Transcranial Magnetic Stimulation as a **predictor** of motor recovery and **treatment** to enhance recovery of motor function

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Organization

- Mechanisms of motor recovery after stroke
- Specific excitability changes in ipsilesional M1:

  Predictors of motor recovery??
- TMS as treatment to enhance recovery of motor function

Disclaimer: this talk does not intend to be an all inclusive discussion of all the TMS literature

Introduction

In the last 2 decades, significant advances have been made on the understanding of the mechanisms underlying recovery of motor function after stroke.

Transcranial magnetic stimulation (TMS) and functional MRI (fMRI) techniques have allowed the study of cortical reorganization after stroke.

Interestingly, TMS was also noted to modulate cortical excitability. These findings open the opportunity to use TMS to modulate behavior, and to investigate the use of other brain stimulation techniques with similar purpose.

Early concepts

- fMRI studies found contralesional activation of primary and secondary motor areas (Chollet 1991, Weiller 1992, Cao 1998, Cramer et al 1997)
- TMS studies showed MEPs from contralesional M1 (Catano 1993, 1996)

⇓

Motor recovery occurs as the contralesional motor cortex takes over the function of the ipsilesional side ?

FOLLOW UP

- Cross sectional and longitudinal fMRI studies described that patients with:
  - Poor recovery > contralesional activation
  - Better recovery > ipsilesional activation

(Callauti 2003, Ward 2004)

- TMS studies found that:
  - Poor recovery > MEPs from contralesional motor cortex
  - Better recovery < MEPs from contralesional motor cortex

(Feydy 2002)

Mechanisms of Motor Recovery after Stroke

FOLLOW UP

While stroke patients perform a reaction time paradigm, TMS applied over:

- Contralesional premotor cortex disrupted performance in the poorly recovered patients (Johansen-Berg et al 2002)
- Ipsilesional premotor cortex disrupted performance in a group of well recovered patients (Fridman et al 2004)
- Similarly, TMS over ipsilesional M1 disrupts performance of motor task with the paretic hand (Werhahn et al 2003).

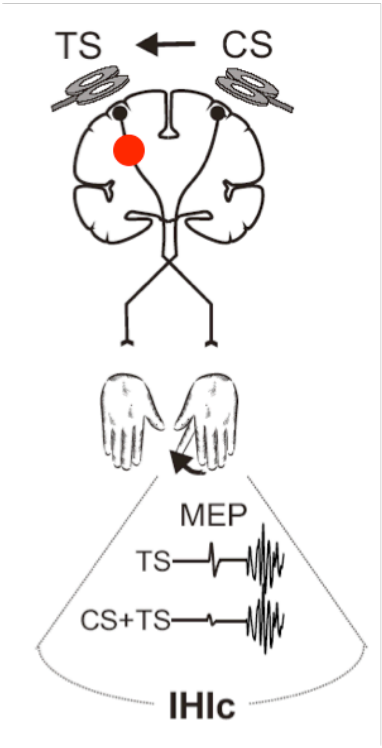
⇓

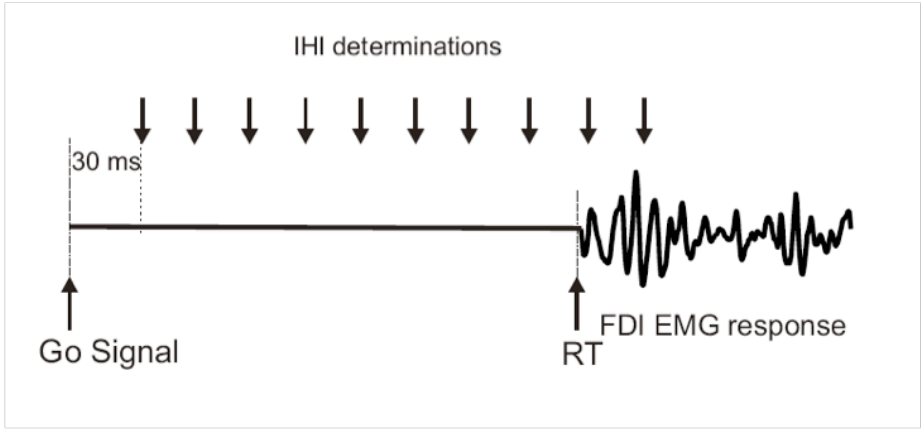
Motor recovery is associated to "**normalization**" of the pattern of motor cortex activation

Interhemispheric Interactions

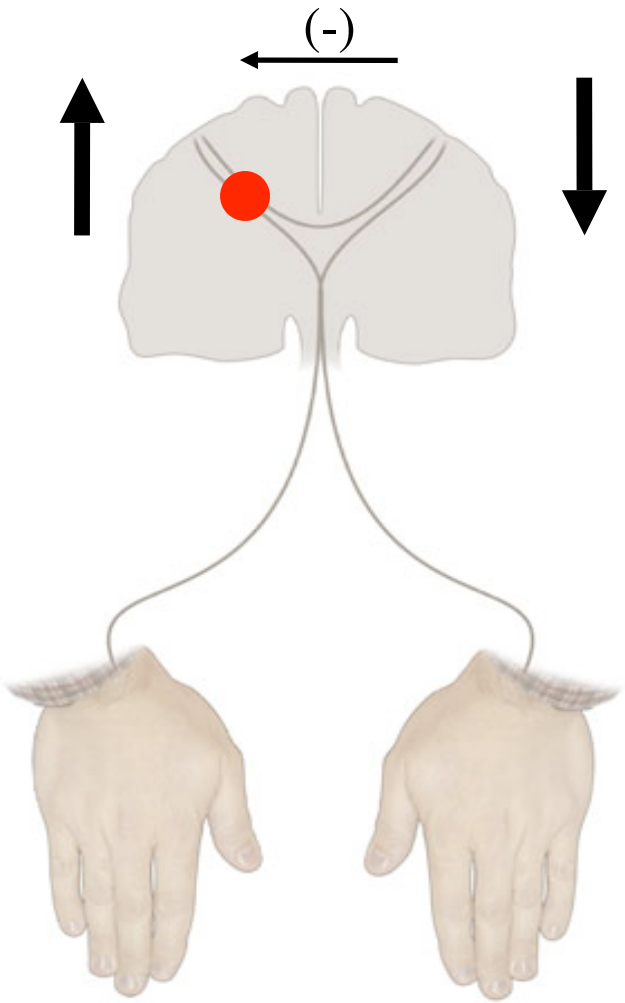
What are other possible roles for the contralesional M1 activation observed in stroke patients?

Murase et al. investigated the role of premovement IHI in a group of stroke patients (Murase et al 2004)

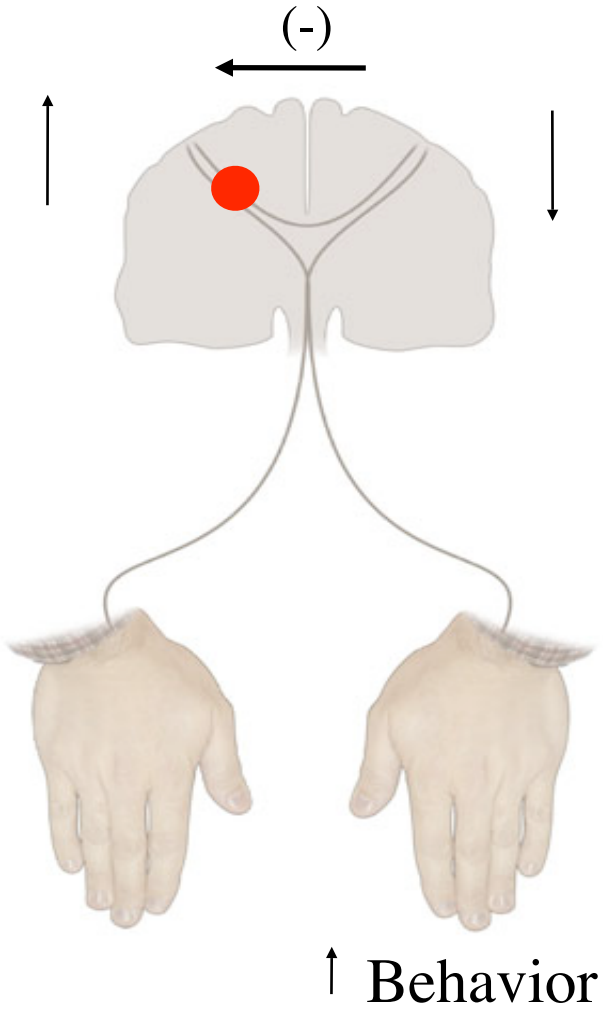




Summary of Recovery Mechanisms



Motor Recovery Model



A Note of Caution:

The model is likely a simplification

Recovery process is dynamic

The model may not apply to all phases or motor behaviors.

Lotze et al showed disruption of the paretic hand when TMS was applied over the **contralesional side** in a group of **chronic well-recovered** subcortical stroke patients when performing a **complex motor task**.

(Lotze et al. 2006)

Ipsilesional M1 Excitability after Stroke

Several studies have assessed M1 excitability changes following stroke

Several have attempted to develop / identify excitability measures as **predictors of motor recovery**.

Ipsilesional M1 Excitability after Stroke

Acute Stroke:

- Motor Thresholds
  - ↑ (Liepert 00', Manganotti 02')
  - ⊥ (Delvaux 03')
- MEP Amplitudes
  - ↑ (Traversa 98', Cicinelli 97', Delvaux 03')
  - ⊥ (Manganotti 02')
- SICI
  - ↓ (Liepert 00', Manganotti 02', Swayne 08')
  - ↑ (Wittenberg 07')

Longitudinal F/U study of M1 excitability
(Swayne 08')

TMS measures obtained almost daily in 1st week, weekly in 1st month, and then at 1, 3, 6 months
Behavioral measures: ARAT, NIHSS, 9HPT, Barthel

"Single physiological measurements made in the first 3 weeks after stroke have little clinical use on their own"

M1 Excitability after Stroke

Motor thresholds

- ↑ rMT and aMT in AH and UH
- Over time, MT normalize
- Correlated with clinical measures acutely (ARAT, 9HPT)
- Persist elevated in > impaired patients

Recruitment curves

- ↓ in AH and UH relative to healthy
- > ↓ in the AH vs the UH
- With time, normalizes
- Correlated with clinical scores acutely

(Swayne 08')

M1 Excitability after Stroke

Intracortical excitability

AH

- ↓ SICI (disinhibition)
- ⊥ ICF
- ↓ LICI
- All measures normalize at 3 months

UH

- ⊥ SICI, ICF and LICI

- All measures correlated with clinical performance at 3 month, but not acutely.

(Swayne 08')

Summary:

- The mean of corticospinal excitability measures (MT and RC) correlated closely with clinical function in the acute period
- Intracortical excitability measures (SICI) correlated well at 3months, but not in the acute period

(Swayne 08')

Discussion:

Acute period:

- Recovery relies on the remains of the pre stroke motor output system.
- Disinhibition is present, releasing connections to adjacent or distant neural populations, but not organized into a useful alternative system.

Subacute period:

- With time and motor practice, synaptic strengthening take place making the newly available networks effective as motor output.
- Continued disinhibition is necessary to maintain access to these areas.

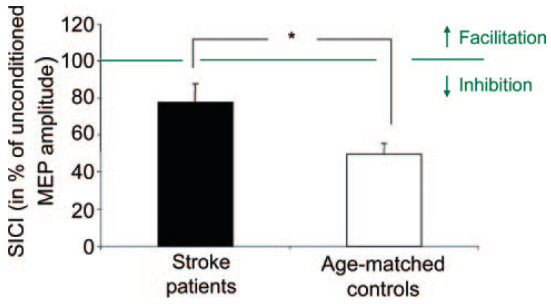
Chronic phase:

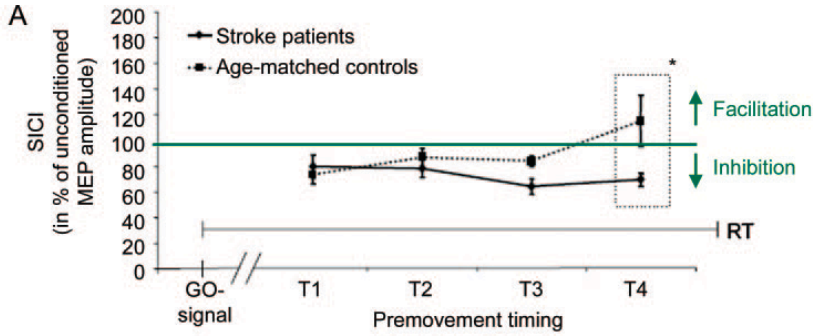
- Decreased reliance on net intracortical disinhibition as training-induced synaptic strengthening becomes better established.
- Possible early network reorganization may give rise to permanent structural changes.

(Swayne 08')

Chronic phase:

Although SICI remains abnormally reduced but not correlated with motor measures, premovement SICI may be better marker.





- Pre movement SICI is reduced

(Hummel 09')

Chronic phase:

Motor function still appears to be predominantly influenced by SICI activity.

- Motor training results in modulation of SICI in healthy, but this effect is reduced in stroke (Blicher 09')
- Interventions that enhance motor function modulate SICI (Celnik 07')

(Hummel 09')

TMS as Motor Recovery Predictor?

- A single TMS measure does **not** appear to be useful as motor recovery predictor
- However, these studies have helped understand the dynamic recovery process, at least in terms of corticomotor excitability
- Hence, it is possible that treatment should focus on different excitability components, as markers of brain function processes, at different stages.

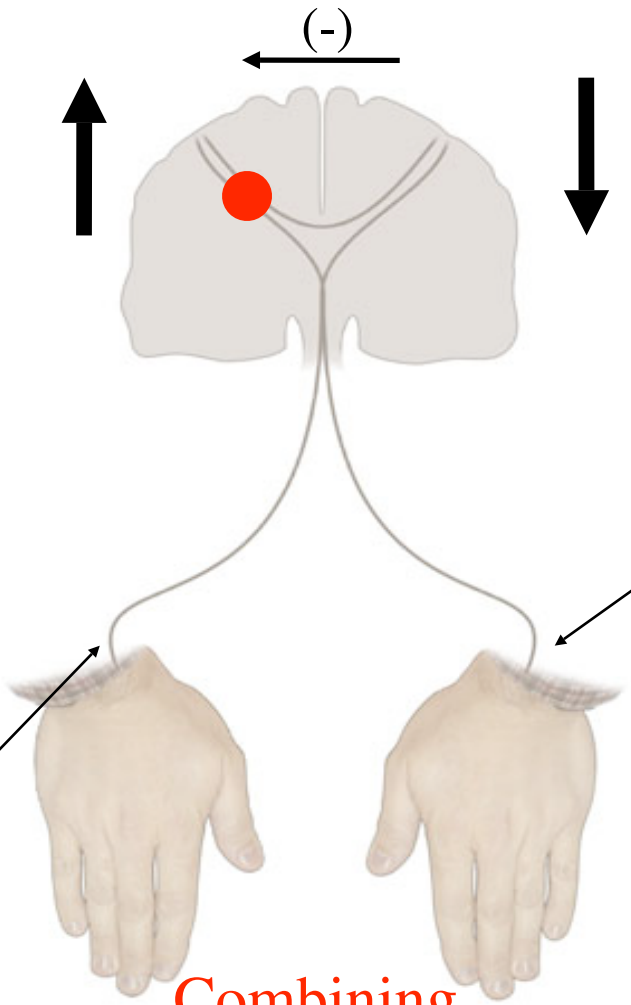
Potential Interventions Based on Recovery Mechanisms

Cortical Stim.

- Non-invasive
  - TMS
  - tDCS
- Invasive Stim.
  - Epidural stim.

Cortical Inhibition

- Non-invasive
  - TMS
  - tDCS



Action Observation

- Celnik et al. 2008

SS Stimulation

- Conforto et al. 2002
- Celnik et al. 2007

INB

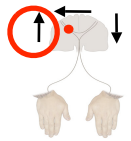
- Werhahn et al. 2002
- Floel et al. 2004.

↑ Behavior

Combining Interventions

- Celnik et al. 2009

TMS Studies increasing Ipsilesional Activity



HIGH LIGHT

Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke

Abstract: Repetitive transcranial magnetic stimulation (rTMS) or sham stimulation was given over the motor cortex daily for 10 days to two randomly assigned groups of 26 patients with acute ischemic stroke. Patients otherwise continued their normal treatment. Disability scales measured before rTMS, at the end of the last rTMS session, and 10 days later showed that real rTMS improved patients' scores more than sham.

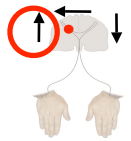
NEUROLOGY 2005;65:466–468

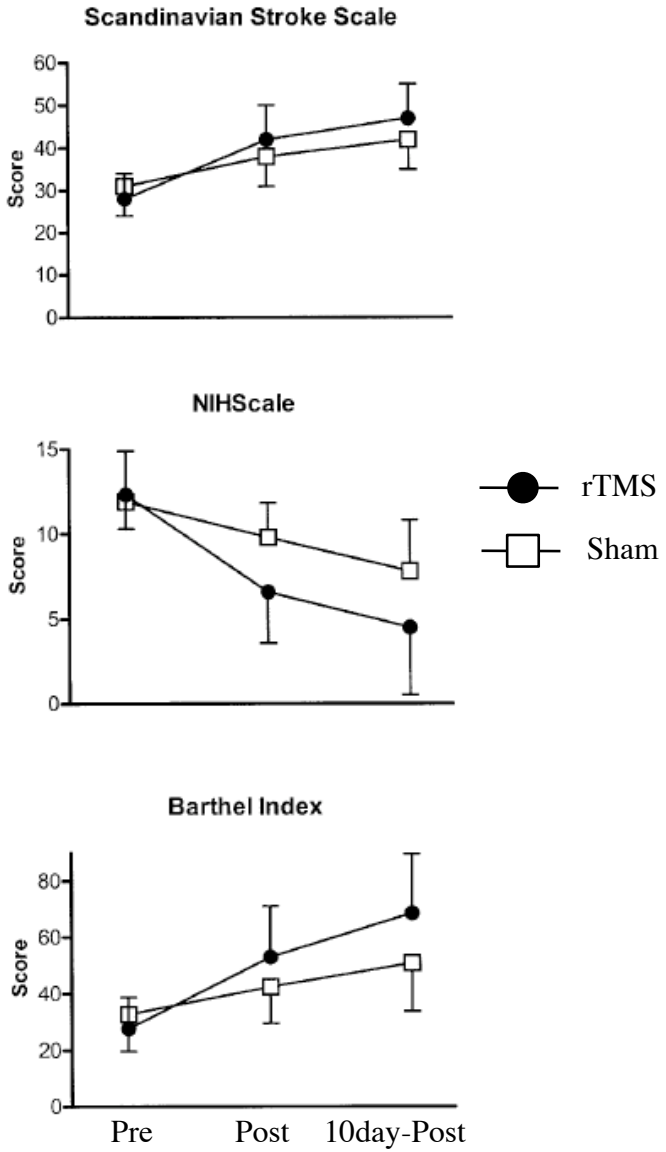
Eman M. Khedr, MD; Mohamed A. Ahmed, MD; Nehal Fathy, MD; and John C. Rothwell, MD

- 52 acute single ischemic stroke patients were randomized to rTMS (10 trains of 3Hz/10secs/120%MT) or SHAM (same as rTMS but coil was angled away)
- Interventions delivered over ipsilesional M1, daily, for 10 days while receiving standard in-patient rehabilitation

(Khedr et al. 2005)

TMS Studies increasing Ipsilesional Activity





Conclusions

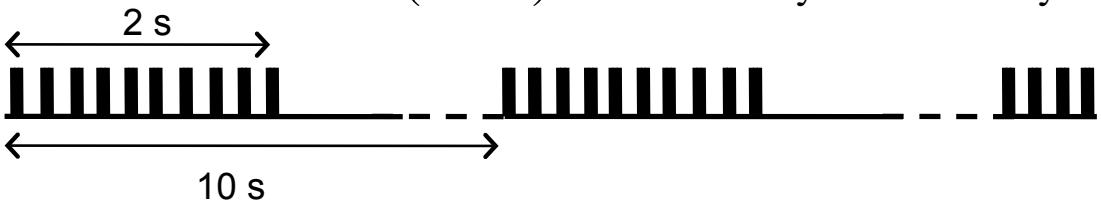
10 consecutive days of rTMS employed as an add-on intervention to regular physical and drug therapies improves immediate clinical outcome in early stroke patients.

(Khedr et al. 2005)

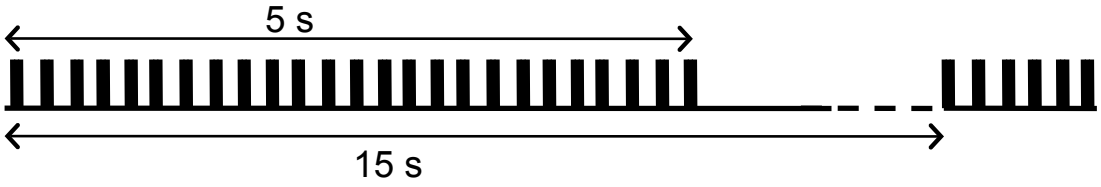
TMS and Theta Burst

- Based on patterns used to induce LTP and LTD
  - Bursts of 3-5 pulses at 100 Hz repeated at 5 Hz (theta)
- In humans
  - Bursts of 3 pulses at 50 Hz repeated at 5 Hz (80% AMT)

- Intermittent TBS (***iTBS***) 10 bursts every 10 s for 20 cycles (190 s)



- Intermediate TBS (***imTBS***) 25 bursts every 15 s for 8 cycles (110 s)



- Continuous TBS (***cTBS***) 200 bursts continuously (40 s)

(Huang et al. 2005)

TMS and Theta Burst

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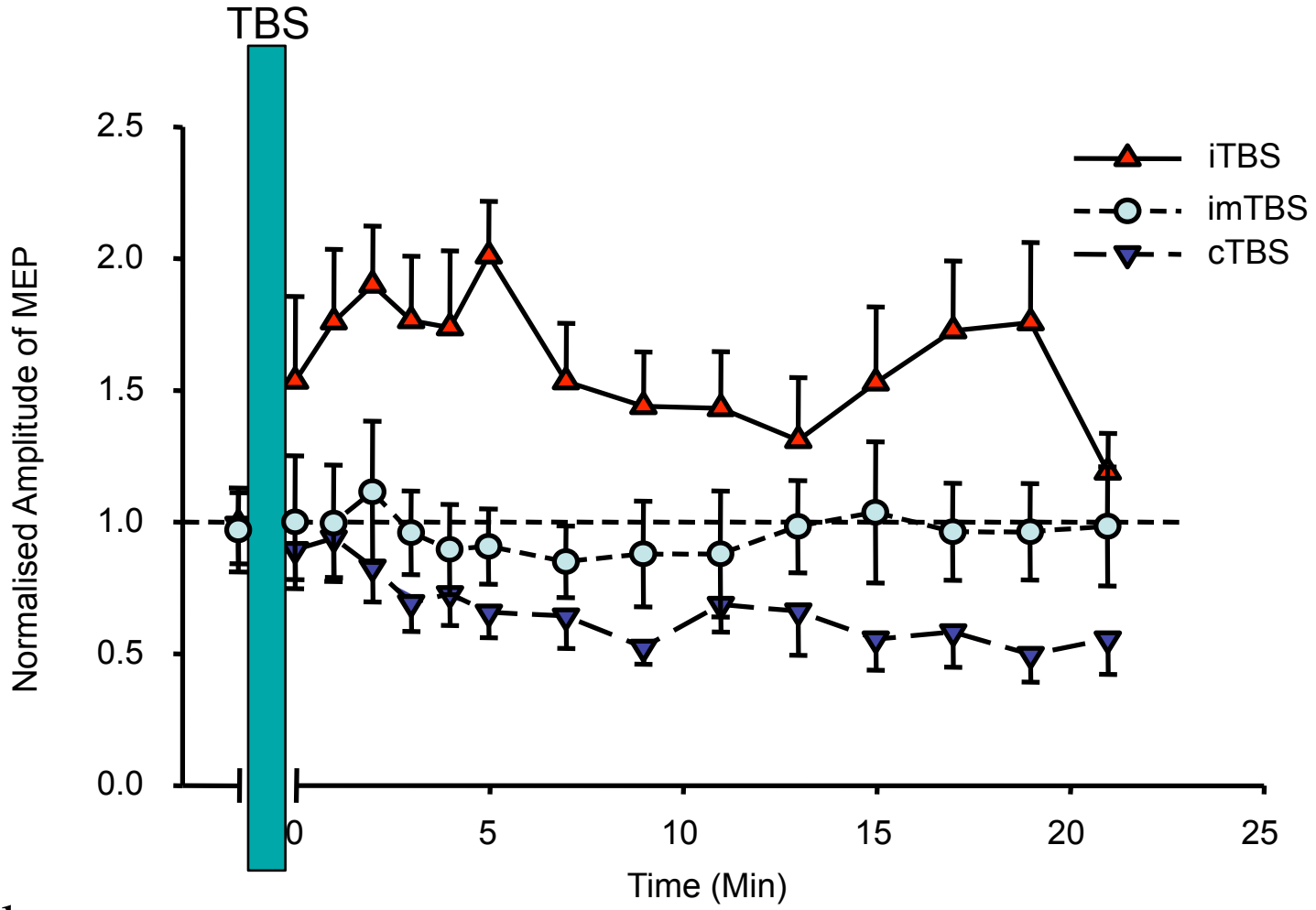

- Advantages:
  - –Fast to apply and modifiable (gives inhibition OR facilitation)
  - –Low intensity pulses (not activating projection neurones)

Theta Burst Stimulation after Stroke

ELSEVIER

Clinical Neurophysiology 118 (2007) 333–342

www.elsevier.com/locate/clinph

Exploring Theta Burst Stimulation as an intervention to improve motor recovery in chronic stroke ☆

P. Talelli [a,*], R.J. Greenwood [b], J.C. Rothwell [a]

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[b] *The National Hospital for Neurology and Neurosurgery, University College London Hospitals (UCLH), UK*

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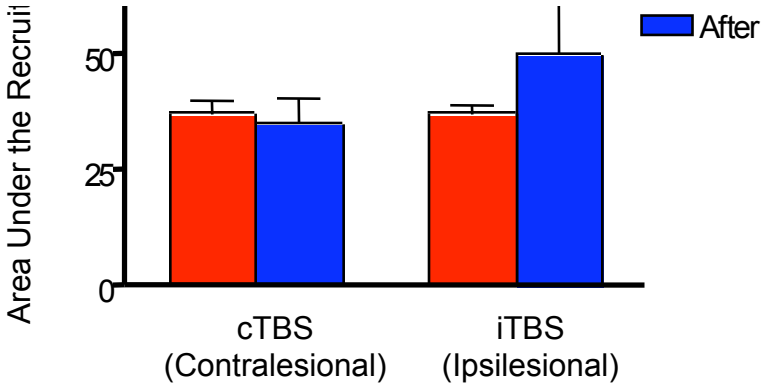
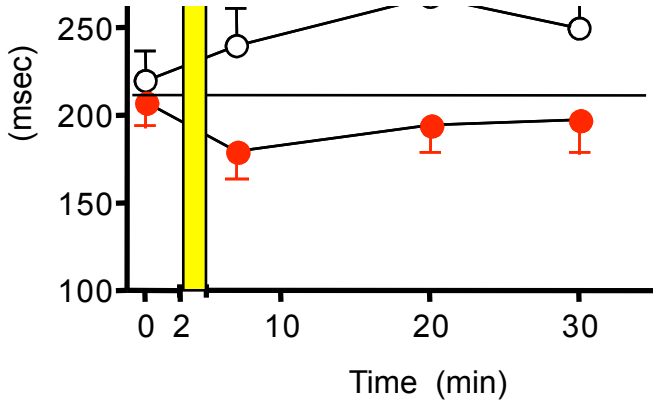
Available online 12 December 2006

iTBS
Sham

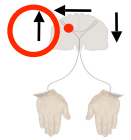




Patients experienced ~10-15% improvement in SRT

(Talelli et al. 2007)

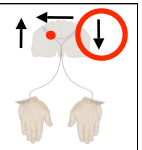
TMS Studies increasing Ipsilesional Activity



Other rTMS studies over ipsilesional M1:

- Kim et al. 2006 investigated rTMS (8 trains of 10 Hz/80% rMT/ 2secs) prior to sequential finger movements. This protocol elicited larger MEPs, which was correlated to accuracy improvement in the same task (no time changes).
- Yozbatiran et al. 2009 performed a safety study in Stroke patients applying over S1 40 rTMS trains (40 pulses at 20 Hz/ intertrain interval 28secs/ total of 1600 pulses/ intensity 90% rMT). This protocol was safe, only mild increase of systolic blood pressure. Additionally, patients experience short term gains in active ROM, 9HPT, and grip strength.

TMS Studies decreasing Contralesional Activity



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A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients

Abstract—The authors investigated the use of slow-frequency repetitive transcranial magnetic stimulation (rTMS) to the unaffected hemisphere to decrease interhemispheric inhibition of the lesioned hemisphere and improve motor function in patients within 12 months of a stroke. Patients showed a significant decrease in simple and choice reaction time and improved performance of the Purdue Pegboard test with their affected hand after rTMS of the motor cortex in the intact hemisphere as compared with sham rTMS.

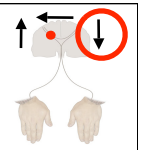
NEUROLOGY 2005;64:1802–1804

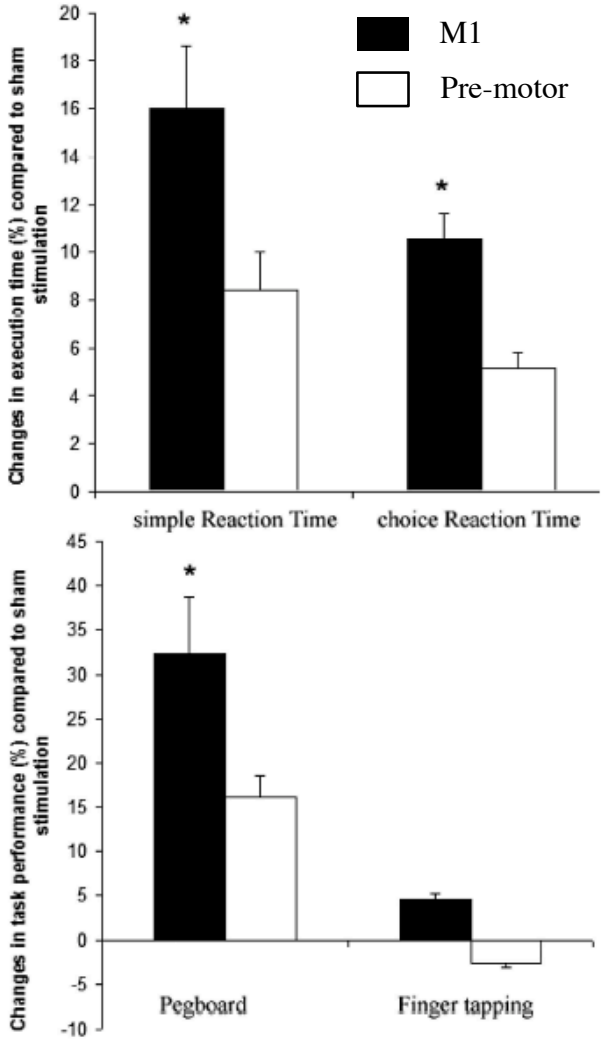
C.G. Mansur, MD*; F. Fregni, MD, PhD*; P.S. Boggio, MSc; M. Riberto, MD; J. Gallucci-Neto, MD; C.M. Santos, MD; T. Wagner, MSc; S.P. Rigonatti, MD, PhD; M.A. Marcolin, MD, PhD; and A. Pascual-Leone, MD, PhD

- 10 patients within 12 months from a stroke participated in a crossover, sham stimulation-controlled, double-blind study
- rTMS (1Hz/600secs/100%MT) or SHAM (delivered with a sham coil) were applied over contralesional M1 and Premotor Cortex.
- Patients were evaluated pre- and post-intervention with:
  - Simple reaction time (sRT)
  - Choice reaction time (cRT)
  - Purdue Pegboard Test
  - Finger tapping

(Mansur et al. 2005)

TMS Studies decreasing Contralesional Activity



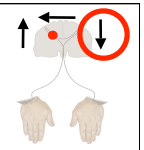


Conclusion

The study suggest that decreasing cortical excitability of the undamaged hemisphere can enhance performance of the lesioned side.

Mansur et al. 2006

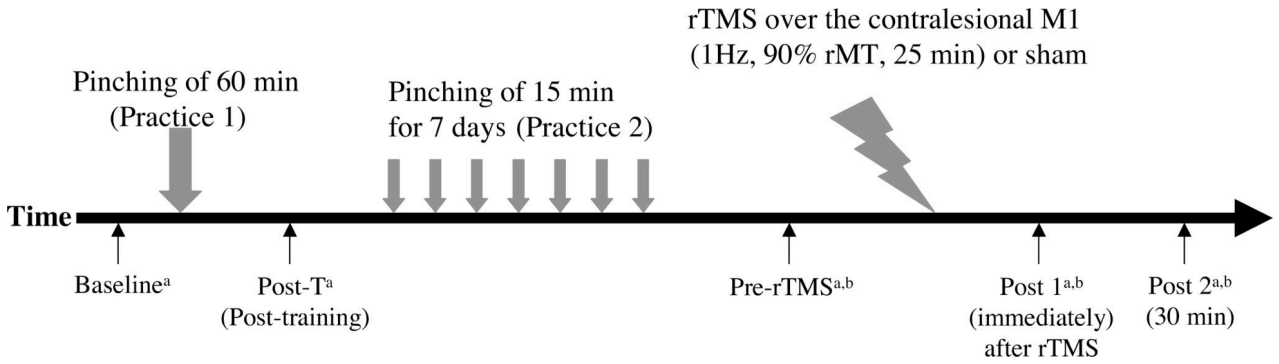
TMS Studies decreasing Contralesional Activity



Repetitive Transcranial Magnetic Stimulation of Contralesional Primary Motor Cortex Improves Hand Function After Stroke

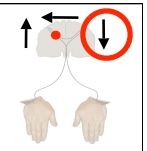
Naoyuki Takeuchi, MD; Takayo Chuma, MD; Yuichiro Matsuo, MD;
Ichiro Watanabe, MD, PhD; Katsunori Ikoma, MD, PhD **(Stroke 2005)**

- 20 patients more than 6 months after stroke participated in a sham stimulation-controlled, blinded study
- rTMS (1Hz/25mins/90%MT) or SHAM (delivered with a sham coil) applied over contralesional M1.



Takeuchi et al. 2005

TMS Studies decreasing Contralesional Activity



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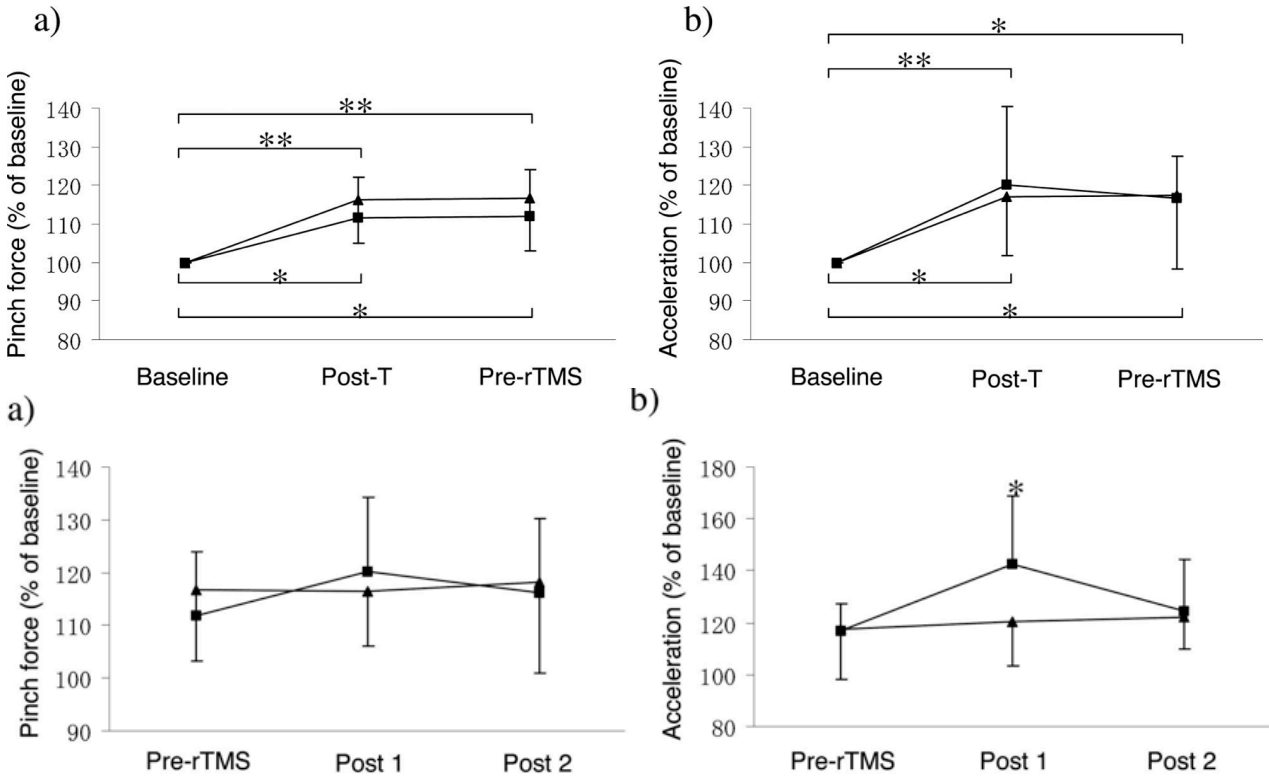
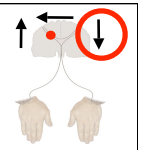


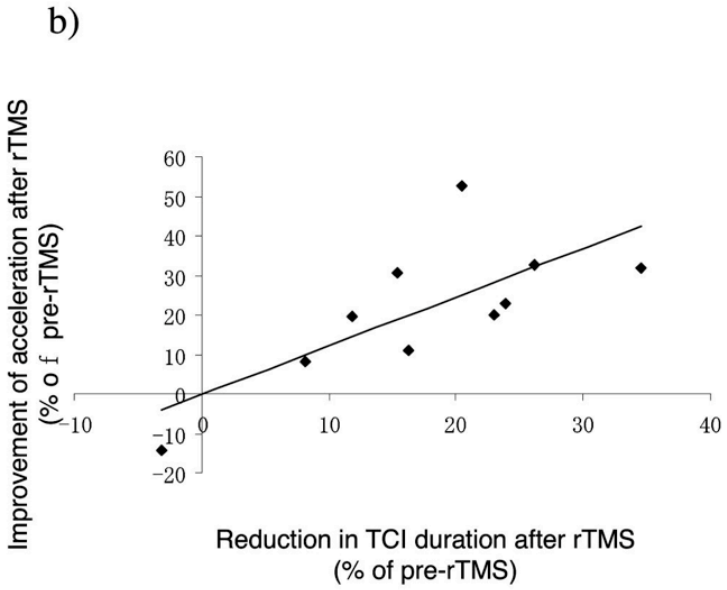
■ rTMS

▲ sham

Takeuchi et al. 2005

TMS Studies decreasing Contralesional Activity



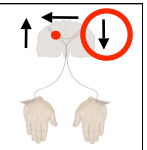


Conclusions:

- rTMS over the contralesional M1 could lead to improvement of motor function in the affected hand of patients with chronic stroke.
- This improvement correlated with decreased TCI from the contralesional M1.

Takeuchi et al. 2005

TMS Studies decreasing Contralesional Activity



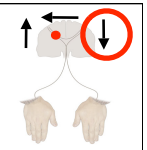
A Sham-Controlled Trial of a 5-Day Course of Repetitive Transcranial Magnetic Stimulation of the Unaffected Hemisphere in Stroke Patients

Felipe Fregni, MD, PhD; Paulo S. Boggio, MSc; Angela C. Valle, PhD; Renata R. Rocha; Julia Duarte; Merari J.L. Ferreira; Tim Wagner, MSc; Shirley Fecteau, PhD; Sergio P. Rigonatti, MD, PhD; Marcelo Riberto, MD; Steven D. Freedman, MD, PhD; Alvaro Pascual-Leone, MD, PhD

- 15 patients more than 12 months after stroke participated in a sham stimulation-controlled, blinded study
- rTMS (1Hz/20mins/100%MT) or SHAM (delivered with a sham coil) applied over contralesional M1, daily for 5 days.
- Patients were evaluated pre- and post-intervention (5d and 19d) with:
  - Simple reaction time (sRT)
  - Choice reaction time (cRT)
  - Purdue Pegboard Test (PPT)
  - Jebsen-Taylor test (JTT)

Fregni et al. 2006

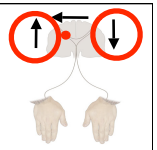
TMS Studies decreasing Contralesional Activity



- Relative to baseline, patients improve sRT, CRT, PTT and JTT in the active treatment group
- Importantly, the effects of rTMS were cumulative and lasted for at least 2 weeks after the end of treatment.
- The authors suggested a similar effect as CIT due to similar changes in excitability and longer lasting beneficial effects.
- Of note, there were no adverse events.

Fregni et al. 2006

Discussion



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- More studies are needed to determine how TMS is affecting recovery (i.e. genes, neurotransmitters, solely excitability?).
- Most of the studies have targeted chronic patients
- Can we enhance the effects beyond the 10-20% gain?
- Almost ALL studies conclude:

  "These findings suggest the potential use of this intervention as a neurorehabilitation strategy"

  ...but few questions remain: How/Who/When are we going to move forward from these lab-based proof of principle studies to determine the true clinical utility?

Conclusions

- Understanding the mechanisms underlying recovery of function after stroke have allowed the development and testing of novel therapeutic interventions to enhance recovery.
- Different stimulation strategies appear to be modestly beneficial in a lab or well-controlled setting.
- Future investigations will determine whether these interventions can be widely applied in a clinical setting