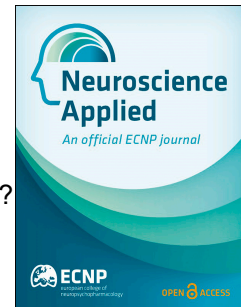


Journal Pre-proof

Deep Transcranial Magnetic Stimulation in combination with symptoms provocation:
An effective treatment in patients with treatment-resistant Body Dysmorphic Disorder?

Michele Di Ponzio, Stefano Pallanti



PII: S2772-4085(23)00119-9

DOI: <https://doi.org/10.1016/j.nsa.2023.101137>

Reference: NSA 101137

To appear in: *Neuroscience Applied*

Received Date: 16 May 2023

Revised Date: 27 August 2023

Accepted Date: 22 September 2023

Please cite this article as: Di Ponzio, M., Pallanti, S., Deep Transcranial Magnetic Stimulation in combination with symptoms provocation: An effective treatment in patients with treatment-resistant Body Dysmorphic Disorder?, *Neuroscience Applied* (2023), doi: <https://doi.org/10.1016/j.nsa.2023.101137>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2023 Published by Elsevier B.V. on behalf of European College of Neuropsychopharmacology.

Deep Transcranial Magnetic Stimulation in combination with symptoms provocation: An effective treatment in patients with treatment-resistant Body Dysmorphic Disorder?

Michele Di Ponzio¹, Stefano Pallanti^{2,3*},

¹Department of Psychology and Cognitive Studies, Institute of Neuroscience, Florence, Italy

²Department of Psychiatry and Health Studies, Institute of Neuroscience, Florence, Italy

³Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY, USA

*Corresponding author: stefanopallanti@yahoo.it

Abstract

Body Dysmorphic Disorder (BDD) concerns an excessive preoccupation concerning a perceived physical defect, associated with function impairment. No FDA-approved treatment exists for BDD, and many patients are resistant to standard treatment. Neuromodulation, especially deep Transcranial Magnetic Stimulation (dTMS) represents an important option in treating resistant patients in the obsessive-compulsive spectrum. No previous studies adopted dTMS in BDD. In this case series we reported the cases of three patients with resistant BDD treated with dTMS in combination with symptom provocation, a cognitive-behavioural therapy technique. Symptoms severity decreased after the treatment in all the three patients. These preliminary data suggested that dTMS plus symptom provocation could be an effective treatment for treatment resistant BDD patients. Further prospective studies are needed.

Key words

Body Dysmorphic Disorder; neuromodulation, Deep TMS; Obsessive-Compulsive Spectrum; symptoms provocation

Introduction

Body Dysmorphic Disorder (BDD) is characterized by an excessive preoccupation concerning a perceived physical defect [1]. In the DSM-5 it was categorized under the Obsessive-Compulsive and Related Disorders [1]. The preoccupation triggers excessive repetitive behaviours aiming to check, fix or hide the perceived bodily defects [1]. BDD tends to have a chronic persistent course unless adequately treated [2] and can be extremely debilitating. BDD is associated with significantly higher levels of suicidality than other psychiatric disorders characterized by high risk for suicidal thoughts and acts [3]. BDD is usually treated with specific cognitive behavioural therapy (CBT) and serotonin reuptake inhibitors (SRI) [4]. However, no FDA-approved treatment for BDD exists and new treatment options are warranted [4]. Among treatments, non-invasive neuromodulation has been proposed as an alternative treatment for individuals in the OCD spectrum [5,6]. Findings regarding the application of TMS in BDD are still preliminary. Van Paridon and colleagues [7] showed that TMS at 10 Hz over the left DLPFC (a protocol developed for depression) can alleviate symptoms of BDD in patients with comorbid diagnosis of MDD. Another study showed a small effect of iTBS over the left and right lateral parietal regions for BDD symptoms, although a change in functional connectivity was reported [8].

Deep transcranial magnetic stimulation (dTMS) is a technique which not only modulates the activity of the cerebral cortex but also the activity of deeper neural circuits [9]. dTMS with the H7-coil was FDA cleared for obsessive-compulsive disorder (OCD) in August 2018 and one RCT reported its superiority (with respect to sham stimulation) in the treatment of OCD, also showing an improvement in the related-disability [10]. dTMS targets deeper structures such as the Anterior Cingulate Cortex (ACC), which is involved in BDD pathophysiology [11], and thus, could represent a potential option for the treatment of BDD. Herein, we reported the cases of three patients with BDD and resistance to standard treatments who were treated with dTMS in combination with symptom provocation, a cognitive-behavioural therapy technique.

Cases description

All patients presented to the outpatient psychiatric clinical at the Institute of Neurosciences (Florence, Italy), complaining BDD symptomatology with an history of at least 2 years and a significant related social impairment. Moreover, they were resistant to standard treatment (SRI and CBT). Patients were diagnosed with BDD after a clinical interview with a psychiatrist and a psychometric assessment, including Body Dysmorphic Disorder Examination (BDDE), BDD Yale-Brown Obsessive Compulsive Disorder Scale (BDD Y-BOCS), Sheehan Disability Scale (SDS) and Clinical Global Impression Scale (CGI).

Case 1: A 17-year-old male with obsessive thoughts concerning his height, who used to surround his legs with paper to avoid that potential traumatic impact could stop his development. Moreover, he wore insoles in his shoes to appear taller. He used to check his height at least 20 times a day. He refused to have social interactions and dropped out of school. He reported anhedonia and apathy. After being accidentally hit by his father, the patient threatened him with a knife. On that occasion he was hospitalized. When he was a child, he was diagnosed with ADHD and high-functioning ASD. Symptoms onset dated back to when he was 14. The patient was treated with CBT with no results. Furthermore, he was treated with escitalopram (24mg/die) and paroxetine (20mg/die), with no improvement.

Case 2: A 16-year-old female with obsessive thoughts regarding her skin, who attempted to camouflage it. She reported frequent mirror checking and avoidance of social interactions, due to the fear of being judged for her “ugly skin”. In the weeks before admission to our clinic, she refused to go out her room at home and spent almost all day in the bed. Her mood was depressed and reported loss of interest. Symptoms emerged when she was 14. During this time, the patient completed in two different times a cycle of CBT sessions, which showed no effect.

Case 3: A 37-year-old male with obsessive thought concerning the shape of his head, which appeared to him non proportional to the rest of the body and asymmetrical. He had no insight into its psychological nature. He was totally convinced that he could only be helped by a surgical correction of his head. At admission, it showed also restricted patterns of behaviours. When assessed with the RAADS, autistic traits emerged. He

remembered that the first time he realized that his head was defected was at the high school. He showed resistance to escitalopram (29mg/die) and fluoxetine (80mg/die).

Methods

Patients underwent 30 sessions of dTMS over a period of 6 weeks in conjunction with symptom provocation during the stimulation. No other treatment was prescribed. Symptom provocation was performed by a trained psychologist based on the model described by Tendler et al [12]. After the patients listed their primary symptoms, these are listed hierarchically. Then, internal, and external provocations are developed based on the hierarchy of symptoms. dTMS (BrainsWay's Deep TMS) consists of a helmet that is fitted onto the patient's head. dTMS was administered with the FDA approved protocol (20 Hz, 100% of the leg resting motor threshold (MT), 50 trains of 2s duration, inter-train interval (ITI) 20s, 2000 pulses per session). The H7 coil was advanced 4 cm anterior to the foot motor cortex and attached to the head. Treatment is designed to regulate the Cortico-Striatal-Thalamic-Cortical (CSTC) circuit and specifically the ACC and the Medial Prefrontal Cortex (mPFC). Patients were assessed with the BDD-YBOCS before the start of the treatment (pre-test), after two weeks since the start of the treatment (mid-test) and at the end of the treatment (post-test).

Results

dTMS + CBT was well tolerated and all three patients completed the protocol. At the end of treatment, standardized metrics reported a reduction of 30% or more in BDD Y-BOCS scores (see Fig.1) as well as an improvement in related disability, measured with the SDS. Significantly, patient 1 and 3 BDD Y-BOCS scores at the post-treatment timepoint were below the cut-off (20) for the presence of a BDD diagnosis. Patient 2 showed a reduction of obsessive thoughts, although they were still reported. Patients' repetitive behaviours were significantly reduced in frequency.

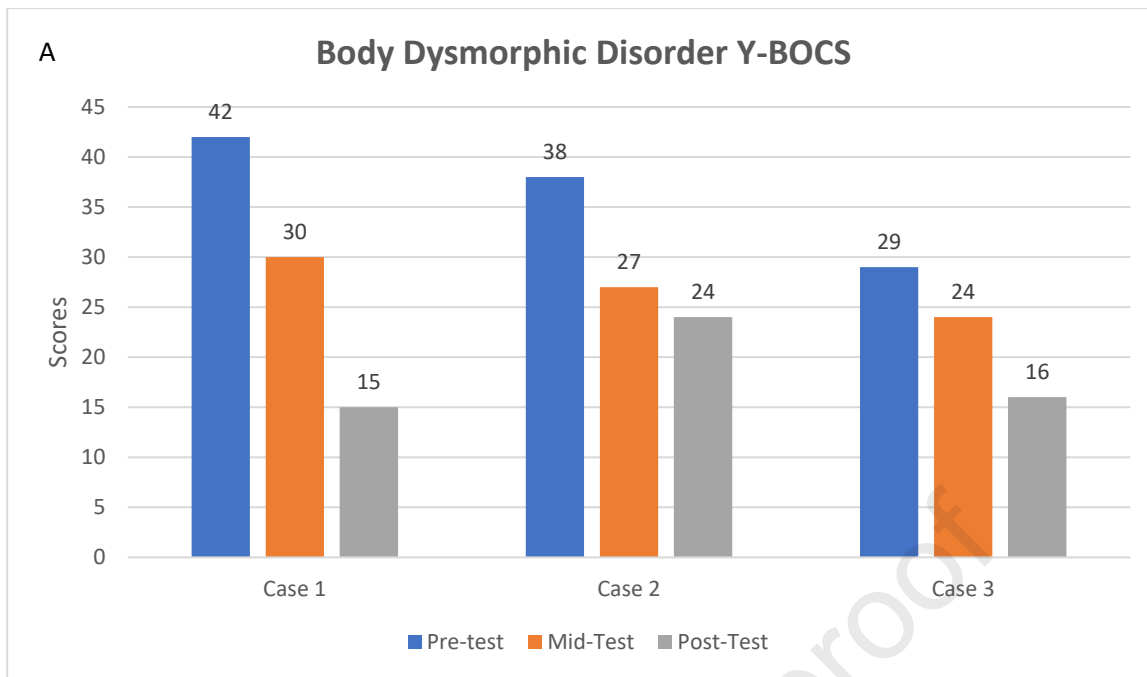


Figure 1 Body Dysmorphic Disorder Y-BOCS scores of the three cases at three timepoints (pre-test; mid-test; post-test): Mid-test corresponded to 15 sessions and post-test to 30 sessions.

Discussion

At our knowledge, this is the first time that dTMS has been reported as a treatment for BDD. Previously, high frequency dTMS over the mPFC and the ACC was found to reduce OCD symptom severity [10]. Moreover, a study found a reduction in anorexia nervosa-related obsessions and compulsions after the treatment with dTMS [13], a condition which shares similarities with BDD [14].

The decision of treating patients with dTMS was taken considering clinical phenomenology of BDD with respect to OCD spectrum disorders according to the hypothesis of the existence of specific dedicated circuits. Indeed, CSTC circuits are known to play a role both in OCD and BDD [15], considering also that several studies reported volumetric reductions in ACC in BDD [11, 16]. Importantly, symptoms reduction was associated with an improvement in related disability and clinical global impression scale score. This means that this treatment could help increasing the quality of life of these patients.

Regarding the combined treatment with exposure therapy, symptom provocations are proposed to activate brain circuitry involved in OCD pathology, specifically abnormalities in CSTC circuits [17]. In this case, we have decided to combine dTMS with concomitant, online symptom provocation, with the idea that this would jointly regulate brain circuits activity. Previous studies have shown the effect of combined, simultaneous psychotherapy and TMS in psychiatry disorders [18, 19]. Hypothetically, symptom provocation + dTMS work by improving inhibitory control and error monitoring, thus enhancing the patients' ability to dismiss obsessions and resist compulsions. The here adopted protocol includes the active participation of the patient and we account this integrative behavioural and neurofunctional approach for the improvement reported in our patients with treatment-resistant BDD.

Two of the patients were also diagnosed with ASD. A previous report showed a reduction in obsessive symptoms in two adults with high-functioning ASD after the treatment with dTMS at high frequency (5Hz) over the mPFC [20]. In recent years there has been increasing interest in and research on the comorbidity of ASD with OCD, identifying phenotypic, pathogenic, and pathophysiologic overlaps [21]. The cases presented here support the notion that BDD can also occur in people with ASD. In cases with this comorbidity, two areas are implicated: detail-focused and 'self'-focused [22]. The focus on detail stems from the positive valence system domain organization of habits described in the Research Domain Criteria (RDoC) framework and local processing biases reflected in the cognitive system domain subconstructs of visual recognition [23]. Self-focus may be a manifestation of abnormal social processes related to RDoC's domain organization of cognition and self-concept regarding social processes in both disorders. Detail-oriented processing bias is associated with frontostriatal involvement and increased local circuitry [22]. Moreover, the ACC has been considered within the RDOC framework as involved in positive valence system, cognitive system as well as social system [24]. This can further explain the reason why dTMS resulted to be effective specifically in cases 1 and 3.

The conclusions of this study are limited by the nature of the study (a case series), which not allowed for the control of confounding factors. Furthermore, future studies should address the question of performing CBT before or during the session and compare the results. Moreover, prospective studies with a sham group and follow-up sessions are needed. In conclusion, this report highlights the possibility that dTMS + CBT could be employed as a new therapeutic option for treatment-resistant BDD.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Informed Consent Statement: Consent was obtained from the patients to publish the case report, and information has been de-identified to protect anonymity.

Conflicts of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth. Arlington, VA: American Psychiatric Publishing; 2013.
2. Phillips, K. A., Menard, W., Quinn, E., Didie, E. R., & Stout, R. L. (2013). A 4-year prospective observational follow-up study of course and predictors of course in body dysmorphic disorder. *Psychological Medicine*, 43(5), 1109-1117.
3. Angelakis, I., Gooding, P. A., & Panagioti, M. (2016). Suicidality in body dysmorphic disorder (BDD): A systematic review with meta-analysis. *Clinical psychology review*, 49, 55-66.
4. Castle D, Beilharz F, Phillips KA, et al. Body dysmorphic disorder: a treatment synthesis and consensus on behalf of the International College of Obsessive-Compulsive Spectrum Disorders and the Obsessive Compulsive and Related Disorders Network of the European College of Neuropsychopharmacology. *Int Clin Psychopharmacol*. 2021;36(2):61-75. doi:10.1097/YIC.00000000000003424.
5. Lusicic, A., Schruers, K. R., Pallanti, S., & Castle, D. J. (2018). Transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder: current perspectives. *Neuropsychiatric Disease and Treatment*, 1721-1736.
6. Di Ponzio, M., Makris, N., Tenerini, C., Grassi, E., Ragone, S., & Pallanti, S. (2022). rTMS investigation of resistant Obsessive-Compulsive Related Disorders: Efficacy of targeting the reward system. *Frontiers in Psychiatry*, 13, 3081.
7. van Paridon, M. W., Neuteboom, D., Denys, D. A., Gilbers, R. N., Vulink, N. C., & Scheepstra, K. W. (2022). Effects of repetitive transcranial magnetic stimulation (rTMS) in patients with body dysmorphic disorder (BDD). *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 15(6), 1495-1497.
8. Wong, W. W., Rangaprakash, D., Larson, M. S., Diaz-Fong, J. P., Tadayonnejad, R., Leuchter, A. F., & Feusner, J. D. (2021). Can excitatory neuromodulation change distorted perception of one's appearance? *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 14(5), 1197-1200.

9. Bersani, F. S., Minichino, A., Enticott, P. G., Mazzarini, L., Khan, N., Antonacci, G., ... & Biondi, M. (2013). Deep transcranial magnetic stimulation as a treatment for psychiatric disorders: a comprehensive review. *European Psychiatry*, 28(1), 30-39.
10. Carmi, L., Tendler, A., Bystritsky, A., Hollander, E., Blumberger, D. M., Daskalakis, J., ... & Zohar, J. (2019). Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: a prospective multicenter randomized double-blind placebo-controlled trial. *American Journal of Psychiatry*, 176(11), 931-938.
11. Atmaca M, Bingol I, Aydin A, et al. Brain morphology of patients with body dysmorphic disorder. *J Affect Disord*. 2010;123(1-3):258-263. doi:10.1016/j.jad.2009.08.012
12. Tendler, A., Sisko, E., Barnea-Ygael, N., Zangen, A., & Storch, E. A. (2019). A method to provoke obsessive compulsive symptoms for basic research and clinical interventions. *Frontiers in Psychiatry*, 10, 814.
13. Knyahnytska, Y. O., Blumberger, D. M., Daskalakis, Z. J., Zomorodi, R., & Kaplan, A. S. (2019). Insula H-coil deep transcranial magnetic stimulation in severe and enduring anorexia nervosa (SE-AN): a pilot study. *Neuropsychiatric disease and treatment*, 2247-2256.
14. Phillips, K. A., & Kaye, W. H. (2007). The relationship of body dysmorphic disorder and eating disorders to obsessive-compulsive disorder. *CNS spectrums*, 12(5), 347-358.
15. McGovern, R. A., & Sheth, S. A. (2017). Role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder: converging evidence from cognitive neuroscience and psychiatric neurosurgery. *Journal of neurosurgery*, 126(1), 132-147.
16. Buchanan B, Rossell S, Maller JJ, Toh WL, Brennan S, Castle D. Regional brain volumes in body dysmorphic disorder compared to controls. *Aust N Z J Psychiatry*. 2014;48(7):654-662. doi:10.1177/0004867413520253
17. Guzick, A. G., Schweissing, E., Tendler, A., Sheth, S. A., Goodman, W. K., & Storch, E. A. (2022). Do exposure therapy processes impact the efficacy of deep TMS for obsessive-compulsive disorder?. *Journal of Obsessive-Compulsive and Related Disorders*, 35, 100756.
18. Vedeniapin, A., Cheng, L., & George, M. S. (2010). Feasibility of simultaneous cognitive behavioral therapy and left prefrontal rTMS for treatment resistant depression. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 3(4), 207-210.

19. Donse, L., Padberg, F., Sack, A. T., Rush, A. J., & Arns, M. (2018). Simultaneous rTMS and psychotherapy in major depressive disorder: clinical outcomes and predictors from a large naturalistic study. *Brain stimulation*, 11(2), 337-345.
20. Avirame, K., Stehberg, J., & Todder, D. (2017). Enhanced cognition and emotional recognition and reduced obsessive compulsive symptoms in two adults with high-functioning autism as a result of deep Transcranial Magnetic Stimulation (dTMS): a case report. *Neurocase*, 23(3-4), 187-192.
21. Meier, S. M., Petersen, L., Schendel, D. E., Mattheisen, M., Mortensen, P. B., & Mors, O. (2015). Obsessive-compulsive disorder and autism spectrum disorders: longitudinal and offspring risk. *PloS one*, 10(11), e0141703.
22. Vasudeva, S. B., & Hollander, E. (2017). Body dysmorphic disorder in patients with autism spectrum disorder: A reflection of increased local processing and self-focus. *American Journal of Psychiatry*, 174(4), 313-316.
23. Morris, S. E., & Cuthbert, B. N. (2022). Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialogues in clinical neuroscience*.
24. Holroyd, C. B., & Umemoto, A. (2016). The research domain criteria framework: The case for anterior cingulate cortex. *Neuroscience & Biobehavioral Reviews*, 71, 418-443.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: