

# Research Update

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## rTMS for Treatment of Post-Traumatic Stress Disorder PTSD – Research Protocol Review and rTMS System Configuration

**Regulatory Note:** rTMS for treatment of PTSD 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. For US: Please consult MagVenture.

### 1. What is Post Traumatic Stress Disorder

Post-Traumatic Stress Disorder (PTSD) is an incapacitating anxiety disorder characterized by intrusive thoughts, hyper-arousal, flashbacks, nightmares, sleep disturbances, emotional numbing, and withdrawal (as classified by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV]). PTSD may develop in susceptible individuals after exposure to a terrifying ordeal that involved physical harm or the threat of physical harm. This severe anxiety disorder remains challenging to treat, with persistent symptoms leading to considerable social, occupational, and interpersonal dysfunction. Symptoms must be present for at least one-month but may last many years.

Epidemiologic studies estimate 7.8% of the United States population experiences PTSD in their lifetime. PTSD often results in significant psychosocial impairment; for example, PTSD-related work impairments are estimated to cost in excess of \$3 billion in annual productivity loss in the United States.

To date, few studies have examined the use of rTMS in patients with PTSD, and results have been mixed using the conventional rTMS target in the dorsolateral prefrontal cortex.

### 2. Basic TMS Theories in PTSD

Neurobiological research suggests that PTSD is characterized by a dysregulated fear response. Several imaging studies have demonstrated a hyperactive amygdala in people with PTSD compared to healthy subjects. In addition, areas involved in modulation of the amygdala, namely the hippocampus and medial prefrontal cortex, have been demonstrated to have decreased activity to fearful cues in functional magnetic resonance imaging studies.

Particularly relevant to treatment research, animal models demonstrate that ventral medial prefrontal cortex activation is critical in extinguishing fearful response. Neuromodulation of prefrontal structures using TMS has been hypothesized to have potential usefulness in treatment of PTSD. Many of these studies have targeted the dorsolateral prefrontal cortex (DLPFC), which resides within a mood regulatory network that includes the amygdala, hippocampus and ventromedial prefrontal cortex. Repetitive TMS applied to the DLPFC has demonstrated antidepressant efficacy via presumed activity changes throughout this distributed network.

Both right- and left-sided stimulation showed significant effects on PTSD symptoms. In the only direct comparison, right-sided high frequency treatment was shown to be more effective than left-sided in reducing core symptoms. Furthermore, there is a trend towards better effect size with higher number of total pulses.

## 2. Clinical Studies

### PTSD right sided low frequency excitation

- 3 clinical papers.
- 1 Hz, 80-100% MT intensity, trains of continuous stimulation, 2 sec stimulation with 58 sec inter train intervals or 20 sec stimulation with 40 sec inter train intervals. 100/400/600 pulses per treatment session, 10 sessions.
- Stimulation of right dorsolateral prefrontal cortex (DLPFC) with figure of 8 coil.
- 65 patients treated real or sham.
- rTMS was safe and well-tolerated, and resulted in reduced PTSD core symptoms.



Based on the reported protocols, the following research 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: Cool-B65.
- Cool Coils (and Coil Cooler) 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.

For double blinded placebo studies:

- Cool-B65 A/P (Active/Placebo) coil with research software.
- Sham Noise Generator.

## PTSD right or left sided high frequency excitation

- 4 clinical papers.
- 5Hz, 10 Hz, 20Hz, 80-100% MT intensity, 2 sec stimulation with 28 sec inter train intervals or 2 sec stimulation with 58 sec inter train intervals. 600/1600 pulses per treatment session, 10 sessions.
- Stimulation of left or right dorsolateral prefrontal cortex (DLPFC) with figure of 8 coil.
- 42 patients treated real or sham.
- rTMS was safe and well-tolerated, and resulted in reduced PTSD core symptoms.

Based on the reported protocols, the following research 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: Cool-B65.
- Cool Coils (and Coil Cooler) provides up to 20,000 pulses before warm-up.
- Flexible Arm for Magnetic Coil Positioning.

For Placebo studies:

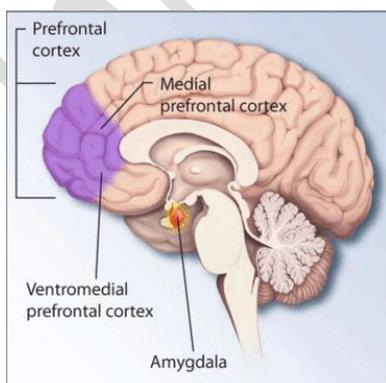
- Placebo Butterfly Coil: MCF-P-B65.
- Sham Noise Generator.

For double blinded placebo studies:

- Cool-B65 A/P (Active/Placebo) coil with research software.
- Sham Noise Generator.

## PTSD excitation, alternative protocol

- 1 clinical paper.
- 20 Hz, 120% MT intensity, 42 trains of 2 sec with 20 sec inter train intervals. 1,680 pulses, 15-20 sessions.
- Stimulation of dorsomedial/ventromedial prefrontal cortex (DMPFC/VMPFC) right then left with H coil to achieve greater depth.
- 26 patients treated.
- rTMS was safe and well-tolerated, and resulted in reduced PTSD core symptoms.



Based on the reported protocol, the following research setup is suitable:

- Stimulator: MagPro R30 (biphasic waveform, up to 30 pps/Hz).
- Coil: Cool DB80 Butterfly Coil/Cool-125 Circular coil/Cool-B70 Butterfly Coil
- Coil Cooler.
- Cool Coil (and Coil Cooler) provides up to 20,000 pulses before warm-up.
- Flexible Arm for Magnetic Coil Positioning.

### 3. References

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