
APPLICATION NOTE

rTMS for Rehabilitation After Stroke – Research Protocol Review and rTMS System Configuration

Regulatory Note: Rehabilitation after stroke is not included in the Intended Use for MagPro stimulators. The use of MagPro stimulators for applications outside the approved intended use in a given country is the responsibility of the researchers performing the trials.

1. What is Stroke?

A stroke is an attack on the brain which cuts off the blood supply to the brain. This causes damage to, or destruction of, brain cells. The blood supply to the brain can be cut off by blockage (Ischemic stroke) or by bleeding (Haemorrhagic Stroke). 80% of strokes are ischemic, 20% are haemorrhagic.

The effects are impaired motor function but a stroke can also affect the ability to communicate, learn, feel, think, see, etc. A stroke in the right hemisphere (half) of the brain can cause paralysis of the left side of the body (left hemiplegia) and can also affect spatial and perceptual abilities. Also, visual field impairment (left-sided neglect) may be present. Stroke in the left hemisphere can cause paralysis of the right side of the body (right hemiplegia). It can also affect speech and language abilities (Aphasia, Dysphasia).

In stroke rehabilitation patients are classified as being in a) acute stage up to 1 month post-stroke, b) sub-acute stage 1 – 6 months post-stroke and c) chronic stage more than 6 months post-stroke.

In this note focus is on rehabilitation of motor functions, primarily of the paretic upper limb.

2. Basic TMS Theories in Stroke Rehabilitation

Stroke leads to relative hyperactivity of the unaffected hemisphere due to the release from reciprocal inhibition by the opposite (affected) hemisphere. This increased interhemispheric inhibitory drive from the unaffected to the affected hemisphere might suppress surviving cortical motor systems and impair motor function. There is growing evidence that low frequency inhibitory stimulation to the unaffected hemisphere reduces this imbalance problem.

In addition, research confirms that excitation of the affected hemisphere with high frequency stimulation enhances corticospinal excitability and this approach also shows promising therapeutic results. However, there is still no clear knowledge of the exact mechanisms of rTMS.

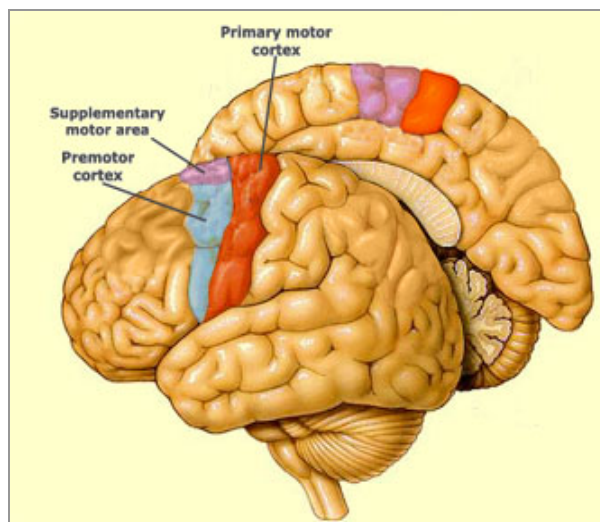
Clinical trials have been performed on patients with acute, sub-acute and chronic stroke. In all cases rTMS cannot stand alone, but is a supplement to physical therapies. Multiple treatment sessions are required (e.g.; daily for 10 days) as effects seem to be cumulative.

3. Published Clinical Studies

Affected Hemisphere (excitation)	Unaffected Hemisphere (inhibition)
<ul style="list-style-type: none"> • 3 clinical articles (PEDro* 6+) • 1-10 Hz, 80-120% rMT, 100-300 stimuli/session, using trains • Stimulation of the Motor Cortex • Significant improvements reported: <ul style="list-style-type: none"> - Barthel Index - Scandinavian Stroke Scale - NIH stroke Scale - Increased mean peak amplitude MEP - EMG frequency bi- and triceps 	<ul style="list-style-type: none"> • 5 clinical articles (PEDro* 6+) • Typically @ 1 Hz, 100% rMT, 600-1.200 stimuli/session (continuously for 10-20 min.) • Stimulation of Primary Motor Cortex (M1) • Significant improvements reported: <ul style="list-style-type: none"> - Increase in MT (= decreased corticospinal excitability) - Grip strength - Nine Holes Peg Test - Simple Reaction Time - Choice Reaction Time - Purdue Pegboard - Pinch Acceleration

* PEDro is the Physiotherapy Evidence Database ranking system for rating the quality of clinical trials. 10 is the maximum rating.

Detailed information on the clinical studies reported above is available on www.medicine.mcgill.ca/strokingengine/module_rtms_intro-en.html



4. rTMS system configuration for Stroke Rehabilitation Research

Based on the reported protocols the following clinical setup is suitable:

- Stimulator: MagPro R30 (biphasic waveform, up to 30 pps/Hz)
- Coil: MCF-B65 Butterfly Coil. Static cool technology provides up to 2.000 pulses before warm-up (at ambient temperature 20°C).
- Alternative coil for several treatment sessions in a row: Dynamic cooling with Cool-B65 Butterfly Coil and Coil Cooler Unit provides up to 20.000 pulses before warm-up.
- Flexible Arm for Magnetic Coil Positioning
- For Placebo studies:
 - Placebo Butterfly Coil: MCF-P-B65.
 - Sham Noise Generator

5. Theta Burst Protocols

Talelli et. al (Clinical Neurophysiology 118 (2007) 333-342) have explored theta burst stimulation (TBS) to improve motor recovery in chronic stroke. Six patients participated in 5 experiments involving facilitation, suppression and sham. They concluded that intermittent TBS (20 trains of 10 bursts given with 8 second intervals – 600 pulses in total, 80% of active MT) over the affected hemisphere significantly improved the motor behaviour and the physiological measures of the paretic hand. iTBS thus works by increasing the excitability at the stimulated site.

Di Lazzaro et. al. have also explored the use of theta burst in stroke, see section 6.

Theta burst stimulation is available with the MagPro X100 stimulator.

6. Published Studies with use of MagPro Stimulator

- Khedr et. al. (2005). “Therapeutic trial of repetitive transcranial stimulation after acute ischemic stroke”. Neurology, 65,466-468. PEDro score: 7.

Randomized controlled trial with 52 patients, 26 real rTMS, 26 sham rTMS. Applied to the motor cortex of the affected hemisphere. 10 * 10-second trains at 3Hz with 50 seconds between trains; 10 minutes per session, 300 pulses per session. 120% MT. 1 session per day for 10 days.

Real rTMS lead to a significant improvement on the Barthel Index, the Scandinavian Stroke Scale and the NIH Stroke Scale, both immediately post treatment and at 10-day follow-up.

- Di Lazzaro et. al. (2006). “Direct Demonstration That Repetitive Transcranial Magnetic Stimulation Can Enhance Corticospinal Excitability in Stroke”. Stroke. 2006; 37:2850-2853.

Test on one patient with complete motor deficit of the right upper limb and severe motor deficit of the right lower limb. Treatment spot was motor cortical hotspot (affected hemisphere) for EMG responses in the right TA muscle. Intermittent theta burst (iTBS) with 10 bursts of high frequency stimulation (3 pulses at 50Hz) applied at 5Hz every 10 seconds for a total of 190 seconds (600 pulses in total). Intensity of 80% of active MT.

The single treatment produced a long-lasting increase in cortical excitability. The iTBS increased corticospinal activity evoked by single-pulse TMS by approximately 80%.

- Khedr et. al. (2009). “Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke”. Acta Neurologica Scandinavia. DOI:10.1111/j.1600-0404.2009.01195.x.

Randomized study of 48 patients classified into 3 groups:

- 16 patients received real rTMS, 3Hz in 5 sec. trains, 50 trains , 750 pulses total at 130% rMT
- 16 patients received real rTMS, 10Hz in 2 sec. trains, 37 trains, 750 pulses total at 100% rMT
- 16 patients received sham

Treatment was performed on the affected hemisphere for 5 consecutive days.

There was a significant improvement of the motor power one year after treatment for patients that received real rTMS. The tendency was for the 3Hz group to produce more significant changes than the 10Hz group, but this was not statistically significant.



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