**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 74694

**Manuscript Type:** LETTER TO THE EDITOR

**Repetitive transcranial magnetic stimulation for post-traumatic stress disorder: Lights and shadows**

Concerto C *et al*. rTMS and PTSD

Carmen Concerto, Giuseppe Lanza, Francesco Fisicaro, Manuela Pennisi, Alessandro Rodolico, Giulia Torrisi, Rita Bella, Eugenio Aguglia

**Carmen Concerto, Alessandro Rodolico, Giulia Torrisi, Eugenio Aguglia,** Department of Clinical and Experimental Medicine, Psychiatry Unit, University of Catania, Catania 95124, Italy

**Giuseppe Lanza,** Department of Surgery and Medical-Surgical Specialties, University of Catania, Catania 95123, Italy

**Giuseppe Lanza,** Clinical Neurophysiology Research Unit, Oasi Research Institute-IRCCS, Troina 94018, Italy

**Francesco Fisicaro, Manuela Pennisi,** Department of Biomedical and Biotechnological Sciences, University of Catania, Catania 95123, Italy

**Rita Bella,** Department of Medical and Surgical Sciences and Advanced Technologies “G. F. Ingrassia”, University of Catania, Catania 95123, Italy

**Author contributions:** Concerto C and Lanza G contributed equally to this work; Concerto C, Lanza G, Fisicaro F, and Rodolico A conceived the study; Pennisi M and Torrisi G performed the literature search; Concerto C and Lanza G wrote the first draft of the manuscript; Bella R and Aguglia E revised the manuscript and supervised the research group; and all authors have read and approve the final manuscript.

**Corresponding author: Giuseppe Lanza, MD, MSc, PhD, Associate Professor,** Department of Surgery and Medical-Surgical Specialties, University of Catania, *Via* Santa Sofia, 78, Catania 95123, Italy. giuseppe.lanza1@unict.it

**Received:** January 2, 2022

**Revised:** January 27, 2022

**Accepted:** May 12, 2022

**Published online:**

**Abstract**

We have read with interest the publication that describes the available data related to the use of neuromodulation strategies for the treatment of post-traumatic stress disorder (PTSD). Despite treatment advances, however, a substantial proportion of PTSD patients receiving psychological and/or pharmacological treatment do not reach an adequate clinical response. In their paper, the authors draw attention to the current understanding of the use of repetitive transcranial magnetic stimulation (rTMS) as a potential treatment for PTSD. Most of the previous studies indeed applied both inhibitory (1 Hz) and excitatory (> 1 Hz, up to 20 Hz) rTMS to the right and/or left dorsolateral prefrontal cortex. Despite larger therapeutic effects observed when high-frequency stimulation was applied, the question of which side and frequency of stimulation is the most successful is still debated. The authors also reported on the after-effect of rTMS related to neuroplasticity and identified the intermittent theta burst stimulation as a technique of particular interest because of it showed the most effective improvement on PTSD symptoms. However, although numerous studies have highlighted the possible beneficial use of rTMS protocols for PTSD, the exact mechanism of action remains unclear. In their conclusions, the authors stated that rTMS has been demonstrated to be effective for the treatment of PTSD symptoms. Nevertheless, we believe that further research with homogeneous samples, standardized protocols, and objective outcome measures is needed to identify specific therapeutic targets and to better define significant changes when active and sham stimulation procedures are compared.

**Key Words:** Post-traumatic stress disorder; Neuromodulation; Repetitive transcranial magnetic stimulation; Translational neuroscience; Neuroplasticity; Metaplasticity

Concerto C, Lanza G, Fisicaro F, Pennisi M, Rodolico A, Torrisi G, Bella R, Aguglia E. Repetitive transcranial magnetic stimulation for post-traumatic stress disorder: Lights and shadows. *World J Clin Cases* 2022; In press

**Core Tip:** The interesting publication of the basic principle, current applications, and future directions of repetitive transcranial magnetic stimulation for the non-pharmacological treatment of post-traumatic stress disorder (PTSD) have been summarized. Therapeutic effects on core PTSD symptoms, such as avoidance, hyperarousal, and intrusions, appear to be larger when high-frequency stimulation over the right dorsolateral prefrontal cortex was used. However, although the technique has demonstrated safety and efficacy, several concerns remain related to the mechanisms of action and protocols to be adopted, including the heterogeneity in the sample selection, stimulation procedures, and outcome measures.

**TO THE EDITOR**

We have read with interest the recent publication by Cheng *et al*[1] summarizing the current understanding on the use of transcranial magnetic stimulation (TMS) as a potential treatment for post-traumatic stress disorder (PTSD). As known, PTSD is a mental health disorder that may occur after experiencing or witnessing a significantly traumatic event. Symptoms include flashbacks, nightmares, and severe anxiety, as well as uncontrollable thoughts about the event, affective symptoms, and negative cognition[2]. These symptoms can significantly impact personal relationships and social and work activities, thus impairing functional independence and quality of life[3,4].

Neuromodulation strategies based on non-invasive brain stimulation techniques, such as repetitive TMS (rTMS) and transcranial direct current stimulation, have been recently investigated and applied in PTSD patients who did not reach an adequate clinical response with conventional therapy[5,6]. TMS has been widely used for the treatment of other psychiatric disorders, in particular it has shown to be highly effective in adults with drug-resistant major depressive disorder[7], including long-lasting effects on depressive-associated cognitive dysfunction[8]. Regarding PTSD, the latest evidence-based guidelines on the therapeutic use of rTMS concluded that level B evidence (probable efficacy) was reached for high-frequency (excitatory) rTMS over the right dorsolateral prefrontal cortex (DLPFC)[9]. However, these recommendations are based on the differences reached in therapeutic efficacy of real *vs* sham (fictitious) stimulation replicated in a sufficient number of independent studies, but this does not mean that the benefit produced by rTMS inevitably reaches a clinical relevance[9].

In their paper, Cheng *et al*[1] suggested the role of rTMS as an effective and promising treatment for PTSD. However, the previous literature they reviewed mainly shows considerable variation regarding stimulation parameters, type of traumatic events, and sample characteristics. Regarding the stimulation area, most of the previous studies identified the DLPFC as the preferential stimulation target, although differences were observed between either the frequency or the side of stimulation. The interest in targeting the right DLPFC comes from previous evidence showing that high-frequency rTMS was able to increase neural activity and blood flow in the right hemisphere, thus improving some of the core PTSD symptoms, such as avoidance, hyperarousal, and intrusions[10]. Conversely, high-frequency rTMS over the left DLPFC has been mainly used as a neuromodulatory protocol for mood disorders[7], suggesting its application for the PTSD-related affective symptoms.

Regarding the rTMS protocols, most studies applied a stimulation intensity of 120% of the individual’s resting motor threshold. Subjects who underwent 1-Hz (inhibitory) stimulation usually received 2250 pulses over 37.5 min, whereas those stimulated at 10-Hz (excitatory) received 3000 pulses over the same time period (4-s stimulation train, with 26-s intertrain interval), for 2 wk of daily treatments[11-14], although some more recent rTMS trial designs in PTSD have delivered more treatments[15-17]. However, the question of which side and frequency of stimulation is the most successful in terms of remission or response from PTSD symptoms is still debated.

Regarding the side of stimulation, it seems that rTMS could be effective over both the left and right DLPFC, as suggested by the authors themselves[1]. Of clinical relevance is also the finding of a better treatment outcome for the high-frequency rTMS applied over the right than the left DLPFC. This is in line with a recent meta-analysis by Harris and Reece[10], who discussed the effects of rTMS on episodic memory retrieval and reiteration of the traumatic event, which is responsible for the flashback symptoms. They suggested that the DLPFC might be involved in the recurrence of trauma reminiscence and, therefore, may participate in the inhibition of the trauma memory. Likewise, Cheng *et al*[1] reported of a previous work by Parson and Ressler[18] on the correlation between dysregulated response to fear and PTSD symptoms. Overall, it appears that DLPFC is involved in emotional regulation, being also thought to influence the activity between the ventral medial prefrontal cortex (vmPFC) and the amygdala[19]. Accordingly, other studies highlighted the role of the vmPFC in modulating fear responsivity[20], as well other cerebral areas, such as the temporal-insular cortex[21].

It should be also considered that an earlier study suggested that the effectiveness of rTMS might depend not only on PTSD symptoms only, but also on the patient’s personality traits, such as impulsivity, risk proneness, and sensation seeking[22]. DLPFC plays indeed a key role in mood-affect and impulsivity regulation and a hyperactivity of the limbic structures has been related to behavioral instability[23]. Emotional dysregulation and disturbed impulse control are also common borderline personality traits. In this context, a previous TMS report explored the influence of comorbid borderline personality traits on treatment response to TMS in major depressed patients[24], whereas a recent study by Ward *et al*[25] reported that borderline personality traits did not affect treatment response to DLPFC-TMS in a large naturalistic dataset of patients receiving conventional clinical treatment for depression. In their conclusion, the authors stated that the antidepressant efficacy of rTMS was independent from comorbid borderline personality disorder.

Interestingly, Cheng *et al*[1] also reported on the after-effect of rTMS on neuroplasticity, and in particular on long-term potentiation and long-term depression, phenomena likely related to glutamatergic (especially to AMPA and NMDA receptor) and GABAergic activity, respectively. They further identified the intermittent theta burst stimulation (iTBS) as a technique of particular interest, because of its most effective improvement on PTSD symptoms. The authors also reported on a sham-controlled study by Philip *et al*[26]. who indicated which PTSD symptoms, including depression, improved the most after iTBS treatment and hypothesized the effects on hippocampal synaptic activity and connections.

Among the cellular and molecular mechanisms underlying distinct forms of synaptic plasticity, however, we believe that more attention should be paid to metaplasticity, which refers to the activity-dependent modulation of synaptic plasticity. This pivotal determinant of learning, memory, and other functions represents a higher order of synaptic plasticity that acts on the threshold for modifying synaptic strength[27]. Moreover, impaired synaptic plasticity, the so-called “maladaptive plasticity”, has been associated with the pathogenesis and trajectory of several brain diseases, including contributions to the dysfunctional remodeling of underlying neural networks[28]. Given its role in regulating synaptic plasticity, alterations to metaplastic mechanisms are likely to represent an important element of many neurological and psychiatric disorders, including PTSD. The development of non-invasive brain stimulation techniques has allowed to induce and modulate metaplasticity in human subjects, both in normal and pathological conditions. In support of this, Thomson and Sack[29] focused on the use of iTBS to develop metaplasticity-based treatments to induce or restore the desired level of plasticity. They further identified accelerated iTBS at longer intervals (60 min) as being of particular interest, as it seems to maximize metaplasticity effects and clinical outcomes[29].

In their conclusions, the authors stated that rTMS demonstrated to be a safe and effective neurostimulation treatment for PTSD[1]. However, although several studies highlighted the beneficial use of TMS protocols for PTSD, the exact mechanism of action remains unclear. Therefore, we believe that further research with homogeneous samples, standardized protocols, and objective outcome measures is needed to better define the optimal stimulation settings (including the active and sham stimulation comparison) and to clarify whether these interventions may be applied not only to the core symptoms of PTSD but also on its cognitive and mood-affect manifestations.

**REFERENCES**

1 **Cheng P**, Zhou Y, Xu LZ, Chen YF, Hu RL, Zou YL, Li ZX, Zhang L, Shun Q, Yu X, Li LJ, Li WH. Clinical application of repetitive transcranial magnetic stimulation for post-traumatic stress disorder: A literature review. *World J Clin Cases* 2021; **9**: 8658-8665 [PMID: 34734044 DOI: 10.12998/wjcc.v9.i29.8658]

2 **American Psychiatric Association**. DSM-5 Task Force 5th ed. Washington: American Psychiatric Publishing, 2013

3 **Signorelli MS**, Costanzo MC, Cinconze M, Concerto C. What kind of diagnosis in a case of mobbing: post-traumatic stress disorder or adjustment disorder? *BMJ Case Rep* 2013; **2013** [PMID: 23761569 DOI: 10.1136/bcr-2013-010080]

4 **Rodolico A**, Vaccino N, Riso MC, Concerto C, Aguglia E, Signorelli MS. Prevalence of Post-Traumatic Stress Disorder Among Asylum Seekers in Italy: A Population-Based Survey in Sicily. *J Immigr Minor Health* 2020; **22**: 634-638 [PMID: 31863404 DOI: 10.1007/s10903-019-00948-9]

5 **Berger W**, Mendlowicz MV, Marques-Portella C, Kinrys G, Fontenelle LF, Marmar CR, Figueira I. Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic review. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33**: 169-180 [PMID: 19141307 DOI: 10.1016/j.pnpbp.2008.12.004]

6 **Gouveia FV**, Davidson B, Meng Y, Gidyk DC, Rabin JS, Ng E, Abrahao A, Lipsman N, Giacobbe P, Hamani C. Treating Post-traumatic Stress Disorder with Neuromodulation Therapies: Transcranial Magnetic Stimulation, Transcranial Direct Current Stimulation, and Deep Brain Stimulation. *Neurotherapeutics* 2020; **17**: 1747-1756 [PMID: 32468235 DOI: 10.1007/s13311-020-00871-0]

7 **Spampinato C**, Aguglia E, Concerto C, Pennisi M, Lanza G, Bella R, Cantone M, Pennisi G, Kavasidis I, Giordano D. Transcranial magnetic stimulation in the assessment of motor cortex excitability and treatment of drug-resistant major depression. *IEEE Trans Neural Syst Rehabil Eng* 2013; **21**: 391-403 [PMID: 23559064 DOI: 10.1109/TNSRE.2013.2256432]

8 **Concerto C**, Lanza G, Cantone M, Ferri R, Pennisi G, Bella R, Aguglia E. Repetitive transcranial magnetic stimulation in patients with drug-resistant major depression: A six-month clinical follow-up study. *Int J Psychiatry Clin Pract* 2015; **19**: 252-258 [PMID: 26398527 DOI: 10.3109/13651501.2015.1084329]

9 **Lefaucheur JP**, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipović SR, Grefkes C, Hasan A, Hummel FC, Jääskeläinen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen JP, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorová I, Rossi S, Sahlsten H, Schecklmann M, Szekely D, Ziemann U. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clin Neurophysiol* 2020; **131**: 474-528 [PMID: 31901449 DOI: 10.1016/j.clinph.2019.11.002]

10 **Harris A**, Reece J. Transcranial magnetic stimulation as a treatment for posttraumatic stress disorder: A meta-analysis. *J Affect Disord* 2021; **289**: 55-65 [PMID: 33940319 DOI: 10.1016/j.jad.2021.04.003]

11 **Cohen H**, Kaplan Z, Kotler M, Kouperman I, Moisa R, Grisaru N. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. *Am J Psychiatry* 2004; **161**: 515-524 [PMID: 14992978 DOI: 10.1176/appi.ajp.161.3.515]

12 **Boggio PS**, Rocha M, Oliveira MO, Fecteau S, Cohen RB, Campanhã C, Ferreira-Santos E, Meleiro A, Corchs F, Zaghi S, Pascual-Leone A, Fregni F. Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *J Clin Psychiatry* 2010; **71**: 992-999 [PMID: 20051219 DOI: 10.4088/JCP.08m04638blu]

13 **Watts BV**, Landon B, Groft A, Young-Xu Y. A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Brain Stimul* 2012; **5**: 38-43 [PMID: 22264669 DOI: 10.1016/j.brs.2011.02.002]

14 **Leong K**, Chan P, Ong L, Zwicker A, Willan S, Lam RW, McGirr A. A Randomized Sham-controlled Trial of 1-Hz and 10-Hz Repetitive Transcranial Magnetic Stimulation (rTMS) of the Right Dorsolateral Prefrontal Cortex in Civilian Post-traumatic Stress Disorder: Un essai randomisé contrôlé simulé de stimulation magnétique transcrânienne repetitive (SMTr) de 1 Hz et 10 Hz du cortex préfrontal dorsolatéral droit dans le trouble de stress post-traumatique chez des civils. *Can J Psychiatry* 2020; **65**: 770-778 [PMID: 32379487 DOI: 10.1177/0706743720923064]

15 **Kozel FA**, Motes MA, Didehbani N, DeLaRosa B, Bass C, Schraufnagel CD, Jones P, Morgan CR, Spence JS, Kraut MA, Hart J Jr. Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: A randomized clinical trial. *J Affect Disord* 2018; **229**: 506-514 [PMID: 29351885 DOI: 10.1016/j.jad.2017.12.046]

16 **Kozel FA**, Van Trees K, Larson V, Phillips S, Hashimie J, Gadbois B, Johnson S, Gallinati J, Barrett B, Toyinbo P, Weisman M, Centorino M, Gibson CA, Catalano G. One hertz versus ten hertz repetitive TMS treatment of PTSD: A randomized clinical trial. *Psychiatry Res* 2019; **273**: 153-162 [PMID: 30641346 DOI: 10.1016/j.psychres.2019.01.004]

17 **Koek RJ**, Roach J, Athanasiou N, van 't Wout-Frank M, Philip NS. Neuromodulatory treatments for post-traumatic stress disorder (PTSD). *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **92**: 148-160 [PMID: 30641094 DOI: 10.1016/j.pnpbp.2019.01.004]

18 **Parsons RG**, Ressler KJ. Implications of memory modulation for post-traumatic stress and fear disorders. *Nat Neurosci* 2013; **16**: 146-153 [PMID: 23354388 DOI: 10.1038/nn.3296]

19 **Lyoo IK**, Kim JE, Yoon SJ, Hwang J, Bae S, Kim DJ. The neurobiological role of the dorsolateral prefrontal cortex in recovery from trauma. Longitudinal brain imaging study among survivors of the South Korean subway disaster. *Arch Gen Psychiatry* 2011; **68**: 701-713 [PMID: 21727254 DOI: 10.1001/archgenpsychiatry.2011.70]

20 **Milad MR**, Quirk GJ. Fear extinction as a model for translational neuroscience: ten years of progress. *Annu Rev Psychol* 2012; **63**: 129-151 [PMID: 22129456 DOI: 10.1146/annurev.psych.121208.131631]

21 **Cantone M**, Lanza G, Bella R, Pennisi G, Santalucia P, Bramanti P, Pennisi M. Fear and disgust: case report of two uncommon emotional disturbances evoked by visual disperceptions after a right temporal-insular stroke. *BMC Neurol* 2019; **19**: 193 [PMID: 31409291 DOI: 10.1186/s12883-019-1417-0]

22 **De Vidovich GZ**, Muffatti R, Monaco J, Caramia N, Broglia D, Caverzasi E, Barale F, D'Angelo E. Repetitive TMS on Left Cerebellum Affects Impulsivity in Borderline Personality Disorder: A Pilot Study. *Front Hum Neurosci* 2016; **10**: 582 [PMID: 27994543 DOI: 10.3389/fnhum.2016.00582]

23 **Coccaro EF**, Sripada CS, Yanowitch RN, Phan KL. Corticolimbic function in impulsive aggressive behavior. *Biol Psychiatry* 2011; **69**: 1153-1159 [PMID: 21531387 DOI: 10.1016/j.biopsych.2011.02.032]

24 **Feffer K**, Peters SK, Bhui K, Downar J, Giacobbe P. Successful dorsomedial prefrontal rTMS for major depression in borderline personality disorder: Three cases. *Brain Stimul* 2017; **10**: 716-717 [PMID: 28196679 DOI: 10.1016/j.brs.2017.01.583]

25 **Ward HB**, Yip A, Siddiqui R, Morales OG, Seiner SJ, Siddiqi SH. Borderline personality traits do not influence response to TMS. *J Affect Disord* 2021; **281**: 834-838 [PMID: 33229022 DOI: 10.1016/j.jad.2020.11.054]

26 **Philip NS**, Barredo J, Aiken E, Larson V, Jones RN, Shea MT, Greenberg BD, van 't Wout-Frank M. Theta-Burst Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder. *Am J Psychiatry* 2019; **176**: 939-948 [PMID: 31230462 DOI: 10.1176/appi.ajp.2019.18101160]

27 **Müller-Dahlhaus F**, Ziemann U. Metaplasticity in human cortex. *Neuroscientist* 2015; **21**: 185-202 [PMID: 24620008 DOI: 10.1177/1073858414526645]

28 **Cantone M**, Lanza G, Ranieri F, Opie GM, Terranova C. Editorial: Non-invasive Brain Stimulation in the Study and Modulation of Metaplasticity in Neurological Disorders. *Front Neurol* 2021; **12**: 721906 [PMID: 34276553 DOI: 10.3389/fneur.2021.721906]

29 **Thomson AC**, Sack AT. How to Design Optimal Accelerated rTMS Protocols Capable of Promoting Therapeutically Beneficial Metaplasticity. *Front Neurol* 2020; **11**: 599918 [PMID: 33224103 DOI: 10.3389/fneur.2020.599918]

**Footnotes**

**Conflict-of-interest statement:** The authors declared no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Unsolicited article; Externally peer reviewed

**Peer-review model:** Single blind

**Corresponding Author's Membership in Professional Societies:** European Academy of Neurology (EAN); Italian Society of Neurology (SIN); Italian Society for Translational Research and Health Professionals (SIRTEPS); Italian Association of Sleep Medicine (AIMS); Italian Stroke Organization (ISO); International Neuromodulation Society (INS); World Sleep Society (WSS); International Parkinson and Movement Disorder Society (MDS).

**Peer-review started:** January 2, 2022

**First decision:** January 23, 2022

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Ge X, China; Kar SK, India **S-Editor:** Wang JJ **L-Editor:** Filipodia **P-Editor:**