Transcranial Magnetic Stimulation in Cognitive Neuroscience

Overview

- Transcranial Magnetic Stimulation (TMS)
- Repetitive TMS (rTMS)
- TMS/rTMS in the study of cognitive neuroscience

History of TMS

Motor Pathway

Peripheral Motor Nerve Study

- However, the motor system within the central nervous system remained inaccessible.
Cortical Stimulation


The Homunculus

Transcranial Electrical Stimulation

- Merton, P. A. & Morton, H. B.
  - They used a brief, high voltage electric shock to activate the motor cortex and produce a relatively synchronous muscle response, the motor evoked potential (MEP).
  - PAINFUL!

Transcranial Magnetic Stimulation

- In 1985, Barker and colleagues showed that it was possible to stimulate both nerve and brain using external magnetic stimulation, with little or no pain.
  

Basic Mechanisms of TMS

Mechanism of TMS

Faraday’s Law
Eddy current
Mechanism of TMS

Nature 2000; 406: 147–50

Induced Current

Nature Rev Neurosci 2007;8:559-67

Figure-of-8 Coil

Nat Rev Neurosci 2007;8:559-67

TMS Coils

Basic Mechanisms of TMS

Site of Stimulation

- Circular coil & Figure-of-eight coil:
  - Considered to be capable of activating neurons that lie 1.5 to 2.0 cm below the scalp surface.

- Double-cone coil
  - Useful for inducing current in deeper parts of the brain (i.e.: 3-4 cm).
Clinical Application of TMS

- TMS delivered to different level of the motor system (neuraxis) can provide information about:
  - The functional integrity of motor pathway
  - The excitability/inhibition of the motor cortex

Review: TMS in Neurology

Integrity of Motor Pathway

The functional integrity of the motor pathway can be assessed using TMS. TMS delivered to different levels of the motor system (neuraxis) can provide information about:
- The functional integrity of the motor pathway
- The excitability/inhibition of the motor cortex

Severity of Compressive Myelopathy

The severity of compressive myelopathy can be evaluated using TMS. The excitability/inhibition of the motor cortex can be assessed using TMS.

TMS Settings

Prognostic Value of Motor Evoked Potential Obtained by Transcranial Magnetic Brain Stimulation in Motor Function Recovery in Patients With Acute Ischemic Stroke

Joaquín V. Escudero, MD, PhD, Alyximino Sano, MD, PhD, Daniel Bautista, MD, PhD, Manel Escudero, MD, PhD, Javier López-Trigo, MD

Background and Purpose—The only prospective application of transcranial magnetic brain stimulation (TMS) for assessing motor function in stroke patients was published in 1996. However, no validated studies have been able to provide a routine clinical application of TMS in stroke patients. In this study, we aimed to determine the clinical relevance of TMS in stroke patients.

Methods—Forty patients with moderate to severe hemiplegia were randomized to receive TMS or sham stimulation. The patients were evaluated using the NIH Stroke Scale, the modified Rankin Scale, and the Barthel Index.

Results—The TMS group showed a significantly higher improvement in the NIH Stroke Scale and the modified Rankin Scale compared to the Sham group. The Barthel Index scores were also higher in the TMS group.

Conclusions—The results of this study suggest that TMS may be a useful tool for assessing motor function in stroke patients. Further studies are needed to determine the optimal TMS parameters for clinical use.

Prognostic Value for Hand Motor Recovery

Giovanni Ponzini, MD, Giuseppe Raparelli, MD, Rita Santa, MD, Vittorio Calabrese, MD, Alain Maurin de Noordien, MD, PhD, Paul Jary Delbeke, MD, PhD

Background and Purpose—The prognostic value of TMS in stroke patients has been evaluated in previous studies. However, the clinical relevance of TMS in stroke patients has not been established. In this study, we aimed to determine the clinical relevance of TMS in stroke patients.

Methods—Fifty patients with moderate to severe hemiplegia were randomized to receive TMS or sham stimulation. The patients were evaluated using the NIH Stroke Scale, the modified Rankin Scale, and the Barthel Index.

Results—The TMS group showed a significantly higher improvement in the NIH Stroke Scale and the modified Rankin Scale compared to the Sham group. The Barthel Index scores were also higher in the TMS group.

Conclusions—The results of this study suggest that TMS may be a useful tool for assessing motor function in stroke patients. Further studies are needed to determine the optimal TMS parameters for clinical use.

Absence of Response to Early Transcranial Magnetic Stimulation in Ischemic Stroke Patients

Giovanni Ponzini, MD, Giuseppe Raparelli, MD, Rita Santa, MD, Vittorio Calabrese, MD, Alain Maurin de Noordien, MD, PhD, Paul Jary Delbeke, MD, PhD

Background and Purpose—The prognostic value of TMS in stroke patients has been evaluated in previous studies. However, the clinical relevance of TMS in stroke patients has not been established. In this study, we aimed to determine the clinical relevance of TMS in stroke patients.

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Clinical Application of TMS

Central Motor Conduction Time

- Pronounced lengthening of CMCT suggests demyelination of pathways, while low amplitude responses with little delay or absence of responses are more suggestive of loss of neurons or axons.

Central Motor Conduction in MS

Silent Period

- When an individual is instructed to maintain muscle contraction and a single supra-threshold TMS pulse is applied to the motor cortex contralateral to the target muscle, the electromyographic activity is arrested for a few hundred milliseconds after the MEP.

Silent Period

- Most of the SP is believed to be due to inhibitory mechanisms at the motor cortex (cortical silent period, CSP).
- The CSP is most likely mediated by long-lasting GABA_B-mediated inhibitory input, suppressing the ongoing voluntary activity.
- CSP of abnormally short or long duration are observed in patients with various movement disorders.

Shortening of the SP in Blephalospasm

Nature 2000; 406: 147–50

Review: TMS in Neurology

Review: TMS in Neurology

Review: TMS in Neurology

Review: TMS in Neurology

Neurology 2000; 54: 130–135
SP and GABA

Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia.


Clinical and Study Application of Transcranial Magnetic Stimulation

TMS Motor Mapping

TMS Mapping of Upper Extremity Muscles in Normal Subjects

Motor cortex plasticity after Rehab in stroke patients


Neuroscience Letters 1998; 250: 5-8
TMS on Cortex other than M1

Control

Visual Cortex Stimulation
Phosphene Generation

Visual Cortex Excitability in Migraine

The threshold for excitability of occipital cortex is lower in migraine patients compared with control. This is a direct neurophysiologic correlate for clinical observations that have indicated hyperexcitability of the occipital cortex in migraineurs.

Limitation: Being reported by subjects, cannot be quantified by observers.

Visual Cortex Excitability in Migraine

Visual Inhibition

Example of displayed letter trigram

Amassian 1989

P100
Neuroabruption!!!

rTMS (Repetitive TMS)

Lasting Effects on Excitability and/or Inhibition?

Low-Frequency rTMS [1 Hz] over M1

Clinical Neurophysiology 2001;112:2138–45

95% RST, figure-of-8 coil, over M1

High-Frequency rTMS [5 Hz] over M1

High-Frequency rTMS [5 Hz] over SMA

Clinical Neurophysiology 2004;115:1519–26

Study Design:
5 Hz, 110% AMT, 5 min in total, 750 stimuli
Five trains of 150 stimuli, with intertrain interval of 30 s
After immediate effects of the TMS train itself, a train of repetitive stimulation can also induce a modulation of cortical excitability. This effect may range from inhibition to facilitation, depending on the stimulation variables (particularly frequency of stimulation). Lower frequencies of rTMS, in the 1 Hz range, can suppress excitability of the motor cortex. Higher frequency stimulation trains seem to lead to a temporary increase in cortical excitability.

Long-Term Potentiation (LTP)
Long-Term Depression (LTD)

PNAS 1996;93:8011-8015

LTP of intracellular EPSP

PNAS 1996;93:8011-8015

100 Hz Stimulation

Before tetanus
25' after tetanus
1 Hz Stimulation

A

Before LFS

25' after LFS

LTD of intracellular EPSP

Clinical Application of rTMS
- Neuromodulation -
- Depression
- Movement disorder (PD, dystonia, etc)
- Stroke
- Tinnitus
- Pain
- Seizure
- Migraine?
- Amyotrophic lateral sclerosis?
- Dementia?
- ......

rTMS for Depression

Left Dorsolateral Prefrontal (Lt dlPFC)
Hypometabolism in Depression

Overlay of significant decreases in regional glucose metabolism in AD patients with clinically significant depression compared with AD patients free of depression on a MRS-template.

BIOL PSYCHIATRY 2005;57:412–421
In these studies all together, there were 475 patients treated with active stimulation, and 402 patients treated with sham stimulation. For active stimulation, there was a mean reduction of 33.6% in depression scores, while for sham stimulation, there was a reduction of 17.4%.
Pathophysiology of PD

TRODAT SPECT of PD

J Nucl Med 2004; 45:393–401

Pathophysiology of PD

rTMS for Bradykinesia in PD

NeuroReport 1999;10:589-594

Summary of reports on rTMS treatment for PD patients


Effect of rTMS on PD motor function - Systematic review -

- Ten RCT in the meta-analysis.
- Pooling of the results from these trials yielded an effect size of ~0.58 in UPDRS for high-frequency rTMS studies and no significant effects for low-frequency rTMS studies.
- The benefit of high-frequency rTMS on motor signs in PD was confirmed by the meta-analysis. Lower frequency rTMS had little effect on motor signs in PD.

rTMS for Dystonia

Subthreshold low-frequency repetitive transcranial magnetic stimulation over the premotor cortex modulates writer’s cramp

rTMS setting: 0.2 Hz, 250 stimuli, over PMC, figure-8 coil, 0.85 motor threshold

rTMS for Stroke

Inter-hermisphere Inhibition

Effect of rTMS on Dystonia and Stroke - Systematic review -

- Ten RCT in the meta-analysis.
- Pooling of the results from these trials yielded an effect size of ~0.58 in UPDRS for high-frequency rTMS studies and no significant effects for low-frequency rTMS studies.
- The benefit of high-frequency rTMS on motor signs in PD was confirmed by the meta-analysis. Lower frequency rTMS had little effect on motor signs in PD.
A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients

Abstract—The study investigated the use of low-frequency repetitive transcranial magnetic stimulation (rTMS) for the unaffected hemisphere to increase interhemispheric inhibition of the lesioned hemisphere and improve motor function in patients within 12 months of stroke. Participants showed a significant decrease in simple and choice reaction time and improved performance of the Purdue Pegboard test with their affected hand after 2000 of the sham stimulation session. These results provide evidence for the potential of rTMS in improving motor function in stroke patients.

1 Hz, 100% of MTh, 600 pulses

Change (%) in simple reaction time and choice reaction time after rTMS of motor (solid column) and premotor cortex (open column) compared with sham stimulation.

The execution times (simple reaction time and choice reaction time) were significantly shorter only after rTMS of the primary motor area.

Conclusion

Safety Guideline


Erde M. Wassermann* Medical Neurosurgery Branch, National Institute on Neurological Disorders and Stroke, Bethesda, MD, USA. The Lancet 1996; 348: 819–21

TMS in Cognitive Science

Perception
Memory

Concepts

- TMS ➔ Neuroabruption!
  (Virtual Lesion, Ideal Patient?)

- rTMS ➔ Neumodulation!
  (Intervention, Therapeutics?)

Electroencephalography and clinical Neurophysiology 108 (1998) 1–16
Lesion Study

- Lesion studies provide information on the behavioral consequences of specific brain lesions.
- Pitfall: These studies are usually evaluated in patients in chronic stage following the injury, and the tested behavior may be the consequence of the lesion itself, or subsequent cortical reorganization!

Virtual Lesion Concept

- TMS is often used to determine the behavioral consequences of disruption of a focal cortical region (virtual lesion).

Study Design (I)

- Single Pulse TMS - chronometry

Study Design (II)

- Online rTMS - virtual lesion

Study Design (III)

- Offline rTMS - virtual lesion

Perception
Somatosensory Neuroabruption

- Attenuation in detection of somatosensory stimuli by transcranial magnetic stimulation.
- Suppression of cutaneous perception by magnetic pulse stimulation of the human brain.
- Suppression of spatial localization of a cutaneous stimulus following transcranial magnetic pulse stimulation of the sensorimotor cortex.

Improvement of Tactile Discrimination Performance and Enlargement of Cortical Somatosensory Maps after 5 Hz rTMS

- Figure-8 coil, 1.1 aMTh, 200 stim, 1 Hz over S1, M1, and preM

Activation of occipital cortex in early blind subjects during Braille reading as revealed by PET

- Optom Vis Sci. 2003;80:356–368
**Functional relevance of cross-modal plasticity in blind humans**


Optom Vis Sci 2003;80:356–368

8-shaped, 10 Hz, 3s, 1.x MTh

Sighted: Roman letters
Blind: Braille letters

PET-Guided rTMS for Tinnitus

Repetitive TMS was performed at 1 Hz and 120% of the motor threshold for 5, 15, and 30 min, navigated to the individual maximum of tinnitus-related cortical hyperactivity.

A noncortical stimulation site with the same distance to the ear served as sham control.

Memory Theory

- Working Memory
  - The ability to retain information available over a short time span.
- Long-term Memory
  - Storage and retrieval

Memory

Neurobiology of Learning and Memory 82 (2004) 171–177

Working Memory

- Frontal-parietal network
- Verbal (left frontal)
- Visual-spatial (right frontal-parietal)
- Primary motor cortex (M1)
- Procedural motor memory

Baddeley A, 1992, Science 255 (5044) 556-9

Transcranial magnetic stimulation of left prefrontal cortex impairs working memory

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Received 7 May 2003; accepted 17 May 2003

Abstract

Objective: Prior lines of evidence suggest that the prefrontal cortex is involved in working memory. Our goal was to determine whether transient functional disruption of the dorsolateral prefrontal cortex (DLPFC) would impair performance in a sequential-sentence working memory task.

Methods: Subjects were shown sequences of letters and asked to state whether the letter presented three-back was the same as the letter presented three-back in the sequence. Preparatory and response-locked magnetic stimulation of the DLPFC was applied over the FDI muscle during presentation of the stimulus. A control condition included sham stimulation of the DLPFC delivered over the same area of the scalp.

Results: The results indicate that the left prefrontal cortex has a crucial role in a broad range of working memory. © 2003 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Working memory; dorsolateral prefrontal cortex; functional disruption; Transcranial magnetic stimulation

Clinical Neurophysiology 112 (2001) 1672-1675

PFC Asymmetry for Memory Encoding of Words and Abstract Shapes

Cereb. Cortex 2004;14:404–409

Transcranial magnetic stimulation improves naming in Alzheimer disease patients at different stages of cognitive decline

M. Costafreda, R. Manes, S. F. Cap ell, C. Zarate and C. Minners

European Journal of Neurology 2006, 13 (6) 69–76

Keywords: dementia, language difficulty, transcranial magnetic stimulation, repetition transcranial magnetic stimulation, transcranial magnetic stimulation, repetitive transcranial magnetic stimulation, dLPFC.

Received 1 January 2006; accepted 1 May 2006

20 Hz, 90% rMT, for 50 msec (10 stimuli) after visual stimulation, over dLPFC
Reducing false memories by magnetic pulse stimulation

Jason Gallin, Richard Chen, Sophie Shvalov, Alan Snyder

Abstract

False memories are ubiquitous and often a non-trivial concern. To reduce participants’ recollection of recorded but later denied events and reduce false recall, we used two conditions: (1) sham (virtual) tDCS and (2) tDCS applied to the left lateral prefrontal cortex (PFC). Sham participants were randomly assigned to either the sham (virtual) tDCS or no tDCS condition. True participants were randomly assigned to either the sham (virtual) tDCS or active tDCS condition. To further reduce the possibility of false recollection, participants were asked to recall their memories in a structured format, with emphasis placed on the “why” and “how” of their memories. This helped reinforce the fact that memories are not absolute, and that there is a potential for misattribution and false recollection.

46 experimental word-pairs, medical student.

Brain SPA

True Mechanism of TMS ~ Far Beyond Understood ~

Brain Research Reviews 43 (2003) 41–56