



# Future Perspectives From a Case Report of Transcranial Magnetic Stimulation, Cognitive Behavioral Therapy, and Psychopharmacological Treatment for Post-traumatic Stress Disorder

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## INTRODUCTION

Post-traumatic Stress Disorder (PTSD) is a stress-related condition that occurs after experiencing or witnessing a traumatic event, such as a threat to physical integrity, or a potentially life-endangering situation, including a serious car accident, physical and/or psychological abuse, or sexual assault. It is a severe and debilitating psychiatric disorder, often resulting in professional disability, weakened relationships, decreased cognitive and psychosocial functioning, and frequent use of health care services due to physical conditions and mental comorbidities, such as substance abuse, major depressive disorder (MDD) or even suicide. The occurrence of PTSD throughout life varies between 0.56 and 6.67% among the European population (Burri and Maercker, 2014), with concerns of increasing rates due to the COVID-19 pandemic (Salehi et al., 2021). In Portugal, where the authors are based, PTSD was found to be one of the most disabling mental health conditions, with patients reporting disability with six times higher likelihood than study controls (Antunes et al., 2018). Hence, there is an urge for effective and fast acting treatments in this condition. One potential successful strategy, which has become a common practice in mental health, particularly when the outcomes of first-line treatments are unsatisfactory due to inefficacy or debilitating side-effects, is combining different therapeutic modalities.

Currently available treatment options, such as psychopharmacology (Brady et al., 2000; Marshall et al., 2001) and/or psychotherapy (Monson and Shnaider, 2014; Forbes, 2020), are frequently insufficient (Hoskins et al., 2015), and innovative therapeutic strategies are necessary. In similarly debilitating disorders, such as MDD, options for therapeutic neuromodulation, such as Transcranial Magnetic Stimulation (TMS), are clinically effective (Berlim et al., 2013; Gaynes et al., 2014; Mutz et al., 2018). In fact, following approval by the US Food and Drug Administration (FDA) in 2008, TMS has been highly successful in alleviating symptoms of treatment resistant MDD and, in 2015, the UK's National Institute for Health and Care Excellence also recommended the use of TMS in MDD treatment. TMS is a non-invasive and safe neuromodulation technique, resulting from generation of an electromagnetic field by a coil which, when applied over the skull, elicits a focal electric current in the underlying cortical tissue. Such stimulation, when applied repetitively (repetitive TMS; rTMS), has more long-lasting modulatory effects on the activity of the underlying cortical nervous tissue (Radhu et al., 2016).

Over the last years, evidence has accumulated that rTMS may be effective in the treatment of PTSD (Cohen et al., 2004; Boggio et al., 2010; Watts et al., 2012; Ahmadzadeh and Rezaei, 2018), with guidelines prepared by a large group of European experts suggesting that it is probably effective (Lefaucheur et al., 2020), and supporting off-label use in selected patients. In one sham-controlled study (Ahmadzadeh and Rezaei, 2018), 58 patients with PTSD were randomized to receive 20 Hz-rTMS over the right dorsolateral prefrontal cortex (DLPFC;  $n = 19$ ), or over the right and left DLPFC ( $n = 19$ ), or sham stimulation ( $n = 20$ ), for 10 sessions over 4 weeks. The parameters of stimulation for the active rTMS arms consisted in 2,400 pulses/session over the right DLPFC or 1,200 pulses over the right DLPFC followed by 1,200 pulses over the left DLPFC, performed at 100% of the resting motor threshold (RMT). A larger proportion of responders, as assessed by reduction of total score in the PTSD checklist military version, was found among the real stimulation groups, with no significant difference between unilateral and bilateral stimulation, when compared to the sham group (41.2 and 62.5 vs. 0% of responders, respectively).

Importantly, other studies have shown moderate to significant improvements when using a combination of rTMS with cognitive and behavioral interventions (Osuch et al., 2009; Isserles et al., 2013; Kozel et al., 2018). These studies combined different TMS treatment protocols with various interventions such as imaginal exposure before rTMS sessions (Osuch et al., 2009), brief script-driven exposure during deep TMS sessions (Isserles et al., 2013) and cognitive processing therapy (CPT) after rTMS sessions (Kozel et al., 2018). This is, at least in part, consistent with evidence for the therapeutic effects of psychotherapy assisted by 3,4-methylenedioxymethamphetamine (MDMA) to treat PTSD (Mitchell et al., 2021), and the use of brief symptom provocation prior to rTMS for obsessive-compulsive disorder, in accordance with the protocol cleared by the FDA (Carmi et al., 2019). Positive findings regarding the combination of rTMS and psychotherapy have also been described for other disorders, namely MDD. For example, in a large naturalistic study of 196 patients treated with at least 10 sessions of rTMS and simultaneous cognitive therapy for MDD, the authors found 66 and 56% response and remission rates, respectively, with sustained remission rates of 60% at 6 month follow up (Donse et al., 2018). Nevertheless, little is known about the neurobiological and psychological factors that might contribute toward enhancement of treatment efficacy, with further research necessary for a better understanding of such enhancement and contributing factors.

At our center, rTMS is delivered mostly for depression, but only rarely as monotherapy. In most cases, given that it is delivered due to resistance to other treatments, rTMS is applied in combination with other strategies, namely psychopharmacological treatments, but also psychotherapy. In fact, despite our current psychotherapeutic interventions not being tailored for rTMS treatment, in several patients we have observed a positive impact of rTMS on ongoing psychotherapeutic work, possibly reflecting an interaction between the two treatments. To illustrate the potential benefits of this combined intervention in PTSD, here we will present the case

of a patient diagnosed with PTSD, with apparent benefit from the combination of both treatment strategies.

## CASE DESCRIPTION

The case is that of a 45-year-old woman that, 4 years before coming to our center, had been involved in a severe car accident, while driving. After this event she reported the beginning of nightmares and daydreams involving the accident as well as disabling avoidant behaviors, such as not leaving the house due to fear of having another accident. She also reported frequent panic attacks and loss of balance without any related medical findings. She referred important relational difficulties, which culminated in separating from her husband just 1 month after the accident. Additionally, despite being highly functioning prior to the accident, 2 years after she had lost her job and since then had been incapable of resuming any working activity, due to her mental symptoms as well as chronic back pain.

Treatment for her condition had been attempted by different psychiatrists with several psychopharmacological treatments, including sertraline, trazodone, venlafaxine and quetiapine, with little or no relief. When first observed she was also taking high doses of several benzodiazepines, and attending long-term psychotherapy, as well as a pain-management program in a group setting, all without success. Concerning past psychiatric history, she had suffered a major depressive episode at ~20 years old, when her grandmother passed away. This episode was successfully treated with 2 years of psychopharmacological treatment, and it had not recurred since. The patient did not recall which specific agents were prescribed at that time. Apart from dyslipidemia, no other medical conditions were reported.

In this clinical context, she was diagnosed with PTSD and comorbid benzodiazepine use disorder. The current psychopharmacological treatment was optimized with fluoxetine, pregabalin, clorazepate dipotassium, and quetiapine. Additionally, a new psychotherapeutic treatment was offered. Due to her depressive symptoms and anxiety, the patient adhered to this treatment with difficulty, attending a total of 11 cognitive-behavioral psychotherapy (CBT) sessions over 8 months. While it was possible to discontinue almost all benzodiazepines, after 8 months of treatment with optimized doses of fluoxetine (60 mg qid), clorazepate dipotassium (30 mg qid), pregabalin (250 mg qid) and quetiapine (up to 150 mg qid), little clinical improvement was observed for PTSD symptoms, and alternative treatment options were proposed. Specifically, the patient agreed to, and signed informed consent for, off-label use of rTMS for PTSD, as an augmentation strategy for ongoing medication and psychotherapy.

## rTMS TREATMENT

The protocol for off-label use of rTMS for PTSD was defined according to data described in the evidence-based guidelines for therapeutic use of rTMS (Lefaucheur et al., 2020). High frequency (20 Hz) rTMS, was performed daily, Monday through Friday, in ~30 min-long sessions, with 2,400 pulses (2 s on and

**TABLE 1** | Clinical outcomes for combined rTMS treatment.

Session	BDI-II (% change)	STAI-S (% change)	PCL-5 (% change)	CAPS-5 (% change)
1	32	69	76	47
30	16 (−50%)	61 (−11.6%)	65 (−14.5%)	29 (−38.3%)
36	14 (−56.3%)	55 (−20.3%)	60 (−21.1%)	19 (−59.6%)

BDI-II, Beck Depression Inventory; STAI-S, State-Trait Anxiety Inventory State Subscale; PCL-5, Posttraumatic Stress Disorder Checklist for DSM-5; CAPS-5, Clinician-Administered PTSD Scale for DSM-5.

28 s off) delivered at 100% of the RMT over the right DLPFC, across 6 weeks (i.e., an acute treatment cycle of 30 sessions). We used the MagVenture Coil Cool-B65, targeting the DLPFC using the “5.5 cm rule” localization method (McClintock et al., 2018). Following the acute treatment, 6 continuation sessions, performed every 2 weeks with the same stimulation protocol, were offered. During acute and continuations rTMS, the patient attended a total of 5 CBT sessions in 5 months. At the same time, the psychopharmacological treatment remained stable for fluoxetine (60 mg qid) and quetiapine SR (150 mg qid). The dose of pregabalin was gradually raised to 400 mg qid while clorazepate dipotassium (30 mg qid) was terminated.

In addition to the clinical evaluations by the treating clinicians, symptoms were assessed at the beginning, during and at the end of the rTMS treatment as presented in **Table 1**. The Beck Depression Inventory (BDI-II) (Beck et al., 1996; Campos and Gonçalves, 2011) was used to assess the severity of depression at baseline, weekly and at the end of the acute and continuation treatment cycles. The State Trait Anxiety Inventory (STAI) (Spielberger et al., 1983; Silva and Campos, 1998) was collected at the same time points in order to measure self-reported anxiety symptoms that commonly co-occur with PTSD (Brady et al., 2000). In order to assess PTSD symptomatology, the self-rated PTSD Checklist for DSM-5 (PCL-5) (Blevins et al., 2015; Carvalho et al., 2020), was used. Finally, at baseline and at the end of acute and continuation treatment cycles, PTSD symptoms were also assessed using Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (Weathers et al., 2018; Oliveira-Watanabe et al., 2019). After 4 weeks of the acute rTMS cycle, depressive symptom severity reduced 50% (from a BDI-II total score of 32–16) and the CAPS-5 score reduced 38% (from a total score of 47–29). A smaller reduction in symptoms severity was observed on self-reported anxiety (−11.6%; STAI-State) and PTSD symptoms (−14.5%; PCL-5). Nevertheless, an impressive symptom reduction continued until the end of rTMS continuation sessions, especially on the CAPS-5 score, that reduced almost 60% at the end of rTMS (**Table 1**).

In the years after completing rTMS treatment, the patient continued attending psychotherapy sessions and psychiatric appointments, albeit less frequently. Contrary to prior to rTMS, throughout the post-rTMS CBT sessions, she became able to elaborate on cognitive restructuring, as well as conduct breathing and relaxation techniques. Before rTMS treatment, she was

unable to engage in any exposure techniques implemented by her cognitive-behavioral psychotherapist due to severe sadness, anguish and unbearable anxiety. For the first time, she was generalizing the use of behavioral and cognitive control strategies between sessions. Currently, the patient reports stable remission of her symptoms, as well as significant recovery of functionality.

## DISCUSSION

In the present case, the addition of an off-label rTMS protocol for PTSD to ongoing treatments was successful. While the psychopharmacological and CBT treatments offered previously had produced unsatisfactory results, after rTMS the patient rapidly showed a decrease in symptom severity. While this may simply result from the benefit of rTMS *per se*, we believe this case report may reflect the potential impact of combining rTMS with psychotherapy. In this case, the rapid symptomatic improvement of both depressive and PTSD symptoms, once rTMS was offered, helped the patient to finally engage in psychotherapeutic work that was being offered in psychotherapy. Moreover, the well-known positive effects of rTMS on cognitive functioning (Bajbouj and Padberg, 2014) might have contributed to her deeper engagement in psychotherapy sessions. In fact, she became more prone to working with her psychotherapist and participated in techniques that had been emotionally unbearable and of limited use before starting rTMS. On the other hand, the already established psychotherapeutic relationship (Horvath et al., 2011) might have potentiated the expectation regarding TMS, prompting patient commitment to daily TMS treatment sessions, a critical moderator for clinically effective rTMS neurobiological effect (Galletly et al., 2012; Modirrousta et al., 2018). Often, for patients with PTSD, daily outings for TMS treatment might be challenging. This combined setting may have contributed to treatment adherence, since no rTMS session was missed for the ~5 months duration of rTMS acute and continuation treatments. Importantly, treatment adherence and expectations are known to be important contributors for better outcomes in various treatment modalities (Horwitz, 1993; Constantino et al., 2021).

Concerning the current evidence, well-illustrated by this case report, we believe that combining neuromodulation techniques with psychotherapy, as well as psychopharmacologic agents, is a promising approach in treatment of neuropsychiatric disorders, particularly in challenging or treatment-refractory cases. Nevertheless, the augmenting effect of TMS on psychotherapeutic work should be further explored, using carefully designed randomized control trials. Additionally, we believe that the neurobiological mechanisms supporting the clinical efficacy of combining these treatment modalities should also be clarified. Such path will certainly allow improving psychotherapy design as well as that of rTMS protocols. Ultimately, increasing the knowledge about combined TMS, psychopharmacological and psychotherapeutic strategies will help develop individualized treatments, increasing the likelihood of symptom remission while improving quality of life.

## AUTHOR CONTRIBUTIONS

CS, GC, and AO-M conceived and designed the work. CS, GC, JG, and AO-M acquired and discussed the clinical case. CS and GC drafted the work. JG and AO-M revised the manuscript

critically for important intellectual content. All authors approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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