Can we modulate obsessive-compulsive networks with neuromodulation?

Neuromodulazione dei network ossessivo-compulsivi: è possibile?

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Summary

Neuromodulation techniques represent a network pathway-oriented treatment that can be considered as a promising tool in the achievement of "precision medicine" and a research domain criteria -based approach to treat several psychiatric disorders, including obsessive-compulsive disorder (OCD).
Both repetitive transcranial magnetic stimulation (rTMS) targeting the pre-supplementary motor area (pre-SMA), deep TMS (dTMS) targeting the orbitofrontal cortex (OFC) and deep brain stimulation (DBS) targeting the nucleus accumbens (Nacc) and ventral capsule/ventral striatum (VC/VS) seem to be effective in improving obsessive-compulsive symptoms and to restore dysfunctional prefrontal-striatal and pre-motor circuitries. Transcranial direct current stimulation (tDCS) effects on obsessive-compulsive symptoms have been less investigated, and the bulk of the available data is from case reports. Nevertheless, promising results are shown for cathodal stimulation of the OFC, while stimulation of the dorsolateral prefrontal cortex (DLPFC) failed to improve symptomatology. The aim of this review is to discuss the effects of both invasive and non-invasive neuromodulation techniques in OCD, focusing on its core dysfunctional networks such as prefrontal-striatal and SMA networks.

Key words

Obsessive-compulsive disorder • Neuromodulation • Transcranial magnetic stimulation • Transcranial direct current stimulation • Deep brain stimulation

Introduction

Current systems of classification in psychiatry, such as the DSM-5 and the ICD-10, are based on a categorical approach that often fails to align to emerging findings from genetics and neuroscience and do not capture the underlying mechanism of dysfunction [1]. Moreover, despite the rigid boundaries between disorders, the presence of clinically observed overlaps and neutral territories give rise to hybrid diagnoses, such as atypical or mixed forms. This results in limited knowledge regarding the neurobiological underpinnings of most psychiatric disorders and their exact pathophysiology. In the last years, the United States NIMH (National Institute of Mental Health) launched the Research Domain Criteria (RDoC) project as an attempt to overcome the limitations of current diagnostic systems and to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" [1]. Therefore, RDoC projects aim to create a framework integrating the most recent contributions in neuroscience and genomics to guide future classification schemes. The RDoC project is based on the idea that psychiatric disorders result from underlying alterations in neural circuits, and that these dysfunctions can/will be identified by current or future tools of neuroscience: its ultimate goal is "precision medicine" for psychiatry, or, in other words, a diagnostic refinement based on a deeper understanding of the circuitries and networks of psychiatric disorders considered to be responsible for brain diseases [2].
Neuromodulation techniques represent a network pathway-oriented treatment that can be considered as a promising tool in the achievement of "precision medicine" and a RDoC-based approach to treat several psychiatric disorders. Both invasive (deep brain stimulation, DBS) and non-invasive (transcranic magnetic stimulation, TMS, and transcranial direct current stimulation, tDCS) techniques have been used in the last years in order to modulate several dysfunctional networks underlying different psychiatric disorders and to optimise treatment [3].
Non-invasive techniques (TMS and tDCS) are able to modulate cortical and brain regions with electromagnetic fields or direct electrical currents over the scalp, which can either increase or decrease cortical excitability in relatively focal areas depending on stimulation parameters. Repetitive TMS (rTMS) is a TMS protocol usually employed for treatment: high-frequency stimulation (≥5 Hz) stimulation is usually excitatory, whereas low-frequency (< 5 Hz) is

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usually inhibitory [4], with effects on the brain such as long term potentiation (LTP) and long term depression (LTD) [5]. The electromagnetic field generated from an rTMS coil placed over the scalp is able to reach a depth of 2 cm, so that some deep areas of the brain cannot be targeted: for this reason, a coil with greater intracranial penetration has been developed to reach limbic areas, administrating a protocol of stimulation termed deep TMS (dTMS). tDCS uses direct electrical currents to stimulate specific parts of the brain. A constant, low intensity current is passed through two electrodes placed over the head, which modulates the membrane potential depending on the type of electrode application. In fact, anode is able to facilitate the depolarisation of neurons, while in contrast cathode hyperpolarises the resting membrane potential, reducing the neuronal firing [6].

On the other hand, DBS is an invasive technique, which requires the stereotactical implantation of uni/bilateral electrodes in specific target brain regions through a neurosurgical procedure. Therefore, it resembles a kind of brain pacemaker that electrically stimulates specific areas to achieve a reduction in symptoms.

Both invasive and non-invasive procedures have been investigated in a broad range of neuropsychiatric disorders, among which, obsessive-compulsive disorder (OCD) and related disorders. Even if still unclear, the neurobiology of OCD is one of the most characterised among all psychiatric disorders. Thus, the aim of this paper is to review the effects of neuromodulation techniques on dysfunctional networks in OCD, focusing on its core dysfunctional networks such as prefrontal-striatal and supplementary motor area (SMA) networks [3 7].

Main dysfunctional networks in OCD

Structural and functional neuroimaging research has shown that the pathophysiology of OCD is associated with dysfunction of the orbitofronto-striato-pallido-thalamic circuitry, including several prefrontal and subcortical areas [8]. More recently, several studies have shown reward circuitry and frontal areas dysfunctions [9], so that the neurobiology of OCD has shifted from the anxiety-avoidance paradigm – involving amygdala and prefrontal cortex networks dysfunctions – to the reward-dysfunction one, involving nucleus accumbens (NAc) and frontal network dysfunctions [9 10]. Moreover, several studies showed the relevance of networks involving pre-motor areas, such as the pre-supplementary motor area (pre-SMA), in regulating inhibitory control functions (response inhibition and error monitoring) in OCD patients [11 12]. Therefore, neuromodulation studies have focused on these two main dysfunctional networks (prefrontal-striatal and premotor networks).

Neuromodulation targeting prefrontal-striatal networks

In the last years increased functional connectivity between the orbito-frontal cortex (OFC) and the ventral striatum (VS) has been reported in patients with OCD [13 14]. These data have also been confirmed by recent optogenetic studies on animal models of OCD [15]. Repeated stimulation of the OFC-ventromedial striatum (VMS) projections in mice using optogenetic techniques that increased the firing of postsynaptic VMS cells and the frequency of over-grooming behaviour, which represents OCD-like symptoms in mice [15]. Recently, the hyperactive connection from the OFC to the VS has been further confirmed by a resting-state fMRI study performed in non-medicated OCD patients and healthy volunteers [16]. This fronto-striatal hyperconnectivity has been targeted with several neuromodulation techniques, such as DBS, repetitive and deep TMS, and tDCS.

Several studies have investigated the effectiveness of DBS targeting different spots of prefrontal-striatal networks. DBS targeting the NAc and the ventral capsule/ventral stiatum (VC/VS) seems to be the most promising [3]. In a relevant paper of 2013, Figee et al. investigated NAc-frontal network modulation of DBS in OCD patients using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) in a DBS-ON/OFF paradigm [17]. In this study DBS was effective in reducing OCD symptoms and restored blunted NAc activity during a reward anticipation task. Moreover, DBS reduced the hyperconnectivity between the NAc and prefrontal areas (the lateral prefrontal cortex (lPFC) and medial prefrontal cortex (mPFC). DBS-induced changes in connectivity were correlated with changes in obsessions and compulsions, suggesting that DBS reduces OCD symptoms by decreasing excessive frontostriatal connectivity. Finally, the authors also found that DBS attenuated the increase in low-frequency activity elicited by symptom-provoking stimuli, suggesting that DBS tapered the frontal brain response evoked by symptom-provoking events [17].

Several TMS and one tDCS studies targeted the prefrontal-striatal network stimulating the dorso-lateral prefrontal cortex (DLPFC) in OCD patients. However, a recent meta-analysis shows that rTMS over both the left and right DLPFC does not seem to be effective in reducing obsessive-compulsive symptoms [7]. Moreover, a study with tDCS over the DLPFC failed to show benefits for obsessive-compulsive symptoms [18]. In fact, in this study the authors reported that cathodal-tDCS applied over the DLPFC decreased anxiety and depressive symptoms, but failed to alleviate obsessive-compulsive symptoms in a patient with treatment-resistant OCD [18].

On the other hand, encouraging results has emerged by a deep-TMS study that explored the effects of dTMS over

the left OFC [19]. The authors found that low-frequency dTMS resulted in significant reductions (> 25 %) on YBOCS score for 8 of 16 patients and a reduction > 35 % for 4 of 16 patients, with benefits lasting up to 10 weeks after the end of dTMS treatment. In addition, the effectiveness of OFC stimulation seems to be supported by a recent tDCS study that reported a 26 % reduction in YBOCS one month after the completion of 10 sessions of cathodal tDCS over the left OFC in a single patient with treatment-resistant OCD [20].

Neuromodulation targeting pre-SMA networks

Recently, both neuroimaging and neurophysiological studies have focused on supplementary motor area (SMA) hyperactivity in the clinical expression of OCD SMA networks seem to be involved in two main cognitive endophenotypes of OCD. In fact, pre-SMA (the more ventromedial region of the SMA) is involved in the cognitive process of response inhibition and has been shown to be hyperactive in OCD patients during response inhibition tasks [11]. Response inhibition deficit is a consistent finding in the OCD literature and has been proposed as the cognitive endophenotype since it also seems to be present in unaffected relatives [21 22]. Furthermore, hyperactive performance monitoring, a well-replicated finding in OCD research (measured by error-related negativity (ERN) in the event-related potential), is correlated to SMA hyperactivity in OCD patients [12].

A recent meta-analysis concluded that rTMS seems to be efficacious in the treatment of resistant OCD [7] and low-frequency protocols targeting the pre-SMA seem to be the most promising interventions [7], even compared to usual augmentation with neuroleptic agents [3]. One open-label and two randomised, sham-controlled studies investigating the effects of low-frequency rTMS over the SMA have shown its efficacy in treatment-resistant OCD patients [23-25]. Moreover, Mantovani et al. found that clinical improvement seems to be correlated to the inhibitor effect of low-frequency rTMS on cortical excitability [26].

A recent study has also investigated the effects of inhibitory (cathodal) tDCS over the pre-SMA [27] in OCD. D'Urso et al. observed differential effects of excitatory (anodal) and inhibitory (cathodal) stimulation of the pre-SMA. After 10 sessions of cathodal tDCS, dramatic clinical improvement (overall 30 % reduction in baseline symptoms severity score on the Y-BOCS) was observed, whereas 10 sessions of anodal tDCS led to worsening of OCD symptoms. These results support the hypothesis that pre-SMA hyperfunction might be responsible for OCD symptoms and, consequently, that inhibitory stimulation of this region might be an effective new treatment strategy (ibidem).

Interestingly, a recent case study [28] investigated the effects of integrated low-frequency (1 Hz) rTMS of the pre-SMA and exposure and response prevention (ERP) for an OCD patient with minimal response to psychopharmacological treatment. The combined protocol showed effectiveness for all obsessive-compulsive symptom dimensions and resulted in large and rapid reduction in symptoms. This suggests the existence of synergistic effects between TMS and ERP that should be further investigated: ERP may mitigate the shortcomings effects of pre-SMA rTMS in OCD and TMS may improve the speed of ERP. Of note, high-frequency rTMS over the left DLPFC has also been employed to enhance the effects of cognitive behavioural therapy (CBT), since its ability to induce long-term potentiation [29] has prompted further investigation and development of combined treatment options.

Conclusions

Neuromodulation techniques allow a network pathway-oriented treatment for several psychiatric disorders, including OCD. The identification of the core dysfunctional networks of the disorder and key nodes to target is crucial to optimise treatment. A range of recent investigations have suggested a central role for prefrontal-striatal networks and SMA networks in OCD, with detected abnormalities in their functional connectivity and cortical excitability. Therefore, a growing number of treatment and functional studies have focused on modulation of these circuitries, targeting specific key nodes.

rTMS targeting the pre-SMA, deep TMS targeting the orbitofrontal cortex OFC and DBS targeting the Nacc and VC/VS seem to be the most effective stimulation protocols in improving OC symptoms and restoring dysfunctional prefrontal-striatal and pre-motor circuitries. The effects of tDCS on OC symptoms have been less investigated, and most evidence is from case reports. Nevertheless, promising results have been shown for cathodal stimulation of the OFC, while stimulation of DLPFC failed to improve symptomatology.

Further research is needed to clarify the exact mechanism of action of this network-targeted treatment approach.

Conflict of interests

None.

References

1 Insel T, Cuthbert B. *Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders*. Am J Psychiatry 2010;167:748-51.

2 Insel TR. *The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry*. Am J Psychiatry 2014;171:395-7.

3 Pallanti S, Marras A, Grassi, G. *Outcomes with neuromodulation in obsessive-compulsive disorder*. Psychiatric Annals 2015;45:316.

4 Rosa MA, Lisanby SH. *Somatic treatments for mood disorders*. Neuropsychopharmacology 2011;37:102-16.

5 George MS, Post RM. *Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression*. Am J Psychiatry 2011;168:356-64.

6 Nitsche MA, Cohen LG, Wassermann EM, et al. *Transcranial direct current stimulation: state of the art 2008*. Brain Stimulation 2008;1:206-23.

7 Berlim MT, Neufeld NH, Van den Eynde F. *Repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials*. J Psychiatr Res 2013;47:999-1006.

8 Menzies L, Chamberlain SR, Laird AR, et al. *Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited*. Neurosci Biobehav Rev 2008;32:525-49.

9 Figee M, Vink M, de Geus F, et al. *Dysunctional reward circuitry in obsessive-compulsive disorder*. Biol Psychiatry 2011;69:867-74.

10 Pallanti S, Hollander E. *Pharmacological, experimental therapeutic, and transcranial magnetic stimulation treatments for compulsivity and impulsivity*. CNS Spectr 2013;19:50-61.

11 de Wit SJ, de Vries FE, van der Werf YD, et al. *Presupplementary motor area hyperactivity during response inhibition: a candidate endophenotype of obsessive-compulsive disorder*. Am J Psychiatry 2012;169:1100-8.

12 Grützmann R, Endrass T, Kaufmann C, et al. *Presupplementary motor area contributes to altered error monitoring in obsessive-compulsive disorder*. Biol Psychiatry 2014 doi: 10.1016/j.biopsych.2014.12.010.

13 Harrison BJ, Soriano-Mas C, Pujol J, et al. *Altered corticostriatal functional connectivity in obsessive-compulsive disorder*. Arch Gen Psychiatry 2009;66:1189-200.

14 Sakai Y, Narumoto J, Nishida S, et al. *Corticostriatal functional connectivity in non-medicated patients with obsessive-compulsive disorder*. Eur Psychiatry 2011;26:463-9.

15 Ahmari SE, Spellman T, Douglass NL, et al. *Repeated cortico-striatal stimulation generates persistent OCD-like behavior*. Science 2013;340:1234-9.

16 Abe Y, Sakai Y, Nishida S, et al. *Hyper-influence of the orbitofrontal cortex over the ventral striatum in obsessive-compulsive disorder*. Eur Neuropsychopharm 2015; in press.

17 Figee M, Luigjes J, Smolders R, et al. *Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder*. Nat Neurosci 2013;16:386-7.

18 Volpato C, Piccione F, Cavinato M, et al. *Modulation of affective symptoms and resting state activity by brain stimulation in a treatment-resistant case of obsessive-compulsive disorder*. Neurocase 2013;19:360-70.

19 Ruffini C, Locatelli M, Lucca A, et al. *Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation*. Prim Care Companion J Clin Psychiatry 2009;11:226.

20 Mondino M, Haesebaert F, Poulet E, et al. *Efficacy of cathodal transcranial direct current stimulation over the left orbitofrontal cortex in a patient with treatment-resistant obsessive-compulsive disorder*. J ECT 2015 [Epub ahead of print].

21 Robbins TW, Gillan CM, Smith DG, et al. *Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry*. Trends Cogn Sci 2012;16:81-91.

22 Fineberg NA, Potenza MN, Chamberlain SR, et al. *Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review*. Neuropsychopharmacology 2010;35:591-604.

24 Mantovani A, Simpson HB, Fallon BA, et al. *Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder.* Int J Neuropsychopharmacol 2010;13:217-27.

23 Mantovani A, Lisanby SH, Pieraccini F, et al. *Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) and Tourette's syndrome (TS)*. Int J Neuropsychopharmacology 2006;9:95-100.

25 Gomes PVO, Brasil-Neto JP, Allam N, et al. *A randomized, double-blind trial of repetitive transcranial magnetic stimulation in obsessive-compulsive disorder with three-month follow-up*. J Neuropsychiatry Clin Neurosci 2012;24:437-63.

26 Mantovani A, Rossi S, Bassi BD, et al. *Modulation of motor cortex excitability in obsessive-compulsive disorder: an exploratory study on the relations of neurophysiology measures with clinical outcome*. Psychiatry Res 2013;210:1026-32.

27 D'Urso G, Brunoni AR, Anastasia A, et al. *Polarity-dependent effects of transcranial direct current stimulation in obsessive-compulsive disorder*. Neurocase 2015 [Epub ahead of print].

28 Adams TG Jr, Badran BW, George MS. *Integration of cortical brain stimulation and exposure and response prevention for obsessive-compulsive disorder (OCD)*. Brain Stimul 2014;7:764-5.

29 Grassi G, Godini L, Grippo A, et al. *Enhancing cognitive-behavioral therapy with repetitive transcranial magnetic stimulation in refractory obsessive-compulsive-disorder: a case report*. Brain Stimul 2015;8:160-1.