Dorsomedial prefrontal cortex repetitive transcranial magnetic stimulation treatment of posttraumatic stress disorder in eating disorders: An open-label case series

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Abstract
Posttraumatic stress disorder (PTSD) is a common comorbid condition in anorexia nervosa (AN) and bulimia nervosa (BN), and may be associated with reduced response to treatment. We report on a case series employing repetitive transcranial magnetic stimulation (rTMS) with a novel target, the dorsomedial prefrontal cortex (DMPFC). Fourteen subjects with eating disorders and comorbid PTSD received 20–30 neuronavigated DMPFC–rTMS treatments on an open-label basis. PTSD symptoms were assessed pretreatment and posttreatment with the PTSD checklist-Civilian (PCL-C) and the Difficulties in Emotional Regulation Scale (DERS). PCL-C scores were reduced by 51.99% overall, from a mean of 54.29 ± 19.34 pretreatment to 24.86 ± 17.43 posttreatment (p < .001). Of the 14, 8 showed an improvement of >50%. DERS scores improved by 36.02% overall, from 140.00 ± 22.09 at pretreatment to 89.29 ± 38.31 at posttreatment (p < .001). Of the 14 subjects, 5 achieved >50% improvement. These data may suggest that DMPFC–rTMS could be helpful in the treatment of PTSD in some ED patients.

KEYWORDS
PTSD, rTMS, treatment

1 | INTRODUCTION

Eating disorders (EDs) are complex psychiatric illnesses often presenting with multiple comorbidities. Research examining Posttraumatic stress disorder (PTSD) and ED has consistently found that PTSD is more prevalent in ED subjects than in non-ED subjects, with reported rates of traumatic experiences as high as 90% and rates of PTSD varying from 12% to 45% (Dansky, Brewerton, Kilpatrick, & O’Neil, 1997; Hudson, Hiripi, Pope, & Kessler, 2007; Mitchell, Mazzeo, Schlesinger, Brewerton, & Smith, 2012)

While PTSD may predispose toward the development of ED, ED subjects with PTSD may be more likely to drop out of treatment or relapse in their ED than those with no history of PTSD (Brewerton, 2004, 2007, 2008; Vrabel et al., 2010). Current management focuses on teaching skills to enhance affect tolerance. Many ED-PTSD patients cannot tolerate standard ED treatment because of worsened PTSD symptoms accompanying reductions in ED symptoms. Developing new approaches for PTSD in the ED-PTSD population could improve ED treatment outcomes.

One promising approach is repetitive transcranial magnetic stimulation (rTMS). rTMS is an emerging brain stimulation therapy that uses powerful, focused magnetic field pulses to induce action potentials in target brain regions noninvasively. Repeated trains of stimulation can induce lasting changes in brain activity in the target region, thereby achieving therapeutic effects across a range of neurological and psychiatric conditions (for reviews on this technique, see Lefaucheur et al. (2014).

The literature on rTMS use for PTSD is limited. One recent meta-analysis of rTMS for PTSD reviewed 5 randomized control trials (RCTs) concluding that active rTMS was superior to sham stimulation (Trevizol et al. 2016). Another exploratory meta-analysis (Berlim, Broadbent, & Van den Eynde, 2013) of randomized and sham-controlled studies using DLPFC–rTMS found significantly improved outcomes overall in anxiety and depressive symptoms.
The majority of therapeutic rTMS studies have targeted the DLPFC. However, the dorsomedial prefrontal cortex (DMPFC) may be a more preferable candidate for several reasons. First, compared to DLPFC, the DMPFC shows more consistent structural and functional abnormalities in neuroimaging studies of PTSD (Goodkind et al., 2015; Meng et al., 2014); second, in healthy controls, the DMPFC is more closely associated with emotional and behavioral self-control. Previously, we have reported beneficial effects for DMPFC-rTMS in major depression (18), binge eating and purging (Downar, Sankar, Giacobbe, Woodside, & Colton, 2012), and obsessive-compulsive disorder (OCD) (Dunlop et al., 2015b). In the same studies, functional magnetic resonance imaging (fMRI) has revealed changes in the activity of frontal lobe circuits involved in emotion regulation, accompanying clinical improvements.

To date, there is only one published study on DMPFC-rTMS in PTSD, and this study showed significant improvements in clinical and psychophysiological measures of PTSD severity following deep-coil DMPFC-rTMS (Isserles et al., 2013). Building upon this work and our own reports on DMPFC-rTMS in related disorders, the aim of this case series is to assess the potential clinical utility of DMPFC-rTMS in ED-PTSD patients.

2 | METHODS

Participants were referred for rTMS from the Program for Eating Disorders, Toronto General Hospital. All participants had received standard treatment, or were receiving treatment, for AN, BN, or eating disorder not otherwise specified (EDNOS), and all had PTSD. This case series was part of a larger study of the effect of DMPFC-rTMS on ED and common comorbidities of ED. Subjects were diagnosed based on clinical interview by ED and PTSD expert psychiatrists using DSM-IV criteria. Mean BMI was 20.8 ± 4.54. Patients with PTSD had chronic complex PTSD, that is, PTSD of long duration and usually as a consequence of multiple adverse life experiences (Brewerton, 2007) and were well known to the treating ED clinicians. Some were receiving hospital-based or outpatient care for their ED, PTSD, or both. PTSD subjects had undergone a wide range of treatments for PTSD and had been unresponsive to any treatment they were receiving for their PTSD. The study was approved by the Institutional REB and all subjects gave informed consent for treatment.

All patients underwent rTMS targeting the DMPFC according to previously described methods (Dunlop et al., 2015a; Salomons et al., 2014), with a course length of 20 sessions extended to 30 sessions in treatment responders (mean number of sessions 24.29, ± SD 5.14). Ten patients received 10 Hz stimulation (120% resting motor threshold, 10 Hz trains, 5 s on 10 s off, 60 trains, 3,000 pulses per hemisphere, bilateral), while 3 patients received intermittent theta-burst stimulation (120% resting motor threshold, 50 Hz triplet bursts, 5 bursts per second, 2 s on 8 s off, 20 trains, 600 pulses per hemisphere, bilateral). One patient received 20 Hz stimulation (120% resting motor threshold, 20 Hz trains, 2.5 s on 10 s off, 30 trains, 1,500 pulses per hemisphere, bilateral). We have previously shown these protocols to have equivalent clinical effects across a sample of $N = 185$ patients suffering from depression. Patients were medication stable for at least 4 weeks prior to initiation of rTMS.

Participants completed two standardized self-report questionnaires at pretreatment and posttreatment: the PTSD Checklist-Civilian version (PCL-C) (Weathers, Litz, Huska, & Keane, 1994) and the Difficulties with Emotional Regulation Scale (DERS) (Gratz & Roemer, 2004). The PCL-C addresses general stressful experiences and specific traumatic events. The DERS is designed to assess multiple aspects of emotional regulation. For the purpose of this trial, we used only the total DERS score.

3 | RESULTS

Fourteen female ED-PSTD participants (mean age = 39.8 ± 10.9 years) were included. Mean age of onset of eating disorder was 16.5 years old and mean duration of illness was 20.8 years. Primary ED diagnoses were as follows: anorexia nervosa: restrictive subtype (AN-R), n = 2; binge-purge subtype (AN-BP), n = 4; BN, n = 5; EDNOS, n = 3. Other comorbid diagnoses included major depressive disorder (MDD n = 6), bipolar disorder (n = 2), social anxiety disorder (n = 3), borderline personality disorder (n = 1), panic disorder (n = 1), and OCD (n = 1). Traumatic experiences related to PTSD included sexual abuse (childhood and adulthood), physical abuse, physical trauma, and emotional trauma.

Patients exhibited improvements on both measures. PCL-C scores improved significantly (mean pretreatment PCL-C = 54.29 ± 19.34; mean posttreatment PCL-C = 24.86 ± 17.43, $p < .001$; mean improvement 51.99 ± 27.24%). Of the 14 participants, 8 (57%) showed a >50% reduction in PCL-C scores. Among responders (>50% improvement), PCL-C scores were improved by 72.3 ± 13.5%. DERS scores also showed a significant improvement (mean pretreatment DERS = 140.00 ± 22.09, posttreatment DERS = 89.29 ± 38.31, $p < .001$; mean improvement, 36.02 ± 24.24%). Of the 14 participants, 5 showed a >50% reduction in DERS scores. In this group, DERS scores improved by 61.8 ± 9.5%. No participant had a worsening of either DERS or PCL-C scores. All subjects tolerated the rTMS treatments well and there were no adverse events aside from transient headaches during the first few treatments.

Two patients were markedly underweight (BMI = 15.7 and 14.5). These patients had lesser responses to treatment, with a mean reduction of 35 ± 15.7% and 17.5 ± 8.9% reduction on PCL-C and DERS, respectively. Neither patient achieved a >50% improvement on either measure.

4 | DISCUSSION

This is the first report of DMPFC-rTMS for PTSD in ED patients. In this population, DMPFC-rTMS appears to improve PTSD symptoms, with 57% of patients improving by >50%. ITBS appears to have been the most effective, followed by 10 Hz stimulation, but these improvements were not tested statistically due to the small number of cases. These outcomes compare favorably to conventional DLPFC-rTMS.
Cohen et al. (2004) reported a 31% PCL-C improvement with 10 Hz DLPFC–rTMS stimulation; Boggio et al. (2010) reported 37% PCL-C improvement with 20 Hz DLPFC–rTMS. However, both these earlier studies gave only 10 sessions of DLPFC–rTMS.

Improvements in emotional regulation, measured by the DERS, accompanied improvements in PTSD symptoms. Given that emotional dysregulation is a central symptom in PTSD, these results may indicate a treatment mechanism for DMPFC–rTMS. The DMPFC is involved in aspects of emotion regulation and the inhibition of prepotent responses (reviewed in Isserles et al., 2013). Furthermore, the DMPFC is abnormally activated in PTSD patients during emotion regulation and appraisal (Shin et al., 2005; Wang et al., 2016). PTSD-related emotion-regulation deficits are related to altered connectivity of the medial PFC to the amygdala (Shin et al., 2005); it is possible that the therapeutic effects of DMPFC–rTMS elicit changes through this circuitry.

Two of our subjects were severely underweight, and seem to have shown a blunted clinical response to DMPFC–rTMS. This may suggest a need to have a period of nutritional rehabilitation prior to initiating treatment with rTMS.

This case series has many limitations. First, it is clear that we cannot definitively state that the observed changes are due to the rTMS treatment. As an open-label series, the contribution of nonspecific/placebo effects cannot be quantified. Second, the small sample size and heterogenous nature of the sample in terms of ED leave open the possibility of nonreplication in a larger sample, and also precludes assessment of moderating effects from other conditions. While the subjects were all well-known to the referring physicians, there was no structured diagnostic interview employed in this case series. The lack of long-term follow-up data leaves open the question of durability of a treatment for treatment-resistant major depressive disorder.

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While suggestive, the present findings cannot be construed to support any conclusions about the efficacy of DMPFC–rTMS in this clinical population. Nonetheless, we find the findings intriguing, and worth further study, given the common comorbidity of PTSD in patients with ED, and the tendency for PTSD symptoms to hamper effective treatment of ED. Future studies should be in the form of a formal randomized controlled trial under double-blind conditions, with assessment of associated comorbidity, functional imaging, and a follow-up period. The possibility of a novel intervention to enhance emotion-regulation capacity in ED–PTSD patients would constitute a significant advance in our ability to offer effective treatment in this challenging population.

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