REVIEW

Deep brain stimulation in the treatment of obsessive-compulsive disorder: current perspectives

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Maud Tastevin[1]
Giorgio Spatola[2,3]
Jean Régis[2,3]
Christophe Lançon[1]
Raphaëlle Richieri[1,4]

[1]Department of Psychiatry, Addictions and Psychiatry for Children, Public Assistance Marseille Hospitals, 13005 Marseille, France; [2]Department of Functional and Stereotactic Neurosurgery, Public Assistance Marseille Hospitals, 13005 Marseille, France; [3]Institut de Neurosciences des Systèmes, Aix Marseille University, Inserm UMR1106, France; [4]Faculté des Sciences de Saint Jérôme, Aix Marseille University, Institut Fresnel - UMR 7249, Marseille, France

Abstract: Deep brain stimulation (DBS) is a neuro-psychosurgical technique widely accepted in movement disorders, such as Parkinson's disease. Since 1999, DBS has been explored for severe, chronic and treatment-refractory psychiatric diseases. Our review focuses on DBS in obsessive-compulsive disorder (OCD), considered as a last treatment resort by most of learned societies in psychiatry. Two main stimulation areas have been studied: the striatal region and the subthalamic nucleus. But, most of the trials are open-labeled, and the rare controlled ones have failed to highlight the most efficient target. The recent perspectives are otherwise encouraging. Indeed, clinicians are currently considering other promising targets. A case series of 2 patients reported a decrease in OCD symptoms after DBS in the medial forebrain bundle and an open-label study is exploring bilateral habenula stimulation. New response criteria are also investigating such as quality of life, or subjective and lived-experience. Moreover, first papers about cost-effectiveness which is an important criterion in decision making, have been published. The effectiveness of tractography-assisted DBS or micro-assisted DBS is studying with the aim to improve targeting precision. In addition, a trial involving rechargeable pace-makers is undergoing because this mechanism could be efficient and have a positive impact on cost-effectiveness. A recent trial has discussed the possibility of using combined cognitive behavioral therapy (CBT) and DBS as an augmentation strategy. Finally, based on RDoc Research, the latest hypotheses about the understanding of cortico-striato-thalamo-cortical circuits could offer new directions including clinical predictors and biomarkers to perform adaptive closed-loop systems in the next future.

Keywords: deep brain stimulation, obsessive compulsive disorder, treatment-refractory, Yale-Brown obsessive-compulsive scale, cortico-striato-thalamo-cortical circuitry, Research Domain Criteria

Introduction

OCD is a disabling and chronic psychiatric disease with an estimated lifetime prevalence of 2.3%.[1] DSM V characterized the main clinical symptoms by presence of "recurrent and persistent thoughts, urges or impulses" called obsessions and by "repetitive mental or behavioral acts" named compulsions "that the individual feels driven to perform, either in response to an obsession or according to rules that must be applied rigidly". Usually, effective treatments for OCD include antidepressants and cognitive behavioral therapy (CBT). Unfortunately, 40–60% of the OCD patients do not respond to serotonin reuptake inhibitors, and about 10% remain severely affected with treatment-refractory OCD.[2] In such cases, deep brain stimulation (DBS) can be a last resort treatment. DBS is

Correspondence: Raphaëlle Richieri
CHU Sainte Marguerite, Pavillon Solaris, 270 Boulevard Sainte Marguerite, 13009 Marseille, France
Tel +3 349 174 6730
Fax + 3 349 174 6216
Email raphaellemarie.richieri@ap-hm.fr

a neurosurgical technique involving the stereotactic implantation of electrodes that send electrical impulses to specific locations in the subcortical or deep cortical structure. The technique consists of a pulse generator that is surgically implanted in the chest and an extension cable which runs from it, under the skin of the neck and scalp, to an electrode implanted in the brain. More precisely, the parameters are set by the clinicians via a computer that communicates with the pulse generator. DBS provides an adjustable and reversible means of neuromodulation with infrequent serious adverse effects. The first use of DBS for treatment-refractory obsessive-compulsive disorder (OCD) was published by Nuttin and colleagues in 1999.[3] Since then, many studies have been conducted and this treatment is approved for use in these situations by the Food and Drug Administration in the United States and has obtained a "Conformité Européenne" mark in Europe.[4]

The aim of this review is to highlight the present situation concerning DBS in treatment-refractory OCD and to reckon the latest clinical outcomes.

Background

Several studies and recent meta-analysis using functional and structural neuroimaging highlighted abnormal activity and neuroanatomical abnormalities in cortico-striato-thalamo-cortical (CSTC) circuits in patients with OCD (including the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), prefrontal cortex (PFC) and the ventral striatum).[5–7] Interestingly, the main hypothesis is that OCD is associated with hyperactivity of the CSTC loop. Even if the mechanism of DBS is still unknown, the possibility of its therapeutic effects could be explained by a global inhibition of this network.[8,9]

Targets

Two main stimulation areas have been widely studied.[10,11] First, the striatal region includes the anterior limb of the internal capsule (ALIC),[3,12,13,14,15] the ventral striatum/ventral capsule (VS/VC),[16,17,18,19] the nucleus accumbens (NAc),[20,21,22,23,24] the bed nucleus of the striata terminalis (BST),[25] the ventral caudate nucleus,[26] the medial forebrain bundle (MFB).[27] The second main area is the subthalamic nucleus (STN)[28–30] (Table 1).

Indications

Since the FDA approval in 2009, several psychiatric and neurosurgical national and international guideline organizations have discussed the use for OCD treatment.

In 2013, the American Psychiatric Association recommended DBS or repetitive Transcranial Magnetic (rTMS)

Stimulation only "after first- and second-line treatments and well-supported augmentation strategies have been exhausted".[31] The National Institutes of Mental Health and neurosciences in 2017 proposed a decision tree in which rTMS should be proposed before DBS.[32] Most of national and international learned societies in psychiatry consider DBS as a last treatment resort.[31–34] In 2014, a "consensus on guidelines for stereotactic neurosurgery for psychiatric disorders" was published by the World Society for Stereotactic and neurosurgical surgery (WSSFN). It mentioned: "all candidates for neurosurgery for psychiatric disorders should meet generally accepted clinical criteria for severity, chronicity, disability and treatment refractoriness".[34]

The WSSFN commended an informed consent (and patients should be assessed for their capacity to provide informed consent for the procedure), a pre-operative evaluation using standardized rating scale and supported by an interdisciplinary team.

According to these guidelines, we can consider the following indications:

- Primary OCD: co-occurring psychiatric disorders and the suicide risk must be evaluated.
- Severe, chronic and debilitating, with a severity score on the Yale-Brown obsessive compulsive scale of at least 28.[35]
- Treatment-refractory:[2] often defined by the failure of:
  o First-line therapy: two trials of serotonin recapture inhibitors (SSRIs) after 12 weeks at maximum dose
  o Second-line therapy:
    o adequate cognitive behavioral therapy
    o SSRIs combination with CBT/atypical antipsychotic/5-HT3 antagonists/memantine/lamotrigine
    o clomipramine after 12 weeks at maximum dose
    o exhaustive augmentation strategies
    o other pharmacological approaches: Mirtazapine, Venlafaxine, Ketamine, N-acetylcysteine.
    o repetitive transcranial magnetic stimulation over the orbitofrontal cortex or the supplementary motor area

Concerning the targets, the FDA approved VS/VC DBS for OCD under the Humanitarian Device Exemption but not for STN DBS.[36] The WSSFN recently considered that DBS in the region of the bed nucleus of BNST/NAc and/or ALIC is a therapy in progress and provides the investigation of other brain targets.

Table I Reports concerning DBS in obsessive compulsive disorder: targets and effectiveness

Authors	Target	Patients	Design	Stimulation parameters	Follow-up (months)	YBOCS reduction	Responders
Nuttin et al, 1999[3]	ALIC	1	Case report Bilateral stimulation	F: 100 Hz, PW: 210 microseconds, AR: 4, 7–5 V	Unknown	Unknown	1
Gabriels et al, 2003[12]	ALIC	3	Open label Bilateral stimulation	Unknown	15–31	21–50%	1
Nuttin et al, 2003[13]	ALIC	4	Double blinded crossover	F: 100 Hz, PW: 210–450 microseconds, AR 4–10,5 V	21–31	17, 6–57, 8%	2
Anderson and Ahmed, 2003[14]	ALIC	1	Case report	F: 100 Hz, PW: 210 microseconds, AR: 2 V	3	81, 10%	1
Abelson et al, 2005[15]	ALIC	4	Double blinded crossover, 3 patients: bilateral stimulation, 1 patient: unilateral stimulation	F: 130–150 Hz, PW: 60–216 microseconds, AR: 2, 5–10, 5 V	4–3	29, 80%	1
Greenberg et al, 2010[16]	VC/VS	26	Multicenter/double blinded/bilateral stimulation	F: 100–130 Hz, PW: 90–450 microseconds, AR: 2–8 V	3–36	0–62.1%	10
Goodman et al, 2010[17]	VC/VS	6	Double blinded crossover	F: 130–135 HZ, 90–210 microseconds, 2.5–8.5 V	12	91.3%	4
Roh et al, 2012[18]	VC/VS	4	Open label	F: 90–130 Hz, PW: 90–270 microseconds, AR: 2-5 V	24	45.7–61.1%	4
Tsai et al, 2012[19]	VC/VS	4	Bilateral stimulation, open label, pilot study	F: 130 Hz, PW: 210 microseconds, AR: initial 2 V steps to reach 0, 2, 4, 6, or 8 V	15–21	0–70.5%	2
Sturm et al, 2003[20]	Nucleus accumbens	4	3 patients: unilateral stimulation, 1 patient: bilateral stimulation	F: 130 Hz, PW: 90 microseconds, AR: 2–6, 5 V	24–30	Unknown	3
Huff et al, 2010[21]	Nucleus accumbens	10	Double-blind sham-controlled crossover study, unilateral stimulation	F: 120 Hz, PW: 120 microseconds, AR: 4–8 V	12	0–55.5%	1
Denys et al, 2010[22]	Nucleus accumbens	16	Double blinded crossover study, bilateral stimulation	F: 130 Hz, PW: 90 microseconds, 5 V	21	46%	9
Franzini et al, 2010[23]	Nucleus accumbens	2	Bilateral stimulation, open label study	F: 130 HZ, PW: 90 microseconds, AR: 5 V patient 1, 5, 5 V patient 2	24–27	33.3–44.7%	1
Grant et al, 2011[24]	Nucleus accumbens	1	Case report	Unknown	8	68.7%	1
Aouizerate et al, 2004[26]	Ventral caudate nucleus	1	Case report	Unknown	27	52%	1
Jimenez-Ponce, 2013[9]	Inferior thalamic peduncle	6	Open-label, bilateral stimulation	F: 130 Hz, PW: 450 microseconds, AR: 5 V	36	40–82, 5%	6

(Continued)

Table 1 (Continued).

Authors	Target	Patients	Design	Stimulation parameters	Follow-up (months)	YBOCS reduction	Responders
Luyten et al, 2016[25]	BST et ALIC	24	Double-blinded, randomized crossover study, 8 patients bilateral ALIC stimulation, 10 patients bilateral BNST, 1 bilateral internal capsule, 4 both BNST and ALIC, 1 unilateral BNST.	F: 130 Hz except two ALIC patients 100 Hz, PW: BST: 120–450 μs; ALIC: 240–450 μs AR: BST: 6.6±2.1 V; ALIC: 6.7±2.3 V	171	50% BST/22% ALIC	16
Fontaine et al, 2004[28]	Subthalamic nucleus	1	Case report	185 Hz, 60 microseconds, 3, 5 V	12	96, 80%	1
Mallet et al, 2008[29]	Subthalamic nucleus	16	Crossover, double-blinded, multicenter study, bilateral stimulation	130 Hz, PW: 60 microseconds, 4 V	3	37, 80%	7
Chabardes et al, 2012[30]	Subthalamic nucleus	4	Cases reports	130 Hz, PW: 60 microseconds, AR: increased progressively 0,5 V steps until side effects are obtained	Unknown	34.3–72.4%	1
Tyagi H et al, 2019[38]	VC/VS and am subthalamic nucleus (amSTN)	6	Double-blind counterbalanced phases of 12-week amSTN or VC/VS DBS, followed by 12-week open phases when amSTN and VC/VS were stimulated together.	130 Hz, PW: 60 microseconds AR: 4 V for amSTN and 8 V for VC/VS	12	>35% after 36 weeks of follow-up no difference in YBOCS score between VC/VS and amSTN	6
Coenen et al, 2017[45]	Medial forebrain bundle	2	Cases reports, tractography assisted	130 Hz, 60 microseconds, patient I: amplitudes were 3.6 mA (left) and 3.5 mA (right). Patient 2: amplitudes were 2.5 mA (left) and 2.7 (right).	3–12	35–50%	2

Abbreviations: F, frequency; PW, pulse width; AR, amplitude range; Hz, hertz; V, volt; mA, milliampere; ALIC, anterior limb of the internal capsule; VS/VC, ventral striatum/ventral capsule; BST, bed nucleus of the striata terminalis.

Contraindications

Criteria often used in the different trials of DBS and according to the WSSFN guidelines (2014)[34] are the following: patients under 18 years old;[37] significant comorbid psychiatric diagnoses (psychotic disorder, manic episode, substance abuse, pregnancy, imminent risk of suicide, severe personality disorder);[16,21,22,29] significant and unstable neurologic or medical illness[16,21,22] provide an informed consent.[16,21,25,34]

Frequency of adverse effects in DBS

In a meta-analysis published in 2015,[10] Alonso et al showed that the main adverse effects in the different studies about DBS in OCD were anxiety worsening (21.6% of the OCD patients) and hypomanic symptoms (19.8%). Other effects were described such as disinhibition (6%), depressive mood (4.3%), suicidal ideations (3.4%), digestive effects (6%), cognitive effects (7.8%), weight gain (4.3%), paresthesia and olfactory perceptions (3.4%) and insomnia (3.4%).

Adverse effects related to surgery were less important with a frequency of intracerebral hemorrhage estimated to less than 3%, infection estimated to 4.3% and headache estimated to 6%.

Adverse effects related to device consisted in feeling the extensions leads (8.6%) or stimulator (1.7%).

The most infrequent effects described were enuresis (2.6%), speech disturbances and impulsivity (1.7%), panic attack (0.9%), weight loss (0.9%) and diplopia (0.9%).

Most of affective effects were transients in particular with the adjustment of stimulation parameters.[16,22,29,30,36] Greenberg et al listed a total of 23 serious adverse effects in 11/26 patients (stimulated in VC/VS) over a period equal to 52 patient years of experience in this cohort. Changes in mood were the most common effects during both titration, acute, subacute stimulation and upon the cessation of stimulation. These changes could concern mood elevation and could be spontaneously resolved in most of the cases and always resolved after a reduction in stimulation settings. Mood decline has often been constated during titration (upon changes in parameters or acute cessation of the stimulation). During chronic stimulation, some cases of mood decline were linked inadvertent battery shutoff or battery depletion. Three patients were concerned by increasing depression/suicidal ideations, but they had had similar episodes during their course of illness prior implantation. One case of hypomania was considered serious.[16] Concerning DBS stimulation in the Nac, Huff et al described similar effects. Indeed, 4/10 cases experienced transient agitation and anxiety for several days after an increase in voltage. These effects reversed after the voltage was reduced. Two of the patients developed a hypomanic state that lasted several days and remitted spontaneously.[21] Afterward, Mallet et al also highlighted the reversibility of hypomania after adjustment of the stimulation settings in the subthalamus nucleus.[29] At this time, no studies discussed the consequences of these modifications' parameters in stimulation efficacy.

Effectiveness

All clinical trials used Y-BOCS (The Yale-Brown Obsessive-Compulsive Scale) as the main outcome measure. This scale examines compulsions and obsessions in 10 items. The validity and reliability of this scale to assess response to treatment and symptom severity was demonstrated in 1989 by Goodman et al.[35]

In these clinical trials involving DBS, responders are mostly defined as a 25–35% reduction in YBOCS. In a recent meta-analysis of 31 studies including 116 patients and 7 different targets, the global percentage of YBOCS reduction was estimated at 45.1% and the global percentage of responders was 60%.[10,16]

Among striatal targets, a multicentric worldwide open-labeled study described the results of DBS in the VC/VS in 26 patients suffering from refractory OCD. At last follow-up, 73% and 61.5% of the patients had, respectively, 25% and 35% improvement on the YBOCS.[16] Simultaneously, Denys et al targeted the NAc.[22] The study was designed in three parts: a first open 8 months treatment by DBS involving 16 patients, followed by a double-blinded crossover phase with randomly assigned 2-week periods of active or sham stimulation; the third part was a 12 months maintenance phase. In the first phase, the YBOCS decreases by 46%. In the second part, the YBOCS score difference between active and sham stimulation was 25%. Nevertheless, the active contacts were located in the ALIC more than the NAc. Later, a meta-analysis, including 8 ALIC-DBS studies showed that 12 out of 27 patients were considered as responders.[10] Nevertheless, most of the studies were case reports, and not double-blinded, neither controlled. Recently, a double-blinded crossover trial with a long-term follow-up phase assessed the efficacy of DBS in the BST/ALIC region for OCD.[25] After the initial optimization period, 24 patients were randomized between two groups one with 3 months of stimulation ON and the other with 3 months of stimulation OFF. The authors

reported 53% responders and a significant improvement in YBOCS score (median 37%) comparing the blinded-ON phase with the blinded-OFF phase during the crossover trial. At last follow-up, they found 67% responders (median improvement 58%). Finally, a Mexican case series reported improvement of 6 OCD-patients after DBS over the inferior thalamic peduncle.[22]

Mallet and colleagues first published in 2002 the results of 2 cases of responders about DBS in the STN for treatment-refractory OCD. In 2008, they published a double-blinded, multicenter, crossover study (8 patients with active then sham stimulation, 8 patients with sham then active stimulation). Six out of 8 patients with first active stimulation vs 3 out of 8 patients with first sham stimulation patients were responders and the mean YBOCS reduction was estimated at 37.8%.[29]

Nevertheless, no randomized controlled trial has compared the efficacy of these two different areas. In their metanalysis, Alonso etd al failed to show a superiority between striatal region and STN.[10]

In 2019, Tyagi et al tried to compare the efficacy of VC/VS and STN in 6 OCD patients. The initial two phases were double-blinded, randomized and counterbalanced. Each phase lasted 12 weeks. Participants received stimulation of either the anteromedial STN (amSTN) or the VC/VS followed by the alternate condition. A 12-week open phase followed, during which electrodes at both sites were active (combined stimulation phase). Two additional 12-week open phases concerned optimized stimulation settings phase (using data from previous phases), followed by an adjunctive CBT phase. All patients were responders at the end of the OPT phase. But, the Y-BOCS reduction did not significantly differ between these sites. Nevertheless, significant results showed that amSTN but not VC/VS improved cognitive flexibility, whereas VC/VS DBS had a greater effect on mood.[38]

To summarize, all studies targeted close but different structures of the classical cortico-striato-thalamo-cortical circuitry, the definition of response and designs were inconstant. The two double-blinded randomized controlled trials that compared active versus sham stimulation showed an acceptable risk–benefit ratio nonetheless, the long unblinded period before randomization remains questionable.[22,25] Thus, DBS cannot be currently considered as an established therapy for OCD.

Perspectives

Researches in DBS for psychiatric disorders raise many questions that remain unresolved. The reasons for the lack of more robust results are numerous: the variety of proposed anatomical targets and stimulation parameters being applied since there is still no consensus, patients' characteristics and the level of treatment resistance. Even when the anatomical location is defined for a specific protocol, the variability of the placement of the device is the first source of concern, due to both inter-operator variability and individual anatomical variability. Optimal stimulation parameters vary substantially according to patients, they may not be entirely programmed a priori in the initial protocol. Finally, the choice of the primary outcome and above all, its timing, are crucial in order to demonstrate a therapeutic effect. This section suggests some answers and offers some lines of thought.

Improving targeting precision

Up to now, clinical trials for DBS in the treatment of OCD used a stereotactic and standardized targeting with identical stereotactic coordinates. However, some papers have described a deviation from the planned targets that did not take individual anatomic variability into account. Moreover, DBS is believed to modulate a large network of interconnected brain regions rather than a specific brain area solely. Tractography provides tridimensional graphic reconstructions of the cerebral white matter fibers via diffusion tensor magnetic resonance imaging. Varying the specific implant coordinates based on individual tractography may guide DBS targeting and improve its therapeutic efficacy.[39]

A study showed an unexpected deviation from the planned targets was discovered in OCD patients when comparing targeting precision between DBS in parkinsonian patients and OCD patients.[35] Indeed, another mapping method, the micro-assisted recording (MER), had been widely studied for the STN in Parkinson's disease.[40–42] This technique enables the recording of extracellular, single-unit neuronal activity. The electrophysiologic properties of the activity so recorded provide an indication of the location of the electrode in relation to the various gray matter nuclei and white matter tracts encountered along the trajectory. MER can identify structural borders and eloquent structures, localize somatotopic arrangements, and provide an outline of the three-dimensional shapes of target nuclei.[43] One of the main limitation with this approach is the difficulty to recognize too medially placed electrodes. Additional trajectories should be separated by at least 2 mm, due to a risk of entering the same tract. Many centers use a simultaneous insertion of multiple

microelectrodes to reduce these problems.[40,43,44] A randomized clinical trial is currently comparing micro-assisted DBS (single MER technique) versus standard DBS in the BST for OCD (NCT02377375).

New stimulation targets

Determining and identifying optimal anatomical targets (gray matter) versus circuit targets (white matter) are still needed.

Promising targets

In their study, Luyten et al subdivided OCD patients into 3 groups: those stimulated primarily in ALIC (6 patients), primarily in BST (15 patients) and patients with comparable stimulation of ALIC and BST (3 patients). Although BST is not part of the classical cortico-striato-thalamo-cortical circuitry, BST-DBS was significantly more efficient than the ALIC stimulation as reflected by the average YBOCS improvement at last follow-up: 22% for ALIC group and 50% for BST group.[25]

In order to determine the most efficient target, a French randomized double-blinded trial has compared two areas for DBS in OCD: the NST and the VC/VS (NCT01329133). Currently, an open-label study is exploring bilateral habenula stimulation in OCD patients. This nucleus is an evolutionarily conserved structure and may play an important role in depression, punishment avoiding, reward, addiction, pain processing and circadian rhythms. (NCT03463590).

Finally, recent studies have proposed promising white fibers tracks targets. A case series of 2 patients reported a decrease in OCD symptoms after DBS in the medial forebrain bundle.[27] Indeed, this target was recently introduced in several papers for the treatment of treatment-refractory major depressive disorder.[45] From the hypothesis of a reward dysfunction related to both MDD and OCD and because of the lack of consensus about the target to stimulate, this team described the results of tractography assisted-DBS in this area. At 12 months follow-up, both patients were responders, of which one was remitter only after 3 months follow-up.

From diagnosis to dimensions: towards new phenotypes of OCD

Because of the individual variability and heterogeneity of the symptoms in mental disorders, a new approach is required to better characterize them in a "neuroanatomical formulation".[8,13,23] Since 2008, the National Institute of Mental Health (NIMH) has been trying to rethink DSM criteria for a research framework that is "based upon dimensions of observable behavior and neurobiological measures." This framework, better known as Research Domain Criteria (RDoc) was first really developed in 2013 by Cuthbert et al,[46] and currently several domains were identified: cognitive system, negative and positive valence systems, arousal and regulatory systems, systems for social processes and a sixth one is under development: sensorimotor process.

Although the physiopathology of OCD remains unclear, the literature implicates several cortico-striatal pathways: OFC, ACC, PFC and striatum area. Medial OFC and lateral OFC (and their associated corticostriatal loop circuits) have distinct contributions to brain function. Lateral OFC appears involved in punishment, escape for danger and ritualized behavioral responses. Medial OFC in emotion regulation and reward processing. Nevertheless, the issue of the contribution of distinct subregions to the pathophysiology of OCD remains unsolved. A recent hypothesis linked the hypoconnectivity of the medial OFC and the hyper-connectivity of the lateral OFC to OCD symptoms. However, this hypothesis was controversial, and Milad and Rauch in 2012 proposed a more nuanced model between these two structures. Further, medial OFC and lateral OFC were linked to transdiagnostic constructs such as "positive valence system" and "negative valence system", respectively.[5]

Considering mental illness as a malfunction in neural circuits and with the emergency of a clear relationship between CTSC pathway and associated brain function, it seems possible to define subtypes of each primary psychiatric disease. This is currently the case for major depressive disorder, for which recent literature is proposing the heterogeneity of the symptoms into neural-dimension and proposed endophenotypes.[47,48] In OCD, a recent review discussed this possibility through the three main dimensions: obsession, compulsion and anxiety. But they would find it easier to apply RDoC Framework to compulsion and anxiety than in obsessions. Indeed, compulsions would be linked to a deficit in the cognitive control system and to abnormalities in the reward-seeking positive valence system. Anxiety would be linked to negative valence system. Some hypotheses discussed the relationships between obsessions and compulsions and the possibility that they would share the same neural dysfunction in cognitive control or that obsessions could be epiphenomena that are driven by compulsions. On the other side, the authors did not rule out the

possibility of a different neuronal pathway that could not be included in the RDoC matrix at this time. They revealed several limitations and suggested that research should be focused on an integrative model which would consider the interplay between several domains, and to apply this consideration to valid, reliable and robust tasks to measure their functioning.[49] In this aim, a recent article presented the connectivity results in 22 patients with treatment-refractory OCD undergoing DBS targeting the ALIC/Nac. The authors calculated stimulation-dependent optimal connectivity separately for patient-specific connectivity data of 10 patients and for 12 additional patients using normative connectivity. Models of optimal connectivity were subsequently used to predict outcome in both and out-of-sample cross-validation and a leave-one-out cross-validation across the whole group. These models successfully cross-predicted clinical outcomes of the respective other sample, and a leave-one-out cross-validation across the whole group further demonstrated robustness of these findings (r=0.630, *p*<0.001). The degree of connectivity between stimulation sites and medial and lateral prefrontal cortices significantly predicted clinical improvement. Nevertheless, these results needed further validation to guide both DBS targeting and programming and to inform noninvasive neuromodulation targets.[50]

At least more than 60 studies discussed the possibility of electrophysiological markers involved in OCD.[51] The most important findings were first the presence of a frontal asymmetry characterized by left-sided increase in frontal alpha[52] and theta[53] bands. However, few studies failed to reproduce these results.[54,55] Moreover, a higher resting, in delta and theta activity was found compared to healthy controls in frontal regions.[56] Furthermore, excess theta band power is generally associated with SSRI resistance. But contrasted results were present in the littérature about theta and delta activity in OCD patients.[57–59] Sleep EEG data could also contribute to Rdoc research. Indeed, Increased REM density, decreased sleep efficiency and duration were linked to OCD.[60,61] But, these observations may be also due to comorbid depression in OCD because similar results were observed in depression.[62] Another study highlighted that OCD sufferers with a shorter concentration stage in sleep EEG data (four vigilance stages leading to sleep: concentration, relaxed wakefulness, drowsiness and sleep onset), were more likely to respond to all treatment modalities especially for combination therapy.[63] Error-related negativity (ERN) is an Event-Related Potential (ERP) that is observed when the participant erroneously responds to a stimulus. It is most commonly measured with executive function and inhibition task. ERN might be a potential candidate endophenotype for OCD.[64] Significant enhancement of ERN amplitude was a consistent finding among OCD patients.[65] Other ERP could reflect cortical hyper-arousal in OCD patients such as P3 and P2.[51] A study published by Pogarell et al demonstrated that low-frequency oscillations in the range of 2–5 Hz over the prefrontal cortex were linked to the severity of symptoms in OCD.[66] Electrophysiological effect of DBS are better understood for movement disorders than psychiatric diseases in several targets. A recent review highlighted that in studies involving Parkinsonian patients; EEG, ECoG (electrocorticography) and MEG (magnetoencephalography) measurements tend to a disruption of neuronal synchronization, particularly in the alpha and low beta frequency ranges.[67] At this time, the electrophysiological effects of DBS were particularly studied in OCD patient for the Nac. Figee et al (2013) showed that stimulation in the region of the NAc decreased the low-frequency oscillation response seen for symptom-provoking stimuli, which correlated with clinical improvement.[68] For Smolders et al (2013), DBS could reduce phase stability of the theta oscillations recorded from frontal regions.[69] This finding may explain how high-frequency DBS decreases the power of low-frequency oscillations by interfering with their synchronization.[67]

Neurostimulation development and its promising results, and recent breakthrough in understanding CTSC circuits and electrophysiological markers suggest that this approach is likely to gain in feasibility for OCD. Effectively, a slightly more anatomo-clinical vision of mental troubles could tend to tailor the stimulation target to the neuroanatomical site of dysfunction.[9,70]

Improving the effectiveness of DBS

Adaptive/closed loop system

The conventional DBS is considered as an open loop model with a manual adjustment of parameters by a clinician. In closed-loop DBS, programming of the stimulation parameters is performed automatically based on the measured biomarkers (action potentials, local field potentials, electrocardiogram potentials or electroencephalogram). The closed-loop is an adaptive model that uses signals from the brain to automatically adjust the DBS stimulation. For example, closed-loop DBS gets

deactivated when the brain enters the normal state.[71] At present, this method is increasingly applied to movement disorders. The difficulty in mental disorders is identifying the biomarkers because despite decades of work, there is no electrical signature known yet of the symptoms of mental disorders. Moreover, the stimulation parameters unlike neurological pathologies are not currently standardized and a personalized method based on RDoC research could be a means to resolve this challenge. With this aim, Widge et al are collecting information through a framework called TRANSFORM DBS (Transdiagnostic Restauration of Affective networks by systematic function oriented real-time modeling and Deep Brain Stimulation). In 2016, they reported two patients with a clinical diagnosis of depression and presented this method as a predictive model of network effects of perturbations. The results were promising because the patients managed to be more clearly separable in terms of their specific impairments, but the data were insufficient to create a closed-loop model.[72] With the emergence of studies including adaptive model, and with the improvement of the quality of the pacemakers (expected to be fully and automatically programmable, compatible with biomarker variations, and flexible in stimulation type and pattern), a closed loop model could be considered in a next future in neurology.[71] But concerning psychiatry, it remained more of a vision than a near-term guarantee.[73] Indeed, the researchers first need to determine endophenotypes to identify candidate predictive algorithms for adjustments settings; which could be transferred to an automatic controller in the DBS system itself (Development of Adaptive Deep Brain Stimulation for OCD, NCT03457675).

Rechargeable pacemakers

These kinds of DBS stimulators could have a positive impact on the cost effectiveness,[74] and they are currently testing for OCD (NCT02685280).

New clinical trial design

In conditions like Parkinson's disease or tremor, the benefit after DBS activation is immediately observable. Given the variability of time to response, we recommend assessing the principal outcome after a period of optimization of DBS toward a maximal clinical benefit for up to 1 year before implementing a randomized double-blinded phase. During the optimization of the stimulation parameters, the delay between two adjustments must be at least two weeks.

Although clinical assessment is the cornerstone of patient management in OCD, there are currently no agreed-upon pre-treatment clinical predictors for treatment outcomes, in particular for DBS. The shortcomings of the standard clinical measures in use have led to a recent focus on the development of novel mechanism-based biomarkers that reflect disruptions to the underlying brain circuitry. Little information is currently available as to patient characteristics that may predict successful response to DBS treatment. However, the identification of predictors for response to DBS seems necessary to optimize its effectiveness. Future researches should focus on clinical predictors and biomarkers as neuroimaging.

New clinical outcomes

Recently, "quality of life" as a primary clinical outcome in DBS studies has been considered as an important variable in the evaluation of treatment success. Considering quality of life as a primary outcome in DBS studies seems to be recently considered.[75] The 16 DBS stimulated OCD patients from the initial Denys and al sample assessed at 8 months then 3–5 years WHO Quality of Life Scale-Brief Version (WHOQOL-BREF) that covers physical, psychological, social and environmental domains. After 3–5 years of DBS, the WHOQOL-BREF showed a significant total improvement of 90%. Moreover, Baseline WHOQOL-BREF scores were lower ($p<0.01$) in all domains compared with a control population with comparable age and sex characteristic ($p<0.01$).[75] But surprisingly, quality of life improved in both responders and non-responders. These results highlighted the necessity to investigate other criteria in this domain. A first multicenter and comparative study involving the quality of life in OCD patients is still underway (NTC02844049).[76]

Furthermore, subjective and lived-experience in DBS would constitute an important part of the remission.[77,78] Patients would have experienced personality and social changes. In this way, a first paper aimed to get a better overview of the variety of changes that OCD patients experience during DBS treatment.[77] A semi-structured topic list was used once to interview a sample of 18 patients. The authors listed the four main changes that participant reported: person, social, characteristic of person world interactions and existential stance. Participants stressed the importance of being well-informed on what to expect from treatment, the authors insisted on the family members implication in the treatment.[77] Two years later, the same authors focused on the personality changes in the

same group of patients. The majority of patients (13/18) felt they had become more themselves in comparison to their previous life that was dominated by their OCD.[78] These findings were even more encouraging as they contrasted with the negative prejudices usually associated with the psychosurgery both by psychiatrists and patients.[79–81]

Nevertheless, the improvement in subjective experience was previously contradicted in a paper concerning DBS in parkinsonian patients who were stimulated in the STN. The patients would indeed describe difficulties in their relations with themselves, their spouses, their families, and their socio-professional environment after DBS.[82] In this line, a new psychological concept "burden of normality" has recently been suggested in OCD.[83] It is based on the difficulty in adjusting to being free of significant symptomatology. The authors reported a narrative analysis of two in-depth interviews with a patient and his father. Consolidated criteria for reporting qualitative studies (COREQ) were a standardized set of questions utilized to facilitate the telling of the experience before, during and after DBS. This concept could explain why after DBS treatment, the patient-reported distress arose only once a final OCD symptom was resolved. "Yet symptom remission was accompanied by expanded horizons, but also by uncertainty and intense distress associated with the changed identity". The patient and his family received a poor post-surgical support and this case report highlighted the work to do in assisting patients in their post-surgical lived-experience.[83]

Finally, cost-effectiveness of DBS in OCD is an essential criterion in decisionmaking for payers, health care providers, and patients. A recent study concluded to an effective but expensive treatment. The main result under a two-year time horizon showed only a 25% probability of being cost-effective under a willingness to pay valued at €80,000 (the commonly accepted maximum society level to pay for a quality-adjusted life year (QUALY) in the Netherlands). Additionally, under a four-year time horizon, the scenario including rechargeable batteries seems more promising, with an 87% probability of being cost-effective.[74] A second study compared cost-effectiveness of DBS in refractory OCD through a Markov model separately in the United Kingdom and Korea. According to a referent indicator, DBS was considered as "cost-effective" in Korea and "highly cost-effective" in the United Kingdom. Moreover, one-way sensitivity analysis showed consistent effectiveness results for most variables except for short-term duration of treatment effects.[84] The common limitation from these papers was the time horizon, the heterogeneity in healthcare usage of therapy-refractory OCD patients. In addition, the authors of the second papers revealed the impact of the conservative assumptions concerning the quality of life in the no-response group (they considered a no improvement in quality of life). As well, they recommended for further analyses to extend the time frame, to drive a more uniform procedure and to incorporate the QUALY improvement more precisely for both the response and non-response group.

Combined CBT-DBS

Cognitive-behavioral therapy (CBT) could optimize the post-operative management in DBS for OCD as augmentation strategy. Indeed, in the Dutch trial, after stabilization of decline in OCD symptoms, a standardized CBT was added to DBS in an open-phase trial.[85] Interestingly, these patients who initially did not respond to CBT before DBS implantation became sensitive to CBT. Tyagi and al in their randomized controlled study, analyzed the effects of adjuvant CBT in STN and VC/VS stimulation, during the last phase of the study. There was no significant improvement, but the authors evoked the possible confounding effect of combined stimulation and CBT with time. They suggested future studies could compare the effect of additional CBT at an earlier stage.[38] Moreover, further controlled studies with larger sample are needed to confirm those results.

DBS or lesion surgery for OCD?

Neurosurgeons and psychiatrists are still debating what the optimal surgical treatment strategy for patients with OCD should be. Lesion neurosurgery has been performed and documented for decades.[86] Currently, bilateral anterior capsulotomy and cingulotomy are well-effective but not FDA-approved procedures.[87–89] They are also reserved for patients with highly refractory OCD.[90] Modern lesion surgery is stereotactically guided by MRI and generates more accurate and smaller brain lesions.[91] Otherwise, the gamma knife radiation surgery which does not need craniotomy appears less expensive and risky than DBS.[92] Conversely, DBS is intended to be non-ablative, adjustable in case of side effects of overstimulation and reversible. Current guidelines and meta-analyses do not favor DBS over lesion surgery in the treatment of OCD.[33,93] To our

opinion, each method presents pros and cons, future researches should focus on identifying predictors of response.

Conclusion

During the last decade, DBS has appeared to be a useful and more widespread therapy of last resort in disabling, resistant, severe and chronic OCD. Nevertheless, it should be noted that in 2014 the WFSNN mentioned that to make a significant conclusion about DBS effectiveness for a target in psychiatric disorders, two studies managed by two different teams are necessary. At present, the literature does not conform to these criteria and the most recent metanalysis failed to show the superiority of a stimulation target to treat OCD.[10] Moreover, International Guidelines Organizations accord to support the use of DBS as a last resort clinical treatment for OCD only in a research framework in which data are being systematically collected. Indeed, from 1999 to 2015, most papers report small case series or single cases, and the lack of control group was regularly highlighted.[94] Since then, scientists and clinicians are improving clinical design and more and more comparative studies with a long follow-up are emerging. New targets are also being investigated. Moreover, other concepts and methods are currently being explored with the aim to obtain a better precision in assessing remission (quality of life, social and family impact, life-experience, personality changes). At the same time, the other actual challenge from these concepts is to get a selective and adaptive stimulation involving symptoms reconsideration in a neuro-anatomical frame, biomarkers, and an empowerment of the equipment. Future efforts may concern tailoring treatments to individual symptoms. On the other hand, these explorations also presented significant limitations such as the size of the sample, the lack of control group, the difficulty to correctly assess subjective data, contradictory physiopathological hypotheses. For all these reasons, a recent review proposed to share databases to limit the biases.[95] To conclude, DBS research in psychiatric diseases is still very active and the limitations are currently well-defined. Moreover, future directions are promising even if better-conducted clinical studies remain undone and should be conducted to promote them.

Disclosure

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