimulation

Single Pulse

- Highlights temporal resolution of TMS
Task Phase Specific Cerebellar Activation During Verbal Working Memory

Encoding Phase

X J F Q V C

Read Letters

Maintenance Phase

Remember (Rehearse) Letters

Retrieval Phase

Decide if Probe Matches a Letter

TMS Target

R L
TMS Three-Step Procedure

**Day 1: Initial fMRI scan**
- Finger tapping for motor cortex
- Cognitive task of interest (working memory) for structure of interest (cerebellum)

**Day 2: Identify MRI landmarks**
- Bridge of nose, tip of nose, ear notches
- Map functional scan onto high-res anatomy

**Day 3: TMS experiment**
- Coregistration: Find MRI landmarks on subject’s head
- Determine motor cortex threshold
- Administer TMS to region of interest while subject performs task
TMS Targeting: Subject-Specific Localization of Right Superior Cerebellar Activation Obtained from Verbal Working Memory Task

Posterior View of Cerebellum for 5 subjects
Targeting Cerebellar Activation

Surface Landmarks

TMS Coil Positioning
Tasks

1. Verbal Working Memory
   - X J F Q V C
   - 1.5 s
   - 4.0 s
   - 0.8 s
   - 2.5 s
   - Identifying the presented letter
   - TMS Stim (50% of trials)

2. Verbal Working Memory (Sham Coil)
   - X J F Q V C
   - 1.5 s
   - 4.0 s
   - 0.8 s
   - 2.5 s
   - Identifying the presented letter
   - Sham Stim (50% of trials)

3. Motor Control
   - # # # # #
   - 1.5 s
   - 4.0 s
   - 0.8 s
   - 2.5 s
   - Identifying the “x”
   - TMS Stim (50% of trials)
TMS Effects on Reaction Time

Motor Control
- Stim: 700 msec
- No Stim: 650 msec
- p < .03

Verbal Working Memory
- Stim: 1200 msec
- No Stim: 1150 msec
- p < .02

Verbal Working Memory (Sham Coil)
- Stim: 1100 msec
- No Stim: 1120 msec
- N.S.

Trial Type
- Stim
- No Stim
Motor vs Cognitive RT Effects from Cerebellar TMS

Motor Control
Verbal Working Memory

TMS - NO TMS Reaction Time diff (msec)

Condition

p < .03
Chronometric Study: N-Back Task

Fig. 3. Accuracy in the 2-back task as a function of time of TMS stimulation. The mean accuracy was 87 ± 5%. The TMS interference peaked at 180 ms at the right inferior parietal cortex (IP), at 220 ms at the left IP and right middle frontal gyrus (MFG), and finally at 260 ms at the left MFG (all P < 0.05).

TMS Control Conditions

• Sham Stimulation
  – Special Sham coils expensive
  – Rotated real coil is cheaper, but watch out for edge stimulation
  – Controls for distracting click, but does not have the same tactile sensation as real coil

• Stimulation of “non-involved” region
  – Vertex has been used in many studies
  – Non-involvement is assumed but not really confirmed
Cerebellar single, paired-pulse and rTMS Studies

• Most studies: Motor control and cerebellar-cortical connectivity (Pablo)

• Fewer cognitive studies:
  – Timing production (e.g. Theoret et al., 2001): Variability increased in paced finger tapping
  – Timing perception (e.g., Koch et al., 2006): Disruption of msec timing perception
  – Procedural learning (e.g., Torriero et al., 2004): Disruption of serial reaction time task
  – Verbal working memory (Desmond et al., 2005): Disruption of encoding
  – Emotion control (e.g., Schutter et al., 2009): Increase in negative emotion after viewing aversive pictures after vermis rTMS
Concurrent TMS/fMRI to Investigate Human Brain Connectivity
Cortico-Ponto-Cerebellar circuitry
Hypothesized Cerebro-Cerebellar Verbal Working Memory Circuitry

Articulatory Control System

Phonological Store

Frontal

Temporal-Parietal

Neocortex

Pontine Nuclei

Cerebellar Cortex

Medial PN

Lateral PN

Superior

Inferior
Combined (Interleaved) TMS/fMRI
Feasibility first demonstrated by Bohning (1998)

Acknowledgement:
Jeff Yau
TMS Papers Published Per Year

### Table 1: Summary of parameters used in combined TMS/fMRI studies to date

<table>
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<th>Loc</th>
<th>Mag (%)</th>
<th>Freq (Hz)</th>
<th>Dur (s)</th>
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<th>ICI</th>
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<td>M1</td>
<td>100, 120</td>
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<td>3</td>
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<td>(16, 17)</td>
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**Interleaved TMS/fMRI Investigations (N=24)**
TMS/fMRI Technical Challenges

- Appropriate TMS pulse and coil construction
- Keeping noise out of the MRI
- Preventing TMS interference with MRI data acquisition
TMS/fMRI Technical Challenges

- Appropriate TMS pulse and coil construction
- Keeping noise out of the MRI
- Preventing TMS interference with MRI data acquisition
TMS Pulse Types

Monophasic

Biphasic
MRI-Compatible TMS Coil
TMS/fMRI Technical Challenges

• Appropriate TMS pulse and coil construction
• Keeping noise out of the MRI
• Preventing TMS interference with MRI data acquisition
TMS/fMRI Technical Challenges

- Appropriate TMS pulse and coil construction
- Keeping noise out of the MRI
- Preventing TMS interference with MRI data acquisition
Interleaved TMS/fMRI
Pilot Testing at the Kirby Center
Closed End Head Coil
Difficult for TMS
Flex Coil
Fiducial Calculations
Calculation of TMS Trajectory Using Vector Cross Product
Step 1. Locate 3 points along Gd-filled marker

Step 2. Visualize slice to identify marker vertex and to compute TMS projection

Step 3. Estimate and label cortical stimulation site

Step 4. Normalize image and identify estimated cortical stimulation site
TMS/fMRI Sequence

TR = 1 sec

Time

800 ms 100 ms 100 ms
Interleaved TMS/fMRI Block Design

10 sec  20 sec

1 Cycle

5 Cycles Total…
Coregistration of Anatomy With Functional Scan
Spatial Normalization of Anatomy to MNI Template

MNI T1 Template

Subject’s MPRAGE Scan
Apply Normalization Transform to Functional Scan
Cortico-Ponto-Cerebellar Circuitry Visualized with Interleaved TMS/fMRI
TMS/fMRI Average Activations, N = 4
Conclusions

• Concurrent TMS/fMRI can probe connectivity in the human brain
  – Allowing non-invasive neuroanatomy studies in healthy humans
  – A possible clinical tool for assessing altered connectivity, e.g., schizophrenia, TBI
TMS Safety

- rTMS (> 1Hz) is capable of inducing seizures
- spTMS (<= 1Hz) very low seizure risk, even in epileptic patients
Table 4
Crude risk of a seizure occurring in association with TMS in epilepsy subjects: a pooling of published data and UCLA experience

<table>
<thead>
<tr>
<th>Condition</th>
<th>Single-pulse TMS</th>
<th>Paired-pulse TMS</th>
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</thead>
<tbody>
<tr>
<td>Risk of seizure during TMS</td>
<td>8 in 717 (1.1%)</td>
<td>1 in 120 (0.8%)</td>
</tr>
<tr>
<td></td>
<td>8 in 463 (1.7%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 in 56 (1.8%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risk if seizure during or within 4 min of TMS cessation</td>
<td>11 in 717 (1.5%)</td>
<td>2 in 120 (1.7%)</td>
</tr>
<tr>
<td>Risk of seizure during TMS if AEDs were lowered</td>
<td>11 in 463 (2.4%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 in 56 (3.6%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risk of seizure during TMS if no change in AEDs</td>
<td>6 in 213 (2.8%)</td>
<td>1 in 36 (2.8%)</td>
</tr>
<tr>
<td>Risk of seizure during TMS if medically intractable epilepsy</td>
<td>2 in 500 (0.4%)</td>
<td>0 in 84 (0.0%)</td>
</tr>
<tr>
<td>Risk of seizure during TMS in well-controlled epilepsy</td>
<td>8 in 525 (1.5%)</td>
<td>1 in 81 (1.2%)</td>
</tr>
<tr>
<td>Risk of seizure during TMS</td>
<td>0 in 74 (0.0%)</td>
<td>0 in 31 (0.0%)</td>
</tr>
</tbody>
</table>

AED, antiepileptic drug; TMS, transcranial magnetic stimulation.
<sup>a</sup> Excludes subjects from articles that did not specifically comment upon seizures or side effects.

<table>
<thead>
<tr>
<th>Please Indicate that Inclusion Criteria was <strong>met:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
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<tr>
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<table>
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<th>Please indicate that each of the following contraindications is <strong>absent</strong> (Yes = absent):</th>
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<td>Yes</td>
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<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

Person completing eligibility assessment form:

Print Name __________________________ Signature __________________________ Date __________________________
rTMS Safety

Literature lists ranges for safe use of rTMS. The following parameters are of main importance:

- Stimulus strength
- Repetition rate
- Train duration
- Inter-Train interval


Stimulation Guidelines

Table 3
Maximum safe duration (s) of single trains of rTMS based on the NINDS experience

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Intensity (% of MEP threshold)</th>
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<tr>
<td></td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>5</td>
<td>&gt;10</td>
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<tr>
<td>10</td>
<td>&gt;5</td>
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<tr>
<td>20</td>
<td>2.05</td>
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<tr>
<td>25</td>
<td>1.28</td>
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</table>

Numbers preceded by > are the longest durations tested. No after discharge or spread of excitation has been encountered with single trains of rTMS at these combinations of stimulus frequency and intensity.

Inter-Train Intervals

Table 4
Safety recommendations for inter-train intervals for 10 trains of rTMS at < 20 Hz

<table>
<thead>
<tr>
<th>Inter-train interval (s)</th>
<th>Stimulus intensity (% of MT)</th>
<th>100%</th>
<th>105%</th>
<th>110%</th>
<th>120%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Safe</td>
<td>Safe</td>
<td>Safe</td>
<td>Safe</td>
<td>Insufficient data</td>
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<tr>
<td>1</td>
<td>Unsafe (3)</td>
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</tr>
<tr>
<td>0.25</td>
<td>Unsafe a</td>
<td>Unsafe a</td>
<td>Unsafe (2)</td>
<td>Unsafe (3)</td>
<td></td>
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</tbody>
</table>

The minimum number of trains that caused spread of excitation or post-rTMS EMG activity are indicated in the parentheses. The maximum duration/number of pulses for individual rTMS trains at each stimulus intensity should not exceed that listed in Table 3. Stimulus parameters produced by reducing a set of parameters that is considered safe (reduction in stimulus intensity, train duration, or increase in inter-train interval) is also considered safe. rTMS at 25 Hz, 120% of MT (0.4 s duration) is unsafe at inter-train intervals of 1 s or less. The safety of longer inter-train intervals at 25 Hz has not been determined.

*These stimulus parameters are considered unsafe because adverse events occurred with stimulation of lower intensity or longer inter train interval, but no adverse event was observed with these parameters.

Guidelines

Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research

Simone Rossi 1,2, Mark Hallett 3, Paolo M. Rossini 1,4, Alfaro Pascual-Leone 5 and The Safety of TMS Consensus Group 6

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TMS
Safety

ABSTRACT

This article is based on a consensus conference, which took place in Como, Italy. From 18 to July 3, 2009, the European Society for Clinical Neurophysiology, in collaboration with the American Congress of Rehabilitation Medicine, convened an international group of experts in the field of transcranial magnetic stimulation (TMS) to develop an evidence-based consensus statement. The group was composed of individuals from multiple disciplines and backgrounds. The statement includes recommendations for clinical practice and research, with emphasis on safety considerations. The emphasis on safety is based on the need to balance the benefits of TMS with the risks associated with its use in clinical settings.

Consensus Paper

Theta Burst: Safety

- Most TBS studies based on original Huang et al, 2005 report
- ~49 TBS studies Published
- One seizure reported for cTBS at 100% Resting Motor Threshold (RMT), which is about 120% of Active Motor Threshold (AMT)
  - AMT = Motor threshold measured during muscle contraction
  - Most TBS studies use 80% AMT
Theta Burst: Safety

- Still under evaluation for TBS:
  - Total number of pulses. Current limit is 600
  - Interval between TBS sessions: 15 min has been found to be safe
  - Intensity of stimulation: 80% of RMT maximum reported
  - Cumulative daily or weekly applications
Tolerability and Safety of High Daily Doses of Repetitive Transcranial Magnetic Stimulation in Healthy Young Men

Berry Anderson, RN,*† Alexander Mishory, MD,*‡ Ziad Nahas, MD,*‡ Jeffrey J. Barchard, PhD,* Kaori Yamanaka, MD,*† Komal Rustgi,*† and Mark S. George, MD,*‡

Abstract: Repetitive transcranial magnetic stimulation (rTMS) is an experimental technology that involves a powerful magnetic pulse applied to the scalp, which is used to stimulate brain regions. Although thousands of rTMS sessions have been given with few adverse effects, rTMS can produce serious adverse effects such as an unintended seizure. Safety guidelines for frequency, duration, and intensity of rTMS have been established. This study examined whether high doses of rTMS within a day or over a week would produce significant side effects. A total dose of 8000 magnetic pulses per day, with 4000 pulses per session, produced an unintended seizure in one subject. The study concluded that rTMS is safe and well tolerated in healthy young men.

Key Words: rTMS, transcranial magnetic stimulation, safety, seizure

Since its inception in the 1990s, transcranial magnetic stimulation (TMS) has been used safely in many different neurological and psychiatric applications. These include TMS as a diagnostic tool for mapping brain function, an aid for diagnosing brain abnormalities, and a research tool to study motor function, vision, and language. Transcranial magnetic stimulation is also being used as a treatment for major depression, bipolar disorder, posttraumatic stress disorder, obsessive-compulsive disorder, Parkinson disease, borderline personality disorder, and schizophrenia. Transcranial magnetic stimulation involves a powerful magnetic pulse that is generated by passing electricity through a metal coil that is placed on the head. This focused magnetic pulse passes unimpeded through the skull and causes neuronal depolarization. Patients receiving TMS are awake and do not require anesthesia. When TMS is delivered in a repetitive fashion, which is the case for most treatment studies, the term “rTMS” (repetitive TMS) is used.

Typically, rTMS is well tolerated, and only a small number of patients (10%-30%) experience discomfort due to scalp or facial muscle twitching or sensations. The most significant side effect associated with rTMS is an unintended seizure. Although a seizure due to rTMS is more likely to occur in individuals with epilepsy, multiple sclerosis, or stroke, healthy volunteers have experienced seizures to date (Table 1). Half of these seizures in healthy volunteers were induced by TMS of high frequency, intensity, and duration. Most investigators reduce the risk of seizure by following the recommendations of the 1996 International Workshop on the Safety of TMS.

Transcranial magnetic stimulation studies range from a single pulse of magnetic stimulation to repeated pulses delivered over minutes and/or days. For example, many rTMS studies of major depression use frequencies of 1 Hz and 10 Hz and 80% to 120% motor threshold. A TMS device set at 1 Hz delivers 10 pulses per second, whereas a TMS device set at 10 Hz delivers 10 pulses per second. The motor threshold, expressed as the percent of maximum output, is the intensity of the pulse required to depolarize neurons in the motor cortex, resulting in movement of the contralateral adductor pollicis brevis. Several seconds of continuous magnetic pulses is called a train, and the intertrain interval (or interstimulus interval) is the resting period of no stimulation between each train. Typically, an rTMS session in treatment study consists of 1 long train or several trains given once a day, 3 days a week, for 2 or 4 weeks. This regimen in previous depression studies delivered 800 to 3000 pulses per session and 10000 to 30000 pulses over 2 to 4 weeks.

38,880 TMS pulses over 3 days in 1 week.

1 Hz @ 10%, 90%, 120% MT (continuous 720 s runs)

5 Hz @ 90%, 110%, 120% MT (720 s runs of 8 sec on, 32 sec off)

10 Hz @ 90%, 110%, 120% MT (720 s runs of 4 sec on, 36 sec off)

No significant difference in side effects relative to sham TMS.
Side Effects of TMS

• Cognitive and neurological testing after rTMS revealed no deleterious effects, or only mild effects lasting up to 1 hour post-rTMS
TMS Safety

• Initial evidence: No hearing loss (Pascual-Leone et al. *Neurology*, 1992, 42, 647-651.)
• Zangen et al (*Clin Neurophysiol*, 2005, 116, 775-779) reported permanent 30 dB loss in left ear at 4000 Hz for subject whose hearing protection had fallen out
• Earplugs are strongly advised
TMS Side Effects

• Headaches of muscular origin are uncommon, but are the most likely side effect, lasting up to a few hours
  – Managed with ordinary analgesics

• rTMS to prefrontal regions has produced lateralized effects on mood
TMS Safety – Animal Studies

- Monkeys receiving 7000 maximum intensity single pulses delivered in daily increments over thirty days demonstrated no short or long term deficits on higher cerebral function or other adverse effects (Yamada et al., Electroencephalography and Clinical Neurophysiology, 97, 1995, 140-144)
Safety – Histology Studies

• An absence of structural brain damage following repetitive TMS has been documented from lobectomy specimens obtained from two epileptic patients, as well as from rats exposed to long-duration TMS (Keenan and Pascual-Leone, *Science & Medicine*, 6 (1999) 8-17.)
Safety – MRI Studies

• An MRI study investigated whether repetitive TMS affects the blood-brain barrier or induces localized brain edema.
• 1,200 to 3,800 stimuli administered at 5-20 Hz over the visual cortex of 11 healthy subjects.
• No pathologic changes after application of gadolinium (Gd-DTPA), or by determining apparent diffusion coefficients.