From psychopathology to neurocircuits: what we can learn from DBS? The case of obsessive-compulsive disorder

Dalla psicopatologia ai neurocircuiti: cosa possiamo apprendere dal DBS? Il caso del disturbo ossessivo-compulsivo

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Summary

Objectives

The aim of this review is to provide a brief summary of the existing data on the safety and effectiveness of deep brain stimulation (DBS) for treatment-resistant and treatment-refractory obsessive-compulsive disorder (OCD). Another purpose is to discuss the neurobiological mechanisms of DBS and their implications for the understanding of OCD neurobiology and its link to OCD psychopathology. In particular, we will focus on DBS of the nucleus accumbens because of the involvement of this area in the reward system, which seems to be impaired in OCD patients. Finally, we will provide a new psychopathological conceptualization of OCD.

Methods

Extensive review of the DBS literature for OCD patients was performed on PubMed.

Results

According to many neuroimaging studies, the neural circuit that seems to be most involved in OCD is the cortico-striatum-thalamus-cortical circuit (CSTC). Therefore, to date, five different components of this circuit have been tested as targets in DBS of OCD and show different efficacy: anterior limb of the internal capsule (ALIC), nucleus accumbens (Nacc), ventral capsule/ventral striatum (VC/VS), subthalamic nucleus (STN) and the inferior thalamic peduncle (ITP).

Conclusions

DBS is a promising tool in the treatment of refractory OCD patients. The existing data show that the nucleus accumbens and the anterior limb of the internal capsule are the most promising targets for this treatment. Furthermore, DBS has shown new and interesting perspectives in the discovery of the neurobiological underpinnings of OCD. These new insights can provide a new psychopathological conceptualization of OCD, reconsidering this disorder as a primary anxiety disorder, rapidly moving as a behavioural addiction. However, further studies are needed to better clarify the long-term efficacy and safety of the procedure, and to better characterize the ideal patients that might have a good response to DBS.

Key words

Deep brain stimulation • Obsessive-compulsive disorder • Nucleus accumbens

Introduction

Herein, the authors provide a brief summary of the existing data on the safety and effectiveness of deep brain stimulation (DBS) for treatment-resistant and treatment-refractory obsessive-compulsive disorder (OCD). Another aim is to discuss the neurobiological mechanisms of DBS and their implications for the understanding of OCD neurobiology and its link to OCD psychopathology. In particular, we will focus on DBS of the nucleus accumbens because of the involvement of this area in the reward system, which seems to be impaired in OCD patients. Finally, we will provide a new psychopathological conceptualization of OCD.

DBS in psychiatry: safety and uses

DBS is a relatively new neurosurgical procedure, and its first use dates to 1987 for the treatment of Parkinson disease [1]. The use of DBS in the field of psychiatry was serendipitously borrowed from neurology, where DBS is an approved therapy for movement disorders (essential tremor and Parkinson's disease). The observation of non-motor effects in Parkinson's disease when stimulating specific brain targets led neurosurgeons and psychiatrists to hypothesize that DBS could also be an interesting therapeutic option for psychiatric disorders [2]. To date, the psychiatric conditions for which DBS is considered a possible therapeutic, though still experimental, option are: refractory obsessive-

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compulsive, major depressive disorder, addiction and Gilles de la Tourette syndrome.
DBS is a kind of brain pacemaker in which specific areas are stimulated with the purpose of achieving a reduction in symptoms. A DBS device consists of four main components: uni/bilateral electrodes, stereotactically placed at specific target of stimulation; an anchoring device that ensures the electrodes remain in the exact position in which they were placed; a battery powered pulse generator placed subcutaneously in the chest; a subcutaneous system of connection between the pulse generator and the electrodes, consisting in thin cables [3]. Although it is an invasive technique, DBS has two main advantages: reversibility and modifiability. Hence, if the stimulation proves to be ineffective or even harmful, the device can be removed to bring brain areas back to the status quo. Furthermore, if the device settings (in terms of frequency, pulse width, amplitude, and duration) are not able to ensure the desired goals, it can be modified to optimize the therapy [4]. Another important positive aspect is that the clinic effect is obtained through functional impairment, in contrast with ablative procedures where the anatomical damage is permanent. In addition, the patient can immediately turn off the device if excessive adverse effects occur. In this regard, DBS is associated with several types of adverse effects. These can be divided into three main categories: 1) surgery-related adverse events. The most dangerous complication is undoubtedly intra-operative haemorrhage, the incidence of which is around 2% according to literature [5]. Other frequent side effects are post-operative, usually a transient state of confusion and infections that rarely develop into meningitis/encephalitis [6]; 2) device-related adverse events [7]. The failure of the device is a very rare event. The main problem is battery depletion that requires periodic replacement with a new battery through a small surgical intervention [3]; 3) DBS-related adverse effects (depending on site of implant and on type of disorder).

Ethical issues

The use of DBS in OCD involves ethical issues because of the high vulnerability of psychiatric patients. Neurosurgical psychiatric procedures are a very controversial topic. "Psychosurgery" fell into disrepute due to the gruesome use of earlier neurosurgical procedures, but DBS does not stand in a continuous line with the old neurosurgery techniques [2]. The fear of modifications in mood and personality after neurosurgery, is an unexpected positive side effect in DBS [8-10]. At the moment, ethical guidelines for application of DBS, as stated during an important consensus conference [11], include: multidisciplinary teams, at minimum composed by neurosurgeons, psychiatrists, neurologists and psychologists; the recruitment of adult patients only; information from the patient's clinicians to establish possible comorbidities; documentation of the failure of adequate therapeutic courses; evaluation of the patient's social condition and assessment of the patient's capacity to consent after providing all the information about risks and benefits of DBS. Finally, another important ethical issue concerns publication of clinical results to help patients and public opinion to separate solid data from hype [12].

From psychopathology to research domain criteria

In medicine, the transition from a diagnosis based on signs and symptoms to one based on objective data happened decades ago, whereas in psychiatry this is a breakthrough yet to be achieved. By comparison, a heart attack could be diagnosed simply on the basis of chest pain. The problem is that the same symptom can be caused by many different conditions, and clinically different disorders could have the same aetiology [13]. Currently, the diagnosis of mental illnesses depends uniquely on clinical observation according to the DSM-IV [14] and ICD10 [15], which describe all mental disorders and the criteria for each. These, despite being two valid systems of classification, present many limits. One is that they are categorical diagnostic systems. This means that there is a marked separation both between the status of illness and non-illness, and between different illnesses. This approach creates neutral territories between a disorder and another that are identified by hybrid diagnoses such as atypical or mixed forms. Another limit is that drugs do not respect the boundaries of categorical classification (e.g. antidepressants are used to treat both mood and anxiety disorders) [16]. Research has made great strides in the last decades, but there are still many doubts about the pathophysiology of mental disorders. Difficulty in understanding the complex neural circuits and mechanisms underlying the main brain functions, the complexity of genetic alterations and the limitations of animal experiments, have not yet permitted neuroscientific findings that are sufficient to alter the current criteria of classification of psychiatric diseases. However, the time has come to lay the groundwork for the incorporation of objective, neurobiological data.
It is in this context that United States NIMH (National institute of Mental Health) introduced the Research Domain Criteria (RDoC) project to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" [17]. This project has been organized as a two-dimensional matrix, with rows represented by domains and columns represented by units of analysis [18]. Five subsets of domains have been identified, reflecting different con-

ceptual typologies of function: negative valence systems, positive valence systems, cognitive systems, systems for social processes and arousal/regulatory systems. On the other hand, the units of analysis represent the toolkit used to investigate the domains. Eight different typologies of analysis have been proposed: genes, molecules, cells, circuits, physiology, behavior and self-report paradigms. The matrix-organization is very useful, because at the intersections between units of analysis and domains, there cells are populated by the findings of all the research in that particular field. This kind of organization aims to integrate all the existing studies and to highlight possible areas/cells of intersection lacking in findings, in order to boost research. The basic concept of RDoC is that psychiatric disorders result from neural circuits alterations, and that these dysfunctions can/will be identified by current or future tools of neuroscience. In practice, the project includes a series of workshops with the participation of experienced researchers, each focusing on a single domain. These workshops started in November 2011 and were completed in June 2012, leading to an initial framework of the project. Nonetheless, it will take years to have an accurate view for each domain, even with the help of neuroscientific tools that are not yet in use. If RDoC succeeds, it may be that future versions of the DSM will take RDoC findings into account, bringing a revolution in the classification of mental illnesses.
In this view, neuromodulation procedures, such as DBS, could represent important tools for understanding the neurodysfunctional circuits underpinning psychopathology.

DBS in the treatment of obsessive-compulsive disorder

OCD is a very heterogeneous, chronic and disabling disorder. The two distinctive symptoms are obsessions (unwanted recurrent intrusive thoughts causing anxiety) and compulsions (repetitive, ritualized behaviours put in place to reduce the anxiety that obsessions evoke) [19]. If not treated, OCD leads to a significant distress both at work and in social relationships. Currently, the first-line treatment consists of serotonin reuptake inhibitors (SRIs) and cognitive behavioural therapy (CBT). However, despite the best therapeutic approach, about 40-60% of patients continue to experience serious OCD symptoms, and 10% of these patients who do not respond to the second and third line treatments are classified as treatment-refractory [20 21]. Within this 10% of refractory patients, according to strict criteria of selection, a small subgroup is chosen to undergo neurosurgical procedures, which can be divided in two main categories: ablative procedures, such as cingulotomy, capsulotomy, bilateral anterior limbic leucotomy and subcaudatus tractotomy, and neuromodulation procedures, such as transcranial magnetic stimulation, vagus nerve stimulation, magnetic seizure therapy and DBS [1 22].
According to data from many neuroimaging studies, the neural circuit that seems to be most involved in OCD is the cortico-striatum-thalamus-cortical circuit (CSTC) [23]. Therefore, to date, five different components of this circuit have been tested as targets in DBS of OCD: anterior limb of the internal capsule (ALIC), nucleus accumbens (Nacc), ventral capsule/ventral striatum (VC/VS), subthalamic nucleus (STN) and the inferior thalamic peduncle (ITP) [24 25].
Although the precise mechanism of action of DBS is unknown, several studies have found that stimulation decreases the hyperactivity of the CSTC circuit, leading to a parallel decrease of symptoms [26]. The anterior limb of the internal capsule (ALIC) was the first brain area stimulated by DBS in OCD [27]. The rationale of this target is based on the efficacy of anterior capsulotomies in refractory OCD patients and on brain imaging studies that confirm ALIC involvement in the impaired CSTC circuit [28]. Important studies on ALIC-DBS have been published by Nuttin et al. [27] and Abelson et al. [10] with similar outcomes of about 50% of responders (responder definition: > 35% Yale-Brown Obsessive-Compulsive Scale [Y-BOCS] reduction). Ventral caudate/ventral striatum (VC/VS) is another possible target [8 29 30]. VC/VS denomination refers to the junction area between the ventral caudate and ventral striatum. VC/VS was chosen as a target on the basis of the positive outcomes of lesioning procedures in the same regions [31]. With the passing of time, the stimulation became more posterior according to the observation of greater benefits [29]. The reason for this is probably the greater compactness of the bundles interconnecting the cortex and thalamus via the inferior thalamic pedunculus. In 2010, Greenberg et al. published a combined long-term study on 26 patients from four different centres, obtaining a response rate up to 60% [29]. In the same year, a similar result was obtained by Goodman et al. in a blinded staggered-onset study [30 32-34]. It is important to point out that VC/VS stimulation unexpectedly led to a decrease in depressive symptoms, often in comorbidity with OCD. In fact, VC/VS is a current target for major resistant depression [35].
The subthalamic nucleus (STN) is another DBS target. It is also called Luy's body and is part of the basal ganglia. The serendipitous observation of non-motor effects in Parkinson's disease DBS is the main and historical reason of the choice of this target. These effects were confirmed by a multicentre controlled clinical trial [34]. Another study revealed an interesting effect due to STN stimulation in Parkinson's patients, namely punding, a stereotyped motor behaviour with important compulsive traits [36]. Mallet et al. published an important study where 12 of 16 patients resulted responders (but with a responder definition of > 25% Y-BOCS decrease) [34]. Another interesting target

is the inferior thalamic peduncle (ITP), which links the OFC to the thalamus and vice versa. However, only one study has been carried out on this area (Jimenez et al. 2005) and 5 of 5 patients were responders [37].

Finally, one of the most promising targets is the nucleus accumbens (Nacc) [9 32 38 39]. Nacc forms the main part of ventral striatum and plays a central role in the reward system, which may be impaired in OCD [40 41]. This is the main reason to consider Nacc as a target. The main study regarding Nacc-DBS was published by Denys et al. (2010). This study consisted of three phases: the first was an open 8-month treatment phase where 9 of 16 OCD patients responded to treatment with a mean decrease in the Y-BOCS score of 72%; the second was a double-blind, sham-controlled phase with randomly assigned 2-week periods of active or sham stimulation, obtaining a Y-BOCS score difference between the two groups of 25%; the third was an open 12-month maintenance phase study [20]. Furthermore, the authors also observed the same antidepressant effect reported in the ALIC stimulation [8-10]. Denys et al. specified the sequential order of symptom remission: depressive symptoms within seconds, anxiety symptoms within minutes, obsessions within days and compulsions within weeks or months [9].

Predictors of response

Clinical endophenotypic and neuroimaging features may represent predictors of the efficacy of DBS. An interesting recent study observed that intra-operatory stimulation induced laughter predicts an improvement of OCD symptoms. The reason is probably that ALIC and Nacc are important areas involved in emotional processing and in the pleasure and reward system [42 43]. Another important predictor of response is the subtype of OCD. In particular, DBS seems to be less effective in patients with characteristics of perfectionism and symmetries [9]. Moreover, further studies suggest that the pre-DBS metabolic status, evaluated with FDG-PET, is directly correlated with the efficacy of DBS [44 45].

DBS of the Nacc and reward dysfunction in OCD: the link to behavioural addictions

The effectiveness of deep brain stimulation of the Nacc in treatment-refractory OCD patients highlights the role of reward system in the pathophysiology of OCD. In fact, the reward system involves widespread neurocircuitry in the brain. In particular, the mesolimbic dopamine system and its projections to the nucleus accumbens have a central role in reward system [46]. Interestingly, a recent study demonstrated that OCD patients showed a dysfunctional reward system [40]. Figee et al. studied reward function in OCD patients with predominantly contamination fear and high-risk assessment using a monetary incentive delay task and fMRI. In their study, Figee et al. compared brain activity during reward anticipation and receipt in OCD patients and healthy controls. OCD patients showed attenuated reward anticipation activity in the nucleus accumbens compared with healthy controls; brain activity during reward receipt was similar between OCD patients and healthy controls. A hint toward more dysfunctional reward processing was found in treatment-resistant OCD patients who subsequently were successfully treated with deep brain stimulation of the nucleus accumbens. Furthermore, after DBS of the Nacc these patients showed normalization of Nacc activation during reward anticipation.

A clinical example of reward system dysfunction in OCD patients may be represented by a recent study of the same group, focusing on the most powerful natural rewarding stimulus: sex [47]. In this study, the authors compared subjective appreciation of sexuality and sexual functioning between female OCD patients and healthy subjects. They also controlled for the influence of medications or OCD subtypes on sexual functioning and satisfaction. The results showed that female patients with OCD reported low sexual pleasure, high sexual disgust and diminished sexual functioning, which are often attributed to medications or contamination obsessions.

Reward dysfunction represents a key feature of addiction progression. Several studies have demonstrated that addicted patients showed a blunted Nacc activation to natural rewarding stimuli versus drug-related stimuli in comparison to healthy controls [46]. The results of the study by Figee et al. agree remarkably with the findings of functional imaging studies in addiction disorders, showing blunted reactivity of the ventral striatum during anticipation of monetary gain [40]. Moreover, drug-related stimuli in addicted patients showed increased activity of the reward system, and likewise OCD-provoking stimuli seem to increase reward circuitry activity in OCD patients [48].

In addition, data from a recent review of different targets of DBS for patients with treatment-refractory addiction showed that Nacc seems to be the most promising DBS target in order to treat these patients [49]. These data support the hypothesis that addiction and OCD share some common neurobiological dysfunctions and corroborate the idea that OCD may start as an anxiety disorder and become a behavioural addiction through the same stages of addiction. A common link between all the substance abuse and addictive behaviours is their rewarding effect. Compulsion is a suffering reducing activity that might step on the border of rewarding experience due to its capacity to reduce anxiety and distress generated by obsessions [40]. In this perspective, compulsion could be potentially addictive. In fact, many patients report to have a sort of "addiction to compulsions". In this light, it is possible to conceptualize OCD progression as a slow progression to a "com-

pulsion addiction". Accordingly, it is possible to hypothesize a sub-classification of the OCD course by the same way of addiction course. The first stage will be represented by the "binge stage". At this point compulsion is functional and effective in reducing anxiety (cleaning helps to reduce anxiety). Thus, compulsion is rewarding. The second stage would be represented by the "tolerance stage" in which the compulsion increasingly expands because of tolerance to the effect (one needs to clean at least 20 times to reduce anxiety feelings instead of a few times). Gradually, the compulsion loses its effectiveness (cleaning does not help anymore to reduce the anxiety). The final stage would be the "withdrawal/craving stage" in which the compulsion may no longer be omitted to avoid intense distress, and it manifests consequences in many if not all dimensions of the patient's life (cleaning is needed just to live).
This conceptualization of OCD as a behavioural addiction could have relevance in identifying psychopathological dimensions such as craving as new treatment targets. In fact, several agents used in the treatment of addicted patients, such as ondansetron and memantine, have been shown to be effective in the treatment of OCD treatment-resistant patients [50 51]. However, many questions remain unsolved and further neuroimaging, psychopathological and pharmacological studies are needed to support this new conceptualization.

Conclusions and future perspectives

DBS has been shown to be a promising tool in the treatment of treatment-refractory OCD. The existing data show that the nucleus accumbens and the anterior limb of the internal capsule are the most promising targets for DBS in OCD. Furthermore, DBS has highlighted new interesting perspectives in the discovery of the neurobiological underpinnings of OCD. These insights can provide a new psychopathological conceptualization of OCD, reconsidering this disorder as a primary anxiety disorder, rapidly moving as a behavioural addiction. However, further studies are needed to better clarify the long-term efficacy and safety of DBS, and to better characterize the ideal patients that might have a good response.

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