Received: 9 April 2018 | Revised: 20 June 2018 | Accepted: 20 July 2018

DOI: 10.1002/eat.22942

WILEY

International Journal of EATING DISORDERS

BRIEF REPORT

Improving decision-making and cognitive impulse control in bulimia nervosa by rTMS: An ancillary randomized controlled study

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Funding information
Centre Hospitalier Régional Universitaire de Montpellier, Grant/Award Number: PHRC-IR UF 8709

Abstract

Objective: Impaired decision-making and inhibitory control may be involved in the pathophysiology of psychiatric disorders like bulimia nervosa (BN). Their improvement after neuromodulation may underpin clinical improvement. We assessed the effects of rTMS on these cognitive functions in a sample of women with BN.

Methods: Thirty-nine participants (22 in a sham group and 17 in an rTMS group) were assessed before and after 10 high frequency rTMS sessions over the left dorsolateral prefrontal cortex (DLPFC).

Results: The between-group analyses revealed no differences in the final neuropsychological performances. The within-group analyses showed that inhibitory control improved in both the go/no-go task (p = .03) and the BIS cognitive impulsivity subscale (p = .01) in the rTMS group only. Switches toward good choices on the Iowa gambling task significantly improved in the rTMS group only (p = .002), and understanding of the task contingencies increased between the two assessments, also in the rTMS group only (p = .03).

Discussion: This preliminary evidence suggests that modulation of left DLPFC might improve two putative cognitive biomarkers of BN.

KEYWORDS

dorsolateral prefrontal cortex, eating disorders, neurocognition

1 | INTRODUCTION

Decision-making and inhibitory control are core cognitive functions in daily living. It has been hypothesized that their impairment may be involved in the pathophysiology and/or chronicity of psychiatric disorders (Goschke, 2014), and investigation into the neural mechanisms underlying these impaired/unimpaired functions has therefore intensified. The prefrontal region, particularly the dorsolateral prefrontal cortex (DLPFC), is a key area for the neurocognitive processes involved in both decision-making and inhibitory control (Tracy et al., 2015). Decision-making and cognitive inhibition have been proposed as putative cognitive biomarkers of several mental disorders, including addictive disorders, bulimic disorders, and suicidal behavior (Courtet, Gottesman, Jollant, & Gould, 2011). Noninvasive brain stimulation may modulate these cognitive functions (Brevet-Aeby, Brunelin, Iceta, Padovan, & Poulet, 2016), and it has been suggested that clinical improvement after neuromodulation might be underpinned by an improvement in neuropsychological factors, opening new therapeutic alternatives (Trojak et al., 2017). Nevertheless, apart from the studies in healthy controls, few clinical studies have assessed whether

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The study was registered in the ClinicalTrials.gov database with the Identifier: NCT01530906.

noninvasive brain stimulation modulates these potential biomarkers of disease. In a randomized controlled trial, we therefore assessed the effects of a two-week program of high frequency (HF) rTMS over the left DLPFC on the cognitive performances of women with bulimia nervosa (BN).

2 | MATERIAL AND METHODS

This study is an ancillary to a larger scale study showing that 10 sessions of HF rTMS over the left DLPFC did not provide better results than placebo in treating the bulimic symptoms of women with BN. A full description of the study protocol and results can be found elsewhere (Gay et al., 2016). The local ethics committee approved this study and written informed consent was obtained from all participants. The study was registered at ClinicalTrials.gov (NCT01530906). Participants were randomized to real or sham stimulation. They received 10 sessions of real (20 trains of 5 s with 55-s intervals between trains at a frequency of 10 Hz and 110% of motor threshold intensity) or sham rTMS over two consecutive weeks (from Monday to Friday).

At baseline and after the last rTMS session, all participants underwent neurocognitive assessment along three dimensions: inhibitory control with a go/no-go task (Schmitz et al., 2008) and the Barratt Impulsiveness Scale (BIS) (Bayle et al., 2000), decision-making with the Iowa gambling task (IGT) (Bechara, Damasio, Tranel, & Damasio, 1997), and sustained attention with the D2 test of attention (Uttl & Pilkenton-Taylor, 2001). These dimensions and tasks were targeted as they have been reported to be impaired in people with BN (Guillaume et al., 2015; Wu, Hartmann, Skunde, Herzog, & Friederich, 2013). Assessment was computerized and performed in a quiet room by a trained neuropsychologist blinded to the participants' allocation. Tasks were administered in random order. All participants were initially naive to these tasks.

Clinical and neuropsychological characteristics were compared between the two groups using the chi-squared test or Fisher's exact test for categorical variables and the Mann–Whitney test for continuous variables. Wilcoxon's signed-rank test compared two repeated measurements. Linear mixed models were used to examine the effect of performance over the five blocks of the IGT.

3 | RESULTS

Thirty-nine participants (22 in the sham group and 17 in the rTMS group) completed the neuropsychological battery twice and were included in this study. There were no significant differences between the two groups for either clinical characteristics (age, age of disease onset, current BMI, etc.) or baseline neuropsychological performances.

The between-group analyses revealed no differences in the final neuropsychological performances. The within-group analyses revealed improvement in sustained attention performance between pre- and post-rTMS in both groups ($p < .001$ in both groups). A significant improvement in inhibitory control performance after rTMS was observed only in the rTMS group, both for the number of commission errors on the go/no-go test ($p = .01$ in the rTMS group and $p = .3$ in the sham group) and the BIS cognitive impulsivity subscale ($p = .03$ in

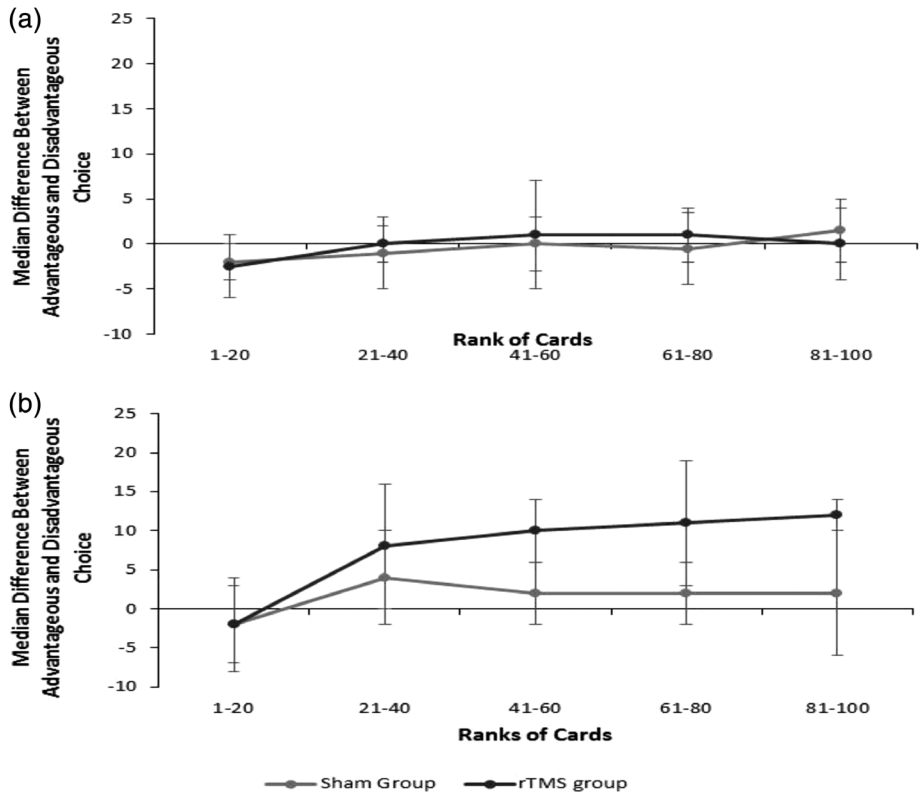

FIGURE 1 Changes in performance during the IGT. (a) IGT before rTMS. (b): IGT after rTMS. For each point median score with median absolute deviation are displayed

the rTMS group and 0.9 in the sham group). There was no improvement in the net score of the IGT 51–100 after rTMS, although it was borderline significant in the rTMS group (p = .07). The intermediate net score significantly improved after rTMS for the rTMS group only (p = .002 vs. p = .12 in the sham group) (Figure 1). An increase in the proportion of participants who understood the contingencies of the task between the two assessments was noted in the rTMS group only (p = .03).

Last, there were no correlations between IGT and inhibitory control performances and no correlations between neuropsychological performances and clinical variables (number of binge episodes and vomiting episodes, impulse regulation level and bulimia symptom levels).

4 | DISCUSSION

These results suggest preliminary evidence that stimulation of the DLPFC in individuals with BN may improve two putative biomarkers of the disease: inhibitory control and decision-making, although in independent ways. These results agree with the few studies available in clinical samples. Del Felice et al. (2016) found that HF rTMS over the left DLPFC improved inhibitory control in alcohol dependence. Similarly, McClelland et al. (2016) found that HF rTMS over the left DLPFC transiently reduced core symptoms of anorexia nervosa and encouraged prudent decision-making. Fecteau et al. suggested that transcranial direct current stimulation (tDCS) over the right DLPFC modulates decision-making in smokers (Fecteau et al., 2014). Our findings also agree with the findings of studies in healthy participants using rTMS (Brevet-Aeby et al., 2016). Nevertheless, despite improvement in decision-making and inhibitory control in our sample, rTMS had no benefit over placebo regarding bulimic symptoms (number of binges, length of the longest binge episode, features of the binge episodes, etc.) (Gay et al., 2016). Similar results were found for people with alcohol dependence (Del Felice et al., 2016), with HF rTMS over the left DLPFC improving performance of a cognitive inhibition control task but ineffective at reducing alcohol intake. We can only speculate on these results. It is possible that this improvement in our participants preceded a behavioral improvement. In addition, these participants had severe and long-standing disorders resistant to a validated treatment for BN. It is therefore possible that the number of stimulation trains was sufficient to improve neurocognition but insufficient to modify a deeply engrained behavior. The physiological effects of the rTMS protocol can vary and the same 10-Hz intervention has had widely divergent effects across individuals, impacting the results (Dunlop, Woodside, & Downar, 2016). As the bulimic symptoms were collected 15 days after the end of the rTMS program, the cognitive improvement might also have been transitory with no long-lasting effect. The clinical manifestations of BN that result from impaired cognitive functions are multidimensional and interact with many factors, including environmental triggers, the motivational system, interoceptive factors, and so on. An rTMS effect on cognitive functions only might not be sufficient to induce clinical change. It is likewise possible that improving these impairments is insufficient to improve clinical symptoms as they do not underlie a clinical response. It is therefore important to determine whether and how the improvement in these biomarkers is able to affect the core clinical symptoms of the disease. The main limitations of this study are the absence of differences in the between-group analyses, which may have been due to the lack of statistical power as the sample size calculation was not estimated on neuropsychological outcomes. Other limitations are methodological, such as the lack of neuronavigation, the low number of sessions, and the severity of the clinical sample (Gay et al., 2016). All of these point to the need for replication studies.

The left DLPFC has received the most attention in this field thus far. Although we targeted it on the basis of previous studies (Van den Eynde et al., 2010), it has shown somewhat mixed results with regard to BN symptoms (Dalton, Bartholdy, Campbell, & Schmidt, 2018). The dorsomedial prefrontal cortex (DMPFC) may thus be a valuable alternative target for several reasons. The DMPFC plays an important role in self-regulation, including impulse control. Stimulation of the medial prefrontal cortex using rTMS may alter the top-down executive control of the DMPFC to the striatal regions associated with the urge to binge and purge, thereby improving BN symptoms. In a study of refractory binge/purge behavior targeting the DMPFC, 16 of the 28 participants showed at least 50% improvement in weekly binge/purge frequency after rTMS (Dunlop et al., 2016). Enhanced frontostriatal connectivity in responders might explain the improvement in the binge/purge behaviors. Recently, a case series suggested that rTMS targeting the DMPFC could be helpful in treating people with comorbid eating disorders and post-traumatic stress disorders (Woodside et al., 2017). These studies strongly suggest the interest of further work targeting the DMPFC in BN.

We suggest that 10 sessions of HF rTMS over the left DLPFC might improve two putative cognitive biomarkers in several mental disorders, including addictive disorders, bulimic disorders and suicidal behavior (Courtet et al., 2011). We also underline the importance of determining whether changes in these cognitive biomarkers through neuromodulation are sufficient to clinically impact the targeted disease and/or whether this change is an early response marker. A larger confirmatory trial is now needed.

ACKNOWLEDGMENTS

This study received financial support from CHRU Montpellier (PHRC-IR UF 8709). The CHRU Montpellier had no role in the design, analysis, interpretation, or publication of this study.

CONFLICT OF INTEREST

All authors declare they have no conflict of interest related to this study.

FUNDING INFORMATION

CHRU Montpellier, Grant/Award Number: PHRC-IR UF 8709

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REFERENCES

Bayle, F. J., Bourdel, M. C., Caci, H., Gorwood, P., Chignon, J. M., Ades, J., & Loo, H. (2000). Factor analysis of french translation of the Barratt impulsivity scale (BIS-10). *Canadian Journal of Psychiatry*, *45*(2), 156–165.

Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science*, *275*(5304), 1293–1295.

Brevet-Aeby, C., Brunelin, J., Iceta, S., Padovan, C., & Poulet, E. (2016). Prefrontal cortex and impulsivity: Interest of noninvasive brain stimulation. *Neuroscience and Biobehavioral Reviews*, *71*, 112–134. https://doi.org/10.1016/j.neubiorev.2016.08.028

Courtet, P., Gottesman, I. I., Jollant, F., & Gould, T. D. (2011). The neuroscience of suicidal behaviors: What can we expect from endophenotype strategies? *Translational Psychiatry*, *1*, *pii: e7*. https://doi.org/10.1038/tp.2011.6e7

Dalton, B., Bartholdy, S., Campbell, I. C., & Schmidt, U. (2018). Neurostimulation in clinical and sub-clinical eating disorders: A systematic update of the literature. *Current Neuropharmacology*, *16*, 1. https://doi.org/10.2174/1570159X16666180108111532

Del Felice, A., Bellamoli, E., Formaggio, E., Manganotti, P., Masiero, S., Cuoghi, G., … Serpelloni, G. (2016). Neurophysiological, psychological and behavioural correlates of rTMS treatment in alcohol dependence. *Drug and Alcohol Dependence*, *158*, 147–153. https://doi.org/10.1016/j.drugalcdep.2015.11.018

Dunlop, K. A., Woodside, B., & Downar, J. (2016). Targeting neural Endophenotypes of eating disorders with non-invasive brain stimulation. *Frontiers in Neuroscience*, *10*, 30. https://doi.org/10.3389/fnins.2016.00030

Fecteau, S., Agosta, S., Hone-Blanchet, A., Fregni, F., Boggio, P., Ciraulo, D., & Pascual-Leone, A. (2014). Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: a preliminary study. *Drug Alcohol Depend*, *140*, 78–84. https://doi.org/10.1016/j.drugalcdep.2014.03.036

Gay, A., Jaussent, I., Sigaud, T., Billard, S., Attal, J., Seneque, M., … Guillaume, S. (2016). A lack of clinical effect of high-frequency rTMS to dorsolateral prefrontal cortex on bulimic symptoms: A randomised, double-blind trial. *European Eating Disorders Review*, *24*(6), 474–481. doi:https://doi.org/10.1002/erv.2475

Goschke, T. (2014). Dysfunctions of decision-making and cognitive control as transdiagnostic mechanisms of mental disorders: Advances, gaps, and needs in current research. *International Journal of Methods in Psychiatric Research*, *23*(Suppl 1), 41–57. https://doi.org/10.1002/mpr.1410

Guillaume, S., Gorwood, P., Jollant, F., Van den Eynde, F., Courtet, P., & Richard-Devantoy, S. (2015). Impaired decision-making in symptomatic anorexia and bulimia nervosa patients: A meta-analysis. *Psychological Medicine*, *45*(16), 3377–3391. https://doi.org/10.1017/S003329171500152XS003329171500152X [pii].

McClelland, J., Kekic, M., Bozhilova, N., Nestler, S., Dew, T., Van den Eynde, F., … Schmidt, U. (2016). A randomised controlled trial of Neuronavigated repetitive transcranial magnetic stimulation (rTMS) in anorexia nervosa. *PLoS One*, *11*(3), e0148606. https://doi.org/10.1371/journal.pone.0148606

Schmitz, N., Arkink, E. B., Mulder, M., Rubia, K., Admiraal-Behloul, F., Schoonman, G. G., … van Buchem, M. A. (2008). Frontal lobe structure and executive function in migraine patients. *Neuroscience Letters*, *440*(2), 92–96. https://doi.org/10.1016/j.neulet.2008.05.033

Tracy, D. K., Shergill, S. S., David, A. S., Fonagy, P., Zaman, R., Downar, J., … Bhui, K. (2015). Self-harm and suicidal acts: A suitable case for treatment of impulsivity-driven behaviour with repetitive transcranial magnetic stimulation (rTMS). *BJPsych Open*, *1*(1), 87–91. doi:https://doi.org/10.1192/bjpo.bp.115.000315

Trojak, B., Sauvaget, A., Fecteau, S., Lalanne, L., Chauvet-Gelinier, J. C., Koch, S., … Achab, S. (2017). Outcome of non-invasive brain stimulation in substance use disorders: A review of randomized sham-controlled clinical trials. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *29*(2), 105–118. https://doi.org/10.1176/appi.neuropsych.16080147

Uttl, B., & Pilkenton-Taylor, C. (2001). Letter cancellation performance across the adult life span. *The Clinical Neuropsychologist*, *15*(4), 521–530. https://doi.org/10.1076/clin.15.4.521.1881

Van den Eynde, F., Claudino, A. M., Mogg, A., Horrell, L., Stahl, D., Ribeiro, W., . . . Schmidt, U. (2010). Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. *Biological Psychiatry*, *67*(8), 793–795. doi:https://doi.org/10.1016/j.biopsych.2009.11.023S0006-3223(09)01416-4 [pii]

Woodside, D. B., Colton, P., Lam, E., Dunlop, K., Rzeszutek, J., & Downar, J. (2017). Dorsomedial prefrontal cortex repetitive transcranial magnetic stimulation treatment of posttraumatic stress disorder in eating disorders: An open-label case series. *The International Journal of Eating Disorders*, *50*(10), 1231–1234. https://doi.org/10.1002/eat.22764

Wu, M., Hartmann, M., Skunde, M., Herzog, W., & Friederich, H. C. (2013). Inhibitory control in bulimic-type eating disorders: A systematic review and meta-analysis. *PLoS One*, *8*(12), e83412. https://doi.org/10.1371/journal.pone.0083412

How to cite this article: Guillaume S, Gay A, Jaussent I, et al. Improving decision-making and cognitive impulse control in bulimia nervosa by rTMS: An ancillary randomized controlled study. *Int J Eat Disord*. 2018;51:1103–1106. https://doi.org/10.1002/eat.22942