Use of TMS in Therapeutics

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Disclosures

- Conflicts of interest
  - NIH holds the patent for the H-coil and I am one of the co-inventors
  - Other irrelevant conflicts
- Off-label use (in regard USA)
  - rTMS with “NeuroStar TMS Therapy®” and for the Brainsway H-coil is indicated for treatment of major depressive disorder; all other uses are off-label

Learning objectives

1. To be able to discuss the applications of rTMS for the treatment of neurological disorders (main objective)
2. To appreciate the role of brain plasticity in the mechanism of therapy
3. To learn the principles of therapeutic protocols
4. To be able to discuss the future prospects for therapy

Key messages

1. Therapy with rTMS depends on its ability to make plastic changes of the brain
2. Generally, it is valuable to have a good rationale for what changes might be valuable
3. Multiple sessions are necessary
4. Efficacy will likely be improved by coupling rTMS with drugs or behavior

The possibility of therapy with rTMS depends on its ability to use plasticity to change the brain.

Mechanisms of Plasticity

- Synaptic strengthening/weakening
  - LTP/LTD
  - Homosynaptic & heterosynaptic
    - Spike Timing–Dependent Plasticity
  - Note the homeostatic feature
- Anatomical changes
  - Dendritic spines
  - Axonal spouting, new connections
- Turning circuits on and off

rTMS can modify brain function

- There are many possible methods for rTMS and each one will likely have different effects
  - Coil shape, coil current
  - Pattern & time of stimulation
  - Site of stimulation
  - Repetition of treatment

Types of rTMS

- Simple repetitive (rTMS)
- Theta burst (cTBS, iTBS)
- Quadripulse (QPS)

- Paired associative stimulation (PAS)
- Electrical stimulation
  - tDCS
  - tACS

Therapy with rTMS

- Psychiatry
  - Depression (and possibly mania)
  - OCD
  - Suppression of auditory hallucinations
- Tinnitus
- Stroke
- Movement disorders
  - Parkinson's disease
  - Dystonia
  - Essential tremor?
  - Ataxia?
- Epilepsy
- Pain

Logic of rTMS for Depression

- Left dorsolateral prefrontal cortex is hypometabolic
- Reversal of hypometabolism might improve mood
- This has been quite successful

The expanding evidence base for rTMS treatment of depression

Mark S. George, Joseph J. Taylor, and E. Baron Short

Purpose of review
Daily left prefrontal transcranial magnetic stimulation (TMS) for several weeks was first proposed as an acute treatment for depression in the early 1990s, and was Food and Drug Administration (FDA) approved in 2008. In the past year, several important studies have been published that extend our understanding of this novel treatment approach.

Recent findings
The first round of multisite clinical trials with TMS addressed whether prefrontal rTMS has efficacy and were conducted in carefully selected depressed patients who were antidepressant medication free. Several more recent studies assess the clinical effectiveness of TMS and report that about 35–40% of real-world patients who are commonly taking adjunctive antidepressants reach remission with a modest side effect profile. There are also new studies examining the durability of the TMS-induced antidepressant effect. Fifty-eight percent of TMS remitters remain remitted at 3-month follow-up.

Summary
These recent studies suggest that daily left prefrontal TMS over several weeks as a treatment for depression not only appears to have efficacy in rigorous randomized controlled trials, but is effective in real-world settings, with remission in 30–40% of patients. The TMS antidepressant effect, once achieved, appears to be as durable as with other antidepressant medications or interventions. Much more research is needed, particularly with issues such as the TMS coil location, stimulation intensity and frequency, and dosing strategy.

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Lessons

- Have a fundamental logic (that works out!)
- Multiple treatments seem necessary
  - Why?
- In depression, sometimes if a depression can be “broken”, then it is easier to maintain a euthymic state

Logic of rTMS for Parkinson disease

- Motor cortex excitability is low and patients need more time to make movements
- Increasing excitability of motor cortex might make movements easier to initiate and faster

Movement Disorders
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Placebo-Controlled Study of rTMS for the Treatment of Parkinson's Disease

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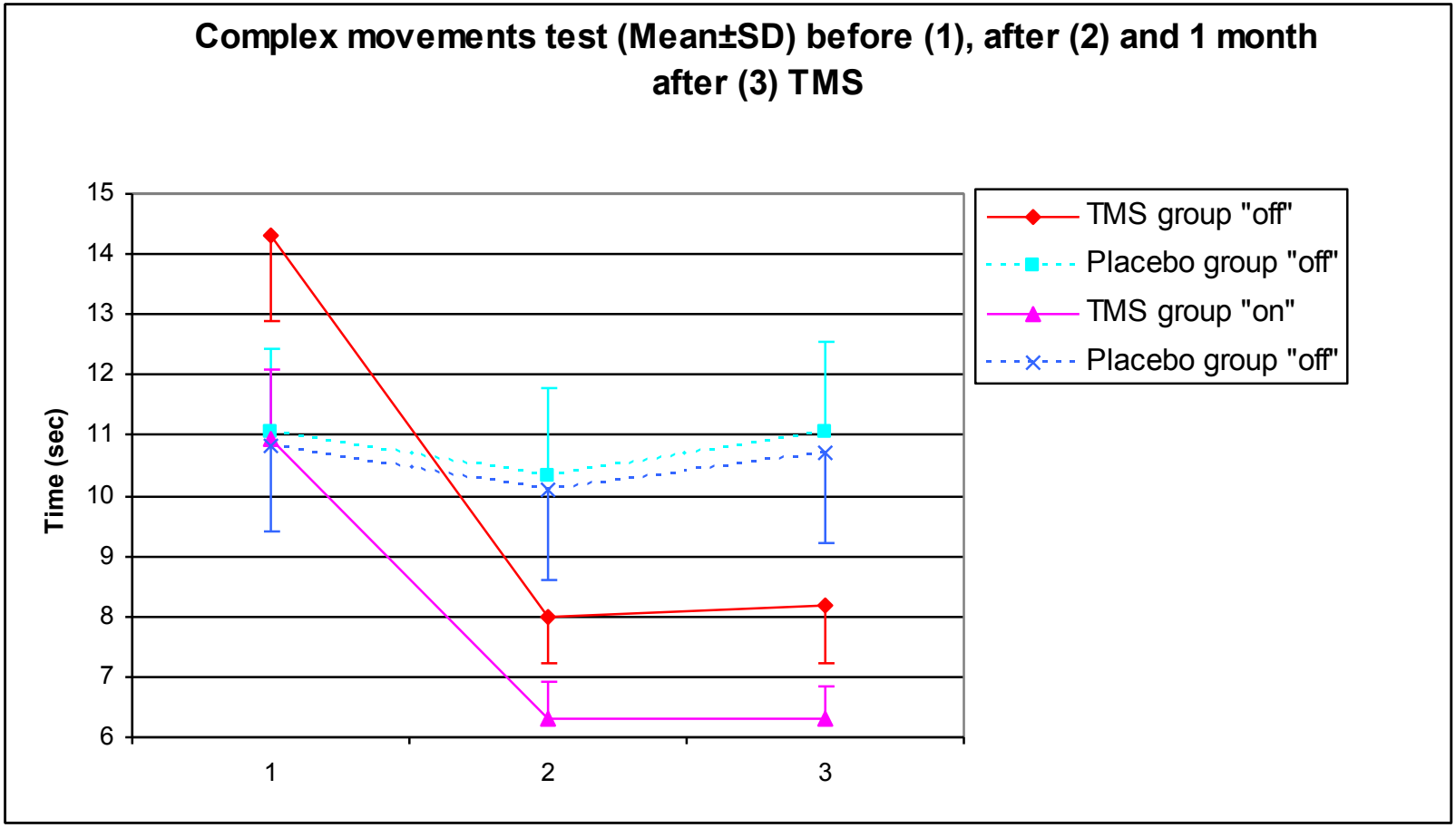
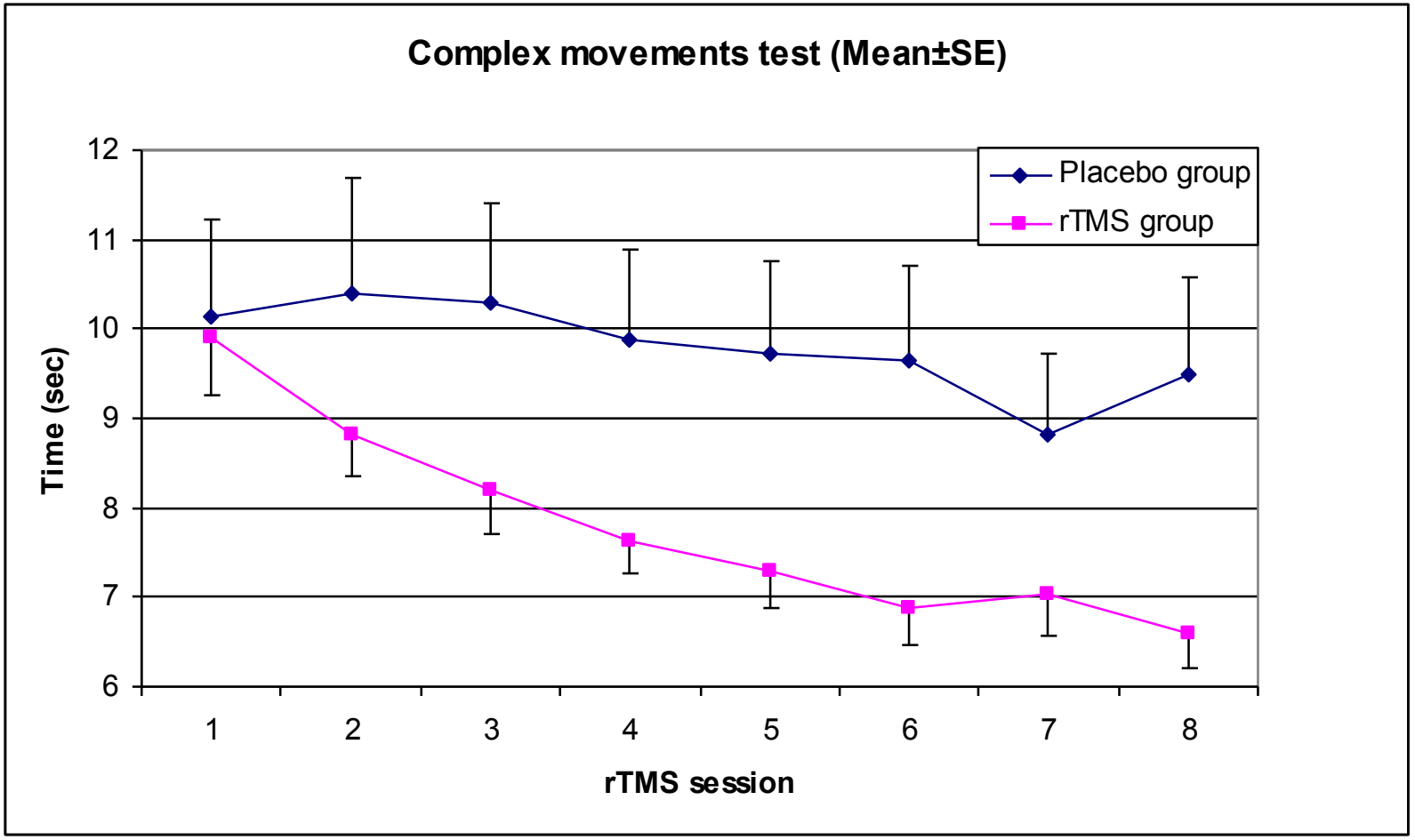
8 sessions over 4 weeks of 25 Hz rTMS at 100% MT delivered to left and right primary motor cortex and dorsolateral prefrontal cortex with 300 pulses each


Complex movements test (Mean±SD) before (1), after (2) and 1 month after (3) TMS
Time (sec)
15
14
13
12
11
10
9
8
7
6
1
2
3
TMS group "off"
Placebo group "off"
TMS group "on"
Placebo group "off"


Complex movements test (Mean±SE)
Placebo group
rTMS group
Time (sec)
12
11
10
9
8
7
6
1
2
3
4
5
6
7
8
rTMS session

rTMS releases dopamine

Strafella et al. 2001

- rTMS of prefrontal cortex causes release of dopamine in ipsilateral caudate nucleus as measured by raclopride binding PET
- 15 10-pulse trains of 1 sec duration at 10Hz at interval of 10 sec composed 1 block and 3 blocks were delivered with an interval of 10 min.

Combination of rTMS and Treadmill Training Modulates Corticomotor Inhibition and Improves Walking in Parkinson Disease: A Randomized Trial

Neurorehabilitation and
Neural Repair
27(1) 79–86

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Table 3. Comparison of Clinical Measures[a]

Measures	Control (n = 10)		Experimental (n = 10)		Time Effect, *P*	Time × Group, *P*
	Pretest	Posttest	Pretest	Posttest		
Comfortable walking speed, cm/s	108.25 ± 28.42	114.11 ± 25.24	107.86 ± 31.17	122.90 ± 30.48	.000	.062
Fast walking speed, cm/s	147.70 ± 45.29	159.29 ± 51.38	140.85 ± 38.75	162.54 ± 40.18	.000	.049
Timed up and go, s	10.00 ± 3.56	9.06 ± 3.42	11.78 ± 5.36	8.85 ± 3.24	.000	.019

[a]Values are mean ± standard deviation.

experimental group and a control group. Participants received rTMS (experimental group) or sham rTMS (control group) followed by treadmill training (30 minutes) for 12 sessions over 4 weeks. Repetitive TMS was applied at a 5-Hz frequency over the leg area of the motor cortex contralaterally to the more affected side for 6 minutes. Outcomes, including corticomotor inhibition and walking performance, were measured before and after training. *Results*. The results showed significant time effects on almost all corticomotor and functional variables. There are significant interaction effects between group and time of evaluation on the motor threshold, duration of the cortical silent period, and short interval intracortical inhibition of the contralateral hemisphere relatively to the more affected side as well as on the fast walking speed and timed up and go. *Conclusions*. The findings suggested that combination of rTMS and treadmill training enhances the effect of treadmill training on modulation of corticomotor inhibition and improvement of walking performance in those with PD.

Lessons

- Have a fundamental logic (that works out!)
- Multiple treatments seem necessary
- Beware of placebo effects and learning effects
- Mechanism might not be what is expected
- Coupling rTMS with behavioral therapy (or drugs) might be good idea

Logic of rTMS for Pain

- Epidural stimulation of the motor cortex has proven efficacy
- rTMS might have similar efficacy
- If not, it might indicate which patients are suitable for epidural stimulation

Pain

Repetitive transcranial magnetic stimulation

Primary motor cortex (precentral gyrus)	Contralateral to pain side, low frequency* (≤ 1 Hz), low intensity (80-90 % RMT), parallel to midline	Lack of efficacy proved in chronic neuropathic pain
Primary motor cortex (precentral gyrus)	Contralateral to pain side or left hemisphere, high-frequency* (≥ 5 Hz), low intensity (80-90 % RMT), parallel to midline	Efficacy proved in chronic neuropathic pain. Possible efficacy in fibromyalgia and CRPS
Primary somatosensory cortex (postcentral gyrus)	Contralateral to pain side, high-frequency* (≥ 5 Hz), low intensity (80-90 % RMT)	Possible lack of efficacy in chronic neuropathic pain
Secondary somatosensory cortex	Right hemisphere, low frequency* (≤ 1 Hz), medium intensity (70 % MSO)	Possible efficacy in chronic visceral pain
Dorsolateral prefrontal cortex	Right hemisphere, low frequency* (≤ 1 Hz), high intensity (110 % RMT)	Possible efficacy in fibromyalgia and chronic neuropathic pain
Dorsolateral prefrontal cortex	Left hemisphere, high-frequency* (≥ 5 Hz), low intensity (100 % RMT)	Possible efficacy in various pain syndromes (postoperative pain, fibromyalgia, chronic neuropathic pain, migraine)

From Lefaucheur, In Lozano & Hallett 2013

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Guidelines

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

Simone Rossi [a,*], Mark Hallett [b], Paolo M. Rossini [c,d], Alvaro Pascual-Leone [e] and The Safety of TMS Consensus Group [1]

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Side effects

- Hearing
- EEG issues
- State-dependency of TMS effects
- Seizures
- Syncope
- Local pain, headache, discomfort
- Psychiatric changes
- Cognitive/neuropsychological changes
- Other biological effects (in humans and animal models) possibly related to safety concerns
- Endocrinological after-effects
- Histotoxicity
- Effects on neurotransmitters and immune system
- Autonomic function

Conclusions

- rTMS can modify brain function and may be therapeutic in some circumstances
  - BUT – treatment must be repetitive
  - AND – combination with behavior or drugs might be useful/necessary
  - Other than for depression, other indications are experimental
- rTMS might also be used to test whether epidural stimulation would be worthwhile

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