Nordic Journal of Psychiatry

ISSN: 0803-9488 (Print) 1502-4725 (Online) Journal homepage: www.tandfonline.com/journals/ipsc20

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To cite this article: Matilda Naesström, Patric Blomstedt & Owe Bodlund (2016) A systematic review of psychiatric indications for deep brain stimulation, with focus on major depressive and obsessive-compulsive disorder, Nordic Journal of Psychiatry, 70:7, 483-491, DOI: 10.3109/08039488.2016.1162846

To link to this article: https://doi.org/10.3109/08039488.2016.1162846

NORDIC JOURNAL OF PSYCHIATRY, 2016
VOL. 70, NO. 7, 483–491
http://dx.doi.org/10.3109/08039488.2016.1162846

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REVIEW ARTICLE

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A systematic review of psychiatric indications for deep brain stimulation, with focus on major depressive and obsessive-compulsive disorder

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ABSTRACT

Background: Deep brain stimulation is a treatment under investigation for a range of psychiatric disorders. It has shown promising results for therapy-refractory obsessive–compulsive disorder (OCD) and major depressive disorder (MDD). Other indications under investigation include Tourette's syndrome, anorexia nervosa and substance use disorders.

Aims: To review current studies on psychiatric indications for deep brain stimulation (DBS), with focus on OCD and MDD.

Method: A systematic search was carried out in MEDLINE, and the literature was searched to identify studies with DBS for psychiatric disorders. The identified studies were analysed based on patient characteristics, treatment results and adverse effects of DBS.

Results: A total of 52 papers met the inclusion criteria and described a total of 286 unique patients treated with DBS for psychiatric indications; 18 studies described 112 patients treated with DBS for OCD in six different anatomical targets, while nine studies presented 100 patients with DBS for MDD in five different targets.

Conclusion: DBS may show promise for treatment-resistant OCD and MDD but the results are limited by small sample size and insufficient randomized controlled data. Deep brain stimulation for OCD has received United States Food and Drug Administration approval. Other psychiatric indications are currently of a purely experimental nature.

ARTICLE HISTORY
Received 27 July 2015
Revised 25 January 2016
Accepted 22 February 2016

KEYWORDS
Systematic review; Deep brain stimulation; Psychiatric indications; Obsessive–compulsive disorder; Major depressive disorder

Many patients suffering from a mental disorder can be successfully treated with conventional non-invasive methods such as pharmacological treatments or psychotherapy. However, there is still a remaining group of patients in whom these methods give little or no relief. With this background, stereotactic deep brain stimulation (DBS) has emerged as a possibility.

Stereotactic functional neurosurgery was first developed in 1947 and is today an established treatment for movement disorders (1). New indications for DBS are under evaluation, such as headache, epilepsy and psychiatric conditions; mainly OCD and MDD (2).

The surgical procedure is initiated by mounting a stereotactic frame on the head of the patient and a magnetic resonance image (MRI) is performed. Using a computerized navigational system the target structure is identified on the MRI and a trajectory chosen. In the operating theatre a burr hole is made on each side of the midline for the implantation of two electrodes. The electrodes are about 1.3 mm in diameter with several contacts at their distal end. An extension cable is tunnelated under the skin, connecting the electrodes with a neuropacemaker placed below the clavicle in a subcutaneous pocket. The hospitalization time after surgery is dependent on the time needed for programming of the device, but the patients can usually return home within 3–5 days (3).

The post-operative phase consists of programming to determine the stimulation parameters: electrode contacts used, voltage, pulse-width and frequency. The optimal parameters are individual for the patient. The aim is to optimize the effect on the psychiatric symptoms, while avoiding stimulation-induced side effects. The initial effects seen while programming in movement disorders are usually rapid and only a few programming sessions are normally necessary during the months after surgery. In psychiatric disorders the first effects are not as noticeable and the experience limited, thus making the programing more challenging.

The major risk in the operative procedure consists of intracerebral haemorrhages. Large studies have estimated the risk to be 1–2% with minor intracerebral haemorrhages taken into account (4). Implant-related complications may occur, but they do not normally pose a serious health risk. Stimulation-induced side effects in DBS vary depending on target area and may include such symptoms as ocular disturbances, dysarthria, paresthesia, sweating and hypomania. In favour of DBS in comparison to lesional surgery, these side effects are reversible and can be removed by altering the stimulation parameters or turning off the neuropacemaker. The stimulation does not seem to result in any residual physiological changes when the treatment is discontinued.

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The exact mechanism of action of DBS in psychiatric conditions is not yet fully understood. Animal studies have demonstrated axonal activation and neuronal inhibition as an effect of DBS. Studies investigating the metabolic changes in depressive patients with DBS in the subcallosal gyrus (SCG) showed a significant decrease in activity (5,6). In addition, PET studies during stimulation in the nucleus accumbens (NA) demonstrated a decrease in metabolic activity of the SCG (7). This lends support to the current theories of pathology in multiple limbic-cortical systems as a cause for MDD rather than dysfunction in specific "mood areas" (5,8). Hence the explorations of different target areas.

New indications for DBS are emerging and among these are a number of various psychiatric disorders. The aim of this review is to briefly describe the technique of DBS and to report on studies published concerning DBS in the treatment of psychiatric disorders, with focus on major depressive disorder (MDD) and OCD. We sought to identify current differences in target areas, results and complications. Due to the novelty of the field and limited number of publications in regard to specific targets, no limitations were made regarding study design, number of participants or primary outcome measurements.

Material and methods

A systematic literature search for publications regarding DBS in psychiatric conditions was conducted in March 2014 in MEDLINE. The search algorithm included [deep brain stimulation] AND [psychiatric], [depression], [obsessive–compulsive disorder] and [Tourette's]. Reference lists from relevant studies were also reviewed. Articles were restricted to English language publications and involving humans. No limitations were made regarding study design or numbers of participants. A total of 54 articles were identified and reviewed in full text. For studies using duplicate data, only the study with the most recent results was included. After this removal a total of 52 studies were included for this review (Figure 1). Available studies are shown in Tables 1–3. The identified studies were analysed based on DBS target areas, patient characteristics, reported treatment results, complications and adverse effects of DBS.

Results

The studied target areas for DBS in depression include the SCG (6,9–11), the NA (7), the inferior thalamic peduncle (ITP) (12), the ventral internal capsule/ventral striatum (VC/VS) (13), the lateral habernula (LH) (14) and the supero-lateral branch of the medial forebrain bundle (MFB) (15). Targets with results for OCD include the NA, VC/VS, STN, IC, ITP and bed nucleus of stria terminalis (BNST) (8,46–64). An anatomic guide to the main targets can be found in Figure 2.

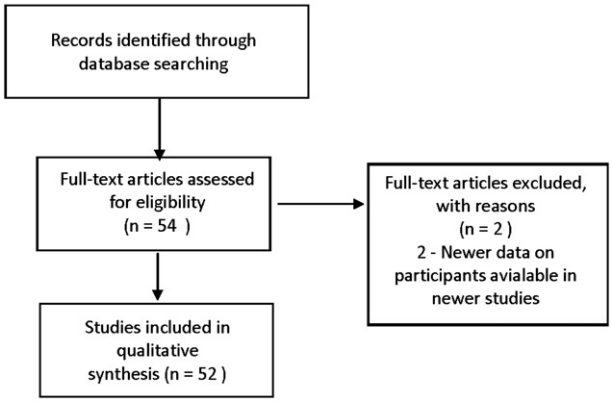

Figure 1. The paper selection process.

Patients in DBS studies for psychiatric disorders

We identified a total of 286 unique patients in 52 studies treated with DBS for psychiatric indications (Tables 1–3). Most of these patients were operated for MDD or OCD. Other various indications included Tourette's syndrome (20–37), primary anxiety disorder (38), alcohol addiction (39), anorexia nervosa (40,41), heroin addiction (42,43) and autism with aggression and self-mutilation (44).

Regarding MDD, nine unique studies have been published, describing a total of 100 patients (Table 1). The NA was targeted in 10 patients (7), ITP in one (12), the SCG in 67 (6, 9–11,45), VC/VS in 15 (13), the LH in one (14) and MFB in seven (15). There were no major differences regarding inclusion criteria in the seven studies that included more than one patient (6,7,9–11,13,15). The patients eligible for DBS treatment were diagnosed with chronic and therapy-resistant MDD. The duration ranged from 12–23 years and the mean major depressive episode prior to surgery was 5–11 years in the studies where this was specified. All patients participating in the studies had tried extensive pharmacological and psychotherapy treatment, and with few exceptions electroconvulsive therapy.

Regarding OCD, 18 unique studies have been published, describing a total of 112 patients. The VC/VS was targeted in 30 patients (46,47), NA in 36 (48–53), STN in 25 (54,55), IC in 12 (56–60) and ITP in five patients (61). Lacking clinical data, additionally four patients received DBS in BNST (62). Three patients with OCD and concomitant Parkinson's disease were also reported (63,64). (Table 4). Similar to DBS studies in MDD, the studies regarding OCD did not differ substantially regarding inclusion criteria. With slight variations patients eligible for DBS had suffered at least 5 years from severe OCD, defined by the Yale–Brown Obsessive Compulsive Scale (YBOCS) as a minimum score of 25–28. The presence of therapy-refractory symptoms after three treatment attempts with selective serotonin-reuptake inhibitors (SSRIs), of which one had to be clomipramine, additive therapy with a neuroleptic and/or a benzodiazepine and attendance to a minimum of 16–20 cognitive behavioural therapy (CBT) sessions. Generally in the studies these inclusion criteria were well surpassed with a mean YBOCS of 32–35 and a mean duration of disease of 22–29 years (Table 5).

Results for DBS in depression

The studies vary in follow-up intervals and tools for evaluation, thus complicating the comparison. They all have in common the use of the Hamilton Depression Rating Scale (HDRS), with variations of the version (17, 21, 24 and 28 questions) (Table 4). Four out of the six studies with more than five participants used HDRS-17 for evaluation (6,9–11). The majority of the studies defined response as a 50% reduction in HDRS from baseline

Table 1. Reports concerning deep brain stimulation for major depressive disorder. Additional publications using data from patients in the selected studies have not been included.

Author	Patients	Target	Complications of surgery/stimulation	Comments
Jimenez et al., 2005(12)	1	Inferior thalamic peduncle	None	Suspicion of bipolar disorder. HDRS score decreased from 42 to 3 points after 24 months
Lozano et al., 2008(6)	20	Subcallosal cingulate gyrus	Adverse events of interest: 1 seizure, 4 infections, 5 perioperative pain	11 patients had a 50% reduction of their original HDRS-17 scores after 1 year; 7 were 1 point or less from remission
Malone et al., 2009(13)	15	VC/VS	2 hardware complications. Stimulation induced reversible effects of hypomania in 1 bipolar patient	1 patient with bipolar disorder; 6 patients in remission within 1 year
Bewernick et al., 2010(7)	10	NA	Adverse events of interest: 3 pain, 2 paresthesia, 1 lead dislodgement. Stimulation-induced reversible effects included hypomania, psychotic symptoms and anxiety	Reduction of HDRS-28 with 50% after 1 year in 5 patients; 3 patients achieved remission
Holtzheimer et al., 2012(9)	17	Subcallosal cingulate gyrus	Adverse events of interest: 1 infection, 3 hardware complications. Stimulation-induced reversible effects: anxiety, gait, hand/arm weakness	Open-label trial with an initial sham-stimulation phase, 7 patients with bipolar disorder; 10 patients were in remission after 2 years' active stimulation
Lozano et al., 2012(10)	21	Subcallosal cingulate gyrus	Adverse events of interest: 1 infection, 2 hardware complications	Multicentre open-label trial. Results with a 50% reduction in 57% at 1 month, 48% at 6 months and 29% at 12 months
Puigdemont et al., 2012(11)	8	Subcallosal cingulate gyrus	3 pain at location of the subdermal cable, 2 headaches	4 patients in remission after 1 year
Schlaepfer et al., 2013(15)	7	MFB	Adverse events of interest: 1 ICH, 2 infections, 1 hardware complication. Stimulation-induced reversible effects: increased sweating, vision/eye movement disorder and dizziness	6 patients fulfilled the response criteria; MADRS of the whole sample was reduced by >50% at day 7 after onset of stimulation. At last observation, from 3-6 months, 6 patients were responders; of which 4 remitters
Torres et al., 2013(45)	1	Subcallosal cingulate gyrus	None	Major depressive episode with psychotic features in a patient with bipolar disorder type I. HDRS reduced from 26 to 7 at nine months. Disappearance of the psychotic features

HDRS: Hamilton Depression Rating Scale; ICH: intracerebral haemorrhage; LH: lateral habenula; MADRS: Montgomery–Asberg Depression Rating Scale; MFB: medial forebrain bundle; NA: nucleus accumbens; VC/VS: ventral internal capsule/ventral striatum.

and remission as scores ranging from <10–7 (6,7,9–11,13). One study used MADRS as their primary outcome measure, with response at 50% score reduction from baseline and remission at <10 points (15).

The SCG was targeted in five publications with a total of 67 patients (6,9–11,45). Response/remission was achieved in 50/17% at 6 months, 58/17% at 12 months.

VC/VS DBS in 15 patients by Malone et al. resulted in six responders and three remissions after 6 months and eight out of six at the last evaluation, after a mean time of 2 years after surgery (13). A study of 10 patients with NA DBS by Bewernick et al. reported five responders and three remitters at 12 months evaluation (7). Schlaepfer et al. presented seven patients with MFB DBS with two responders and four remitters after 3–6 months (15). Two case reports described remission after DBS in LH and ITP (12,14).

Even though no results have been reported it must be mentioned that there have been two unpublished randomized multicentre trials of DBS in SCG and VC/VS. The studies were, however, discontinued due to inefficacy based on futility analysis (65).

Complications in DBS for depression

Complications related to surgery were few and with minor health impact. The most common of these adverse effects were infection and hardware malfunction (6,7,9,10,13,15). Only one minor intracranial haemorrhage (ICH) was reported, with transient hemiparesis and dysarthria (15).

Regarding stimulation-related adverse effects, the large group of patients treated in the SCG, appear to have experienced both the fewest and mildest, with nausea as the most frequent complaint (9,10). The group with the highest frequency of stimulation adverse effects was the 10 patients receiving DBS in the NA. They reported unwanted symptoms such as hypomania, agitation and psychosis (7). The most noted adverse effect in MFB was oculomotor disturbances with strabismus and blurred vision (15). All these side effects were transient and could be abolished by adjusting the stimulation parameters, thus demonstrating the advantage of reversibility in DBS.

Two suicides and four attempts occurred during the studies. However, the authors did not consider these events to be related to the DBS treatment (7,9–11).

Reports on neuropsychological effects were scarce. Two studies reported no significant decline in neuropsychological or cognitive functioning (9,15). Additionally, two studies that focused on such impacts of DBS in SCG noted no adverse neuropsychological effects at the final evaluation (66,67).

The complete list of surgical- and stimulation-related complications of interest are presented in Table 1.

Table 2. Reports concerning deep brain stimulation for obsessive–compulsive disorder. Additional publications using data from patients in the selected studies have not been included.

Author	Patients	Target	Complications of surgery/stimulation	Comments
Greenberg et al, 2010(46)	26	Bilateral VC/VS	1 asymptomatic ICH, 1 ICH with transient apathy, 1 seizure, 1 wound infection, 2 hardware-related complications, stimulation induced reversible effects, including hypomania	Several subgroups. Varying follow-up (Min 3 months, mean 24 months). YBOCS reduced by 38% after 3 months and after 3 years. Anxiety and depressive symptoms reduced by half at last follow-up. Target changed during the study, which improved the results. In the last 17 patients YBOCS was improved by 54% at last follow-up (72% $\geq$ 35% improvement).
Tsai et al, 2012(47)	4	Bilateral VC/VS	1 allergic reaction to implanted pulse generator, 2 hypomania, 1 vertigo	At end of 15 months follow up mean 33% decrease in YBOCS from 36.3 to 24.3.
Abelson et al., 2005(56)	4	Bilateral anterior IC	1 electrode breakage. 1 suicide not considered to be caused by the therapy	Double blind crossover. Follow-up 4-23 months. Largest reduction of YBOCS during the follow-up period was in mean 29.8%. 1 in 4 patients met criteria for response (>35% decrease in YBOCS) under blinded conditions.
Anderson et al., 2003(57)	1	Bilateral anterior IC	None	YBOCS reduced by 81.1% after 3 months
Goodman et al., 2010(60)	6	Bilateral anterior IC	Stimulation induced reversible hypomania in 4 patients	At 12 months of stimulation, 4 of 6 patients met criterion as "responders" (reduction of >35% YBOCS). Patients did not improve during sham stimulation
Chang et al., 2010(59)	1	Bilateral anterior IC	Stimulation induced reversible hypomania and increased libido	Minimal reduction in YBOCS (36 to 32) after 7 weeks
Sturm et al., 2003(48)	4	3 unilateral right NA, 1 bilateral NA	None	"Nearly total recovery from both anxiety- and OCD-symptoms" in 3 patients. No report of YBOCS score post-surgery
Guehl et al., 2008(53)	3	Bilateral NA/NC	None	YBOCS reduced by 31–60% after 1 year
Plewnia et al., 2008(50)	1	unilateral right NA	Wound infection	OCD and residual schizophrenia. YBOCS reduction from 32 to 23 after 1 year. No effect on psychotic symptoms
Denys et al., 2010(52)	16	Bilateral NA	Adverse events of interest: 1 wound infection, 8 stimulation-induced mild reversible hypomania. 5 Mild forgetfulness, 3 mild word finding problems, 7 increased (normalized?) libido	Double blind crossover. Mean YBOCS was reduced by 47% after 1 year, 52% after 21 months (9 responders with a mean reduction of 72%). Anxiety and depressive symptoms reduced with half
Franzini et al., 2010(51)	2	Bilateral NA	None	YBOCS reduced in 2 patients from 38 to 22 and 30 to 20 after about 2 years
Huff et al., 2010(49)	10	unilateral right NA	Adverse events of interest: 4 stimulation-induced reversible agitation/anxiety, 1 affection of memory/concentration, 2 hypomania. 1 temporary suicidal thoughts not clearly related to DBS	Double blind crossover. YBOCS reduced within mean 21% after 1 year (1 responder with >35% improvement). Anxiety and depressive symptoms reduced by 29 and 23%, respectively.
Jiménez-Ponce et al., 2009(61)	5	Inferior thalamic peduncle	Only stimulation-induced reversible confusion and anxiety	3 patients with an addiction, 1 schizoid personality. YBOCS reduced by 49% after 12 months. No effect on co-morbidities
Mallet et al., 2002(64)	2	Bilateral STN		Full remission of OCD symptoms of STN DBS in Parkinson's disease reported in 2 patients with concomitant OCD, with YBOCS reductions from 26 to 5 and 23 to 4 respectively
Fontaine et al., 2004(63)	1	Bilateral STN		Beneficial effect of STN DBS in Parkinson's disease reported in 1 patient with concomitant OCD. Full remission with YBOCS from 32 to 1
Mallet et al, 2008(54)	16	Bilateral STN	Adverse events of interest: 1 ICH with permanent finger palsy, 2 infections, 1 transient clumsiness and diplopia. Stimulation induced reversible hypomania	Double blind crossover. YBOCS reduced by 41% after 3 months of active stimulation
Piallat et al., 2011(55)	6	Bilateral STN		Analysis of neuronal firing. No clinical data
Nuttin et al., 2013(62)	4	BNST (bed nucleus of stria terminalis)		Analysis of targeting during electrode implantation. No clinical data yet on this new target

DBS: deep brain stimulation; IC: internal capsule; ICH: intracranial haemorrhage; NA: nucleus accumbens; OCD: obsessive–compulsive disorder; STN: subthalamic nucleus; VC/VS: ventral internal capsule/venctral sriatum; YBOCS: Yale–Brown Obsession Compulsion Scale.

Table 3. Reports concerning deep brain stimulation for psychiatric indications. Additional publications using data from patients in the selected studies have not been included.

Author	Patients	Indication	Target	Comments
Visser-Vandewalle et al., 2003(21)	3	Tourette's syndrome	CMPf, Voi	Final follow-up 5 years, 1 year and 8 months, respectively, all major motor and vocal tics had disappeared. No serious side effects. Slight sedative effect seen in all patients; 2 had stimulation-induced changes in sexual behaviour
Maciunas et al., 2007(34)	5	Tourette's syndrome	CMPf, Voi	Prospective randomized double-blind study. 3 responders
Bajwa et al., 2007(24)	1	Tourette's syndrome	CMPf, Voi	DBS resulted in a substantial reduction of tics
Servello et al., 2008(22)	18	Tourette's syndrome	CMPf, Voi	All patients responded to DBS, to differing degrees. Duration of follow-up assessments ranged from 3 to 18 months. Mean improvement in YGTSS score was from 40 to 12 at 1-month follow-up
Welter et al., 2008(32)	3	Tourette's syndrome	CMPf, GPi	Prospective randomized double blind sham controlled study. Pallidal stimulation had better effect than thalamic; both were better than sham. No adverse effects were seen
Porta et al., 2009(35)	15	Tourette's syndrome	CMPf, Voi	Mean reduction in YGTSS score from 77 to 37 at 2-year follow up. Significant improvement also seen in symptoms of OCD, anxiety, depression and social function
Diederich et al., 2005(29)	1	Tourette's syndrome	GPi	Tic frequency decreased by 73%. In particular vocal tics became less intense. Small symptomatic bleeding that led to permanent bradykinesia of left hand
Gallagher et al., 2006(31)	1	Tourette's syndrome	GPi	Disappearance of tics during stimulation, but returned when one stimulator was removed due to infection
Ackermans et al., 2007(37)	1	Tourette's syndrome	GPi	Vertical gaze paralysis after DBS due to a small ICH
Shahed et al., 2007(30)	1	Tourette's syndrome	GPi	VTRS improvement not as large as the YGTS, but co-morbidities and quality of life considerably improved
Dehning et al., 2008(36)	1	Tourette's syndrome	GPi	Full remission of tic at 12 months. No adverse effects
Kuhn et al., 2007(27)	1	Tourette's syndrome	NA	Patient with severe self-injurious tics. YGTSS score reduced by 41% and MRVR by 50% at 2.5 years. Self-injury tics and coprolalia especially reduced
Zabek et al., 2008(28)	1	Tourette's syndrome	NA	Alleviation of tics and disappearance of compulsive self-injurious behaviour.
Neuner et al., 2009(23)	1	Tourette's syndrome	NA	YGTSS score reduced by 59% after 3 months. MRVRS decreased by 60% after 3 months and 58% after 36 months
Dueck et al., 2009(25)	1	Tourette's syndrome	GPi	Patient with concomitant mental retardation. Although subscores of YGTSS score improved, overall outcome showed no substantial therapeutic effect
Burdik et al., 2010(33)	1	Tourette's syndrome	ALIC/NAC	Patient with co-morbid OCD. YGTSS and MRVRS scores worsened during first 6 months although subjectively the patient reported mild improvement of tics
Flaherty et al., 2005(26)	1	Tourette's syndrome	Anterior capsule	Reduced tic frequency and severity at 18 months. Same patient was later re-operated on another target; Shields et al., 2008
Vernaleken et al., 2009(20)	1	Tourette's syndrome	Thalamus doromedial nucleus	YGTSS score reduction by 36%. Patient had previously been treated with GPi DBS with no effect
Wu et al., 2013(41)	4	Anorexia nervosa	NA	3 patients had concomitant OCD and 1 generalized anxiety disorder. At final follow up after a mean of38 months all patients exceeded 85% of expected body weight and thus no longer met the diagnostic criteria of anorexia nervosa
Lipsman et al., 2013(40)	6	Anorexia nervosa	SCG	After 9 months, 3 patients had achieved BMI greater than their historical baselines. DBS associated with improvements in mood, anxiety, affective regulation, and anorexia nervosa-related obsessions and compulsions in 4 patients and with improvements in quality of life in 3. 1 severe adverse event as seizure during programming
Zhou et al., 2011(43)	1	Heroin addiction	NA	Patient free from drugs during stimulation for 2.5 years and for 3.5 years even after stimulation discontinued
Valencia -Alfonso et al., 2012(42)	1	Heroin addiction	NA	Stimulation of the 2 dorsal contacts at the border of the internal capsule and nucleus accumbens generated significant reduction of drug use and craving
Müller et al., 2009(39)	3	Alcohol addiction	NA	Craving behaviour disappeared immediately on stimulation in all 3 patients. 2 patients remained completely abstinent in the 1-year follow-up, and alcohol consumption was reduced considerably in the third patient
Kuhn et al., 2007(38)	1	Agoraphobia with panic attacks	NA	No improvement in primary anxiety disorder, but remarkable alleviation of co-morbid alcohol dependency was noted
Sturm et al., 2012(44)	1	Kanner's autism	Amygdala	Effective in improving self-injury behaviour and core symptoms of autism spectrum in emotional, social, and even cognitive domains over follow up of 24 months. However, case reports empirical score relied on subjective, day-to-day impressions of parents who did not have medical, psychiatric, or psychological training

ALIC/NAC: anterior limb of internal capsule/nucleus accumbens; BMI: bodymass index; CMPf: centre median parafascicular complex; DBS: deep brain stimulation; GPi: globus pallidus internus; MRVRS: Modified Rush Videotape Rating Scale; NA: nucleus accumbens; OCD: obsessive–compulsive disorder; SCG: subcallosal cingulate gyrus; Voi: ventral oral internal thalamic nuclei; YGTSS: Yale Global Tic Severity Scale.

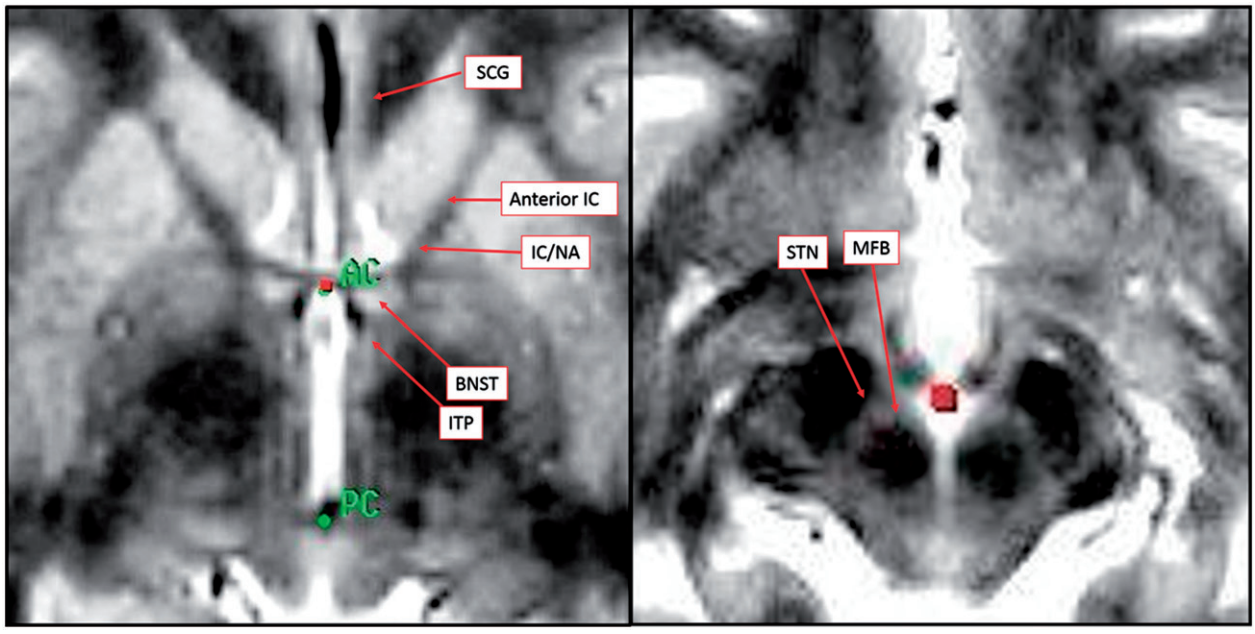

Figure 2. Common targets for DBS in psychiatric disorders. To the right is a transaxial MRI 4 mm below the anterior commissure (AC) and posterior commissure (PC) in the third ventricle. The subthalamic nucleus (STN) and the medial forebrain bundle (MFB) are marked. The area within the red rectangle is seen magnified on the left, 4 mm higher on the AC–PC level. Targets marked here are the subcallosal gyrus (SCG), internal capsule (IC), the nucleus accumbens (NA), bed nucleus of stria terminalis (BNST) and the inferior thalamic peduncle (ITP).

Table 4. Patient characteristics in reports of ≥5 individual patients with deep brain stimulation for major depressive disorder.

	Bewerick et al., 2010(7)	Lozano et al., 2008(6)	Malone et al., 2009(13)	Holtzheimer et al., 2012(9)	Lozano et al., 2012(10)	Puigdemont et al., 2012(11)	Schlaepfer et al., 2013(15)
Target	NA	SCG	VC/VS	SCG	SCG	SCG	Supero-lateral branch of MFB
Patients	10	20	15	17	21	8	7
Male/female	6/4	9/11	4/11	7/10	8/13	2/6	4/3
Mean age at onset (years)	31.7	27.1	25.3	19.9	27.3	24.9	30
Mean duration of current depressive episode (years)	10.8	6.9	>2	5.3	5	6.3	7.6
Age at surgery (years)	48.6	47.4	46.3	42	47.3	47.4	42.6
Evaluation presented (months)	12	12	23.5	24	12	12	3
HDRS pre/post-op	HDRS-28; 30.6/20.3	HDRS-17; 24.4/12.6	HDRS-24; 33.1/18.5	HDRS no. N/A; 23.9/7.3	HDRS-17; 27.6/16	HDRS-17; 21.1/8.9	HDRS-24; 23/14.7

HDRS: Hamilton Depression Rating Scale; MFB: medial forebrain bundle; NA: nucleus accumbens; SCG: subcallosal cingulate gyrus; VC/VS: ventral internal capsule/ventral striatum.

Table 5. Patient characteristics in reports of ≥5 unique individual patients with deep brain stimulation for obsessive–compulsive disorder.

	Goodman et al., 2010(60)	Greenberg et al., 2010(46)	Mallet et al., 2008(54)	Jiménez-Ponce et al., 2009(61)	Huff et al., 2010(49)	Denys et al., 2010(52)
Target	Bilateral IC	VC/VS	STN	ITP	Unilateral right NA	Bilateral NA
Patients	6	26	16	5	10	16
Male/female	2/4	14/12	9/7	3/2	6/4	9/7
Mean age at onset (years)	<18	15.1	13.5	19.4	14.1	14.2
Mean duration of OCD (years)	24	22	29.5	17	22.2	28.4
Age at surgery (years)	36.2	37.1	43.8	37	36.3	42.6
Evaluation presented	12 months	Last data from 24 month follow-up	3 months of active stimulation	12 months	12 months	12 months
YBOCS pre/post-op	33.7/–	34.0/~21	32.1/19	35/17.8	32.2/25.4	33.7/17.8
GAF pre/post-op	Not specified	34.8/59.0	31.6/56	18/72	36.6/53.1	Not specified

GAF: Global Assessment of Function; IC: internal capsule; ITP: inferior thalamic peduncle; NA: nucleus accumbens; OCD: obsessive–compulsive disorder; STN: subthalamic nucleus; VC/VS: ventral internal capsule/ventral striatum; YBOCS: Yale–Brown Obsession Compulsion Scale.

Results for DBS in OCD

All clinical studies used YBOCS as their primary outcome measure. In the larger studies response was defined as a 30–35% reduction in YBOCS (46,47,52,56,58,60).

The most common target for OCD was the NA, with a total of 36 individual patients from six different studies (48–53). Unilateral right-sided stimulation was performed in 14 patients and bilateral DBS in 22. Denys et al. presented

16 patients with bilateral NA DBS and a YBOCS reduction of 47% after 12 months and 52% after 21 months. Nine of the patients went into remission with a mean YBOCS reduction of 72% (52). The remaining three studies with bilateral NA are smaller in sample size with only 1–3 patients (48,51,53). Sturm et al. reported a more modest reduction of 21% after unilateral NA DBS in 10 patients (49).

Greenberg et al. summarized material after 24 months, from four collaborating groups with DBS in VC/VS. The number of responders was 16 of the total of 26 patients (46). They experienced a limited effect and high stimulation parameters needed in the original target of the anterior IC. Based on a continuous evaluation of the results, the target area was gradually moved posteriorly during the course of the study. This divided the material into three groups based on the posteriority of the electrodes. The most anterior of these groups had a reduction in YBOCS of 29% in comparison to a 54% reduction in the group with the most posterior location, while the stimulation voltage could be reduced by 41%. The gradual movement of the target in a posterior direction has resulted in the BNST being suggested as a target point, but no clinical data has yet been reported (62).

Regarding the STN, full remission of OCD symptoms was seen in three patients receiving DBS on the indication of Parkinsons's disease (63,64). With this background a French multicentre study of STN DBS for OCD was initiated (54). The target was chosen in the limbic part of the STN, slightly anterior and medial to the traditional target used in Parkinson's disease. The conducted study consisted of a 10-month double-blind crossover study where the patients were randomized to either 3 months of fictitious stimulation followed by 3 months of actual stimulation and vice versa. In the end 16 operated patients were available for evaluation. Active stimulation for 3 months led to a mean YBOCS of 19.7, in comparison to 28.7 in the group with fictitious stimulation.

Jiménez-Ponce et al. presented five patients with bilateral DBS in the ITP with a mean reduction in YBOCS from 35 to 17.8 after 12 months (61).

Detailed results of the studies are summarized in Table 2.

Complications in DBS for OCD

The majority of side effects were minor and transient. However, three ICHs were reported, of which one resulted in a permanent paresis of one finger (46,54). Regarding stimulation-related side effects; transient hypomania was noted in several different DBS targets (47,49,52,54,59,60).

One suicide was reported and the authors did not consider it related to the DBS treatment (56).

As in the reports for MDD, data on neuropsychological effects were limited. However, two double-blinded sham stimulation studies reported no significant neuropsychological morbidity (49,60).

A selection of complications of interest in regard to surgical- and stimulation-related complications are presented in Table 2.

DBS in other psychiatric indications

Regarding Tourette's syndrome, a total of five studies and 13 case studies have been published, describing a total of 57 patients. Several of these reports have described beneficial effects of DBS with reduction in tic severity and tic frequency, in various targets. The combination of centre median parafascicular complex (CMPf) and ventral oral internal thalamic nuclei (Voi) is the most extensively studied target.

Promising effects of DBS have been reported in small studies and case reports for anorexia nervosa, agoraphobia, Kanner's autism, and substance abuse of alcohol and heroin. However, the published experience is very limited and DBS in such conditions is highly experimental (20–44).

Conclusion

DBS is today a well-established treatment for movement disorders and the technique is evaluated for an increasing number of other conditions, including psychiatric disorders.

DBS in movement disorders has proved to be a safe method with relatively few complications of a more serious nature. This was also demonstrated in this review of DBS for MDD and OCD. The advantage of DBS was demonstrated by the fact that altering the stimulation could abolish all stimulation-induced side effects.

However, even though the interest for this field seems to be high, to judge from the number of reviews, letters and similar publications, there are several limitations to drawing strong conclusions at this point from the available evidence. There is insufficient randomized controlled data, and the available studies vary in follow-up intervals, tools for evaluation and definition of response and remission.

Furthermore, the actual number of patients implanted on the indications of MDD and OCD since the first publication of Nuttin et al. in 2003 is limited to 212 (58). With few exceptions, these patients are evaluated within a large number of small non-randomized studies, which are often heterogeneous and difficult to compare directly.

The targets used in these studies constitute an additional source of confusion. To give just a few examples, the target in the area of the internal capsule has varied considerably over time, currently moving in a posterior direction towards the BNST. The patients implanted in the NA seem to have no or little effect when stimulated in the actual NA, but receive the effect from stimulation of contacts located in the IC. There is an overlap between electrodes placed in what is called the ITP and the BNST on the one hand, and between the BNST and IC on the other hand. Hence, when evaluating these procedures it is not enough to know what the respective group has chosen to call their target, but to know what they are actually stimulating.

Further, no less than eight different targets have been used in these studies for MDD and OCD. The existence of different targets is in itself not a problem, since it is well known from movement disorders that the same condition can be treated by stimulating different targets, and that the same target can be used for different conditions. However, the

number of different targets suggests that we are still a long way from achieving consensus on choice of target/targets.

It is at this point not possible to decide on the relative efficacy and safety of the different targets. Which target/targets will prove to be ''optimal'' remains to be decided, and it is possible that having several targets might increase the possibilities of tailoring the treatment in accordance with the symptoms of the individual patient.

Even though DBS might offer hope to many patients with severe OCD and MDD it is important to stress that DBS for MDD is a purely experimental therapy. OCD has received an FDA approval as a ''humanitarian device exemption'', but cannot be considered as an established therapy. DBS for psychiatric disorders should therefore only be administered in clinical studies driven by multidisciplinary teams including surgeons with substantial experience of DBS in the treatment of other conditions.

Disclosure statement

P.B. is a consultant for Medtronic and a shareholder in Mithridaticum AB. M.N. and O.B. have no disclosures or conflicts of interest. The authors alone are responsible for the content and writing of the article.

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