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REVIEW ARTICLE

The application of deep brain stimulation in the treatment of psychiatric disorders

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ABSTRACT

Deep brain stimulation (DBS) is a last-resort treatment for neurological and psychiatric disorders that are refractory to standard treatment. Over the last decades, the progress of DBS in psychiatry has been slower than in neurology, in part owing to the heterogenic symptomatology and complex neuroanatomy of psychiatric disorders. However, for obsessive-compulsive disorder (OCD) DBS is now an accepted treatment. This study first reviews clinical outcomes and mechanisms of DBS for OCD, and then discusses these results in an overview of current and future psychiatric applications, including DBS for mood disorders, Tourette's syndrome, addiction, anorexia nervosa, autism, schizophrenia, and anxiety disorders. In addition, it will focus on novel techniques that may enhance the application of DBS in psychiatry.

Introduction

Deep brain stimulation (DBS) is a treatment for neurological and psychiatric disorders, in which electrical pulses are delivered to specific brain areas through implanted electrodes and a pulse generator. DBS is a last-resort treatment for the group of severely ill psychiatric patients who are unresponsive to treatment with psychotherapy or pharmacotherapy. In most countries, DBS is now an accepted treatment for treatment-resistant obsessive-compulsive disorder (OCD). Although the number of other psychiatric applications for DBS is rising, the progress of DBS in psychiatry remains slow. Experimental neuromodulation via brain electrodes was first tried in patients with psychiatric disorders during the 1950s (Heath, Russell, Monroe, & Mickle, 1955). Since then, more than 120,000 neurological patients have been treated with DBS, whereas only an estimated 500 psychiatric patients received DBS (Benabid, 2003; Naesström, Blomstedt, & Bodlund, 2016). This might be explained in part by the historically rooted taboo on neurosurgical interventions for psychiatry, but also by the heterogenic symptomatology and complex neuroanatomy of psychiatric disorders.

The majority of psychiatric patients treated with DBS are patients with OCD (Naesström et al., 2016),

which is a disorder with rather well-defined symptoms and neuroanatomy relative to other psychiatric disorders. Much can be learned from the emotional-cognitive changes that have been observed in studies of DBS for OCD, as these changes can be of relevance for many other psychiatric disorders. In addition, imaging studies of DBS for OCD have revealed which psychiatric networks may be successfully modulated with DBS. Finally, there is increasing evidence from clinical trials and case-reports for the application of DBS in the treatment of mood disorders, Tourette's syndrome, addiction, anorexia nervosa, anxiety disorders, autism, and schizophrenia. In this review, we will first summarize the clinical outcomes and mechanisms of DBS for OCD, and then discuss these results in the context of a review of current and future psychiatric applications.

Obsessive-compulsive disorder

Clinical outcomes

A meta-analysis published in 2015 (Alonso et al., 2015) analysed 31 studies in which a total of 116 patients received DBS for OCD. DBS target areas consisted of the ventral internal capsule/ventral striatum (VC/VS), the nucleus accumbens (NAc), the subthalamic nucleus

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(STN), the anterior limb of the internal capsule (ALIC), and the inferior thalamic peduncle (ITP). From 16 studies, the average percentage of responders to DBS was 60.0% (95% CI = 49.0–69.0%), with response being defined as an OCD symptom decrease between at least 30–35% measured on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The mean reduction of Y-BOCS score after DBS was available for 66 patients and was estimated to be 45.1% (95% CI = 29.4–60.8%). The five DBS targets did not differ from each other in terms of percentage of responders and mean Y-BOCS reduction. Except for higher response ratios and greater Y-BOCS-decreases in OCD patients with a later age of onset, no other clinical or demographic outcome predictors of DBS were found.

In addition to improvement of obsessions and compulsions, DBS for OCD has also been associated with improvement of anxiety and depression. DBS for OCD targeted at the NAc (Denys et al., 2010), the ALIC (Abelson et al., 2005), or the VC/VS (Greenberg et al., 2010) improved mood (measured with the Hamilton Depression Rating Scale, HDRS) and induced a sustained decrease of anxiety (measured with the Hamilton Anxiety Scale, HAS). However, STN DBS for OCD did not improve depression and anxiety symptoms in a randomized control trial (Mallet et al., 2008). Some studies reported a temporary elevation of anxiety and panic symptoms following DBS of striatal areas, although these symptoms resolved by changing parameter settings (Abelson et al., 2005; Greenberg et al., 2010; Sousa, Reis, Reis, & Belmonte-de-Abreu, 1999). Studies also frequently reported a transient state of hypomania in patients following stimulation of the STN or ventral striatal targets, but this usually lasted no more than a few days (Goodman et al., 2010; Mallet et al., 2008). Reported positive side-effects of NAc DBS included weight loss (Mantione, Van De Brink, Schuurman, & Denys, 2010), remission of alcohol dependency (Kuhn et al., 2007), and smoking cessation (Kuhn et al., 2009; Mantione et al., 2010).

Some studies assessed the impact of DBS on quality-of-life (QoL), showing an increase of QoL (Goodman et al., 2010; Ooms et al. 2014). Ooms et al. (2014) found an overall QoL improvement of 90% measured with the brief version of the WHO Quality-of-Life Scale, with improvements of the physical (39.5%), psychological (39.5%), and environmental (16%) domains. QoL improved for both responders and non-responders, suggesting that DBS improves QoL independently of OCD symptom improvement. This finding is supported by the study of Huff et al. (2010), that showed a significant improvement of Qol

in a group of 10 patients that included only one responder to DBS. Thus, DBS positively affects QoL in other ways than just improvement of obsessive-compulsive symptoms.

One can conclude that more than half of the treatment-resistant OCD patients are responders to DBS and experience significant reductions of OCD symptoms. However, the clinical effects of DBS appear to go beyond improvement of these core symptoms, since depression, anxiety, and even addiction can also improve following DBS. In the next paragraph, we will discuss the mechanisms of DBS that may mediate these effects.

Mechanisms of DBS for OCD

Current views on the pathophysiology of OCD suggest over-activity of the cortico-striatal-thalamo-cortical (CSTC) circuit (Aouizerate, Guehl, et al., 2004). This idea is based on functional imaging studies in OCD patients showing increased connectivity between cortical areas and the striatum and corticostriatal hyper-activity at rest and during symptom provocation (van Westen, Rietveld, Figee, & Denys, 2015). The cortico-striatal over-activity hypothesis is further supported by studies showing a relative decrease of corticostriatal activity in OCD patients following successful treatment with serotonin reuptake inhibitors (SRIs) or cognitive behavioural therapy (CBT) (Saxena & Rauch, 2000).

Initial theories stated that DBS inhibits excessive pathological activity regionally, comparable to the local lesion effects of ablative surgery (Nuttin et al., 2003). However, recent studies show that DBS restores brain activity and connectivity not only regionally but also distantly. Ventral ALIC (vALIC) DBS for OCD is associated with normalization of local NAc activity during reward processing (Van Laere et al., 2006). In a study targeting the vALIC, OCD patients displayed bilateral NAc hyperactivity before implantation, which normalized after chronic stimulation (Van Laere et al., 2006). With regard to the more distant effects of DBS, clinical response of vALIC DBS was related to decreased PET activity in the OFC (Abelson et al., 2005; Nuttin et al., 2003). Similar to these findings, the therapeutic effect of STN DBS correlated with a decrease of OFC hyperactivity (Le Jeune et al., 2010). Together, these findings suggest that a shared mechanism of DBS at both the vALIC and the STN is normalization of hyperactivity in the ventral frontostriatal circuit. More recent neuroimaging experiments suggest that these network effects of DBS may be mediated by a down-regulation of excessive neural synchronization.

Reduction of obsessions and compulsions after vALIC DBS was correlated with a reduction of excessive frontostriatal functional connectivity as measured with resting-state fMRI (Figee et al., 2013). Effective DBS was also associated with a reduction of EEG measures for corticostriatal synchronization, i.e. diminished cross-frequency coupling and phase-stabilty in cortical low-frequency oscilations (Bahramisharif et al. 2015; Mazaheri et al. 2014).

Hyperactivity of the CSTC-circuit in OCD is most likely mediated by decreased serotonin levels and increased levels of striatal dopamine, as observed in receptor binding studies in OCD patients (Perani et al., 2008; Simpson et al., 2003). DBS studies show that serotonin levels in frontal areas increase following NAc-DBS (van Dijk, Klompmakers, Feenstra, & Denys, 2012), indicating that the therapeutic effects for OCD might be mediated by restoring prefrontal serotonergic neurotransmission. In addition, striatal dopamine was increased in patients with OCD following DBS targeted at the NAc (Moresco et al., 2007), which parallels increased dopamine release after successful treatment of OCD with SRIs (Figee et al., 2014). This association between dopamine increase and therapeutic DBS seems counterintuitive, given the hyperdopaminergic hypothesis of OCD. However, the hyperdopaminergic state in OCD might be a secondary mechanism to compensate for serotonergic deficits, since serotonergic but not dopaminergic dysfunction is correlated with OCD severity (Perani et al., 2008). DBS-induced dopamine release may, thus, reflect enhancement of this compensatory mechanism.

The finding that DBS reduces anxiety symptoms in patients with OCD has led to studies investigating the anxiolytic mechanisms of DBS. DBS of the rat's ventral striatum reduces conditioned anxiety during the elevated plus maze (van Dijk et al., 2013). Furthermore, in rats that were previously conditioned to tones with aversive footshocks, DBS of the VC/VS during extinction training reduced fear expression and strengthened extinction memory (Rodriguez-Romaguera, Do Monte, & Quirk, 2012). These results from animal studies are in line with the finding that CBT, of which extinction is a main element, augments the effect of striatal DBS in OCD patients (Mantione, Nieman, Figee, & Denys, 2014).

Recently, NAc DBS for OCD was also found to improve sensorimotor gating, i.e. the ability to filter out redundant or unnecessary sensory stimuli as reflected by increased pre-pulse inhibition (PPI) (Kohl et al., 2015). PPI is thought to be modulated by the frontal cortex, and NAc via dopaminergic and glutamatergic pathways (Wan, Geyer, & Swerdlow, 1995), and impairments are associated with OCD, but also with schizophrenia and autism.

In conclusion, imaging studies show that DBS for OCD normalizes local and distant brain function. DBS of the vALIC or STN reduces excessive frontostriatal activity and connectivity, especially in ventral frontostriatal pathways. These effects are relevant for the pathophysiology of OCD, but also for mood disorders (Lozano et al. 2008; Mayberg et al., 2005), addiction, and Tourette's syndrome (Cheng et al., 2014; Worbe et al., 2015). In addition, DBS increases serotonin levels in frontal areas and stabilizes dopamine levels in the striatum. DBS enhances extinction learning, suggesting it might be a promising treatment option for a variety of disorders with impaired fear extinction learning such as addiction (Luigjes et al., 2012) and PTSD (Taghva, Oluigbo, Corrigan, & Rezai, 2013). Finally, DBS for OCD improves sensorimotor gating, a neurocognitive process that has been linked to several neuropsychiatric disorders with a presumed neurodevelopmental origin, such as autism and schizophrenia (Braff, Geyer, & Swerdlow, 2001).

Mood disorders

Up to now, seven open-label trials, two randomized-controlled trials, and two case-studies, with a total of 125 participating patients, have investigated the effect of DBS for treatment-resistant major depressive disorder (MDD), which we will refer to as treatment-resistant depression (TRD) in this paper. Studies in OCD noted that DBS of striatal targets (NAc, VC/VS, and ALIC) had a prominent antidepressant effect, often unrelated to the decrease in obsessive-compulsive symptoms (Denys et al., 2010; Greenberg et al., 2010). These observations led to studies exploring VC/VS and ALIC DBS in the treatment of TRD. Malone (2010) and Malone et al. (2009) examined the effect of VC/VS DBS in an open-label trial including 17 patients with TRD. At 12 months follow-up the remission rate (defined as a score of 10 or lower for both the MADRS and HDRS) was 41% and at last follow-up (mean = 37.4 months) the remission rate was 35%. These promising data led to a 16-week double-blind, randomized, sham-controlled trial of VC/VS DBS in 30 patients with TRD (Dougherty et al., 2014), which failed to demonstrate efficacy. The response rate was 20% in the active group and 14.3% in the sham group. Efficacy of DBS for MDD was recently demonstrated in a randomized clinical trial of DBS targeted at the vALIC (Bergfeld et al., 2016).

After an optimization phase during which DBS parameter settings were optimized, 10 out of 25 patients with TRD were classified as responders, and six out of the 15 non-responders were classified as partial responders (> 25% improvement). After the open phase, 16 patients entered a 12-week randomized, double-blind crossover phase in which sham stimulation was followed by active stimulation or vice versa. The HDRS scores were significantly lower during the active phase (mean = 13.6) than during the sham phase (mean = 23.1). The most important difference between this DBS trial and the aforementioned one with negative results might be that the former trial implemented a longer optimization phase and a slightly different target location, i.e. more anterior and ventral in the ALIC compared to the VC/VS target.

Instead of targeting the white matter of the ALIC, more focal DBS of the NAc has been hypothesized to have an effect on depression because of the NAc's role in abnormal reward seeking and motivational behaviour (Sesack & Grace, 2010). Indeed, a preliminary study by Schlaepfer et al. (2007) in three patients with TRD showed a beneficial effect of NAc DBS in all patients, and anhedonia was one of the first symptoms to improve. The same research group published the results of a larger cohort of 11 patients with a longer follow-up (up to 4 years) (Bewernick et al., 2010; Bewernick, Kayser, Sturm, and Schlaepfer, 2012). The response rate was 45%, and the remission rate 9%. In three patients, discontinuation of stimulation resulted in an acute relapse of depressive symptoms and re-initiation led to a reoccurrence of the antidepressant effect. No negative neurocognitive effects were found in MDD patients following acute or chronic DBS of the NAc or VC/VS (Grubert et al., 2011; Kubu et al., 2016; Mantione, Nieman, Figee, Van Den Munckhof, et al. 2014).

The subgenual cingulate cortex (SCC) has been investigated as a DBS target for TRD based on neuroimaging studies showing a reduction of hypermetabolic activity in this area following successful treatment with anti-depressants. Mayberg et al. (2005) were the first to demonstrate that 6 months of open SCC DBS resulted in at least 50% reduction on the HDRS in four out of six TRD patients. In a larger open follow-up trial with 20 TRD patients, including these first six patients, SCC DBS resulted in a 33% remission rate (defined as 50% reduction on HDRS) at 1-year follow-up (Lozano et al., 2008) and 43% at 3 years or last follow-up (up to 6 years) (Kennedy et al., 2011). Two other open-label trials with DBS of the SCC for TRD have been published by the same research group,

including 21 and 17 new patients (Holtzheimer, 2012; Lozano et al., 2012). One open-label trial, including eight patients, has been published independent of the originators of this approach (Puigdemont et al., 2015). Remission rates at 1 year varied between 30–50%. In 2011, the first randomized controlled trial with DBS of the SCC for TRD was initiated (Morishita, Fayad, Higuchi, Nestor, & Foote, 2014). Unfortunately, 2 years later this trial was halted after a failed futility analysis (Morishita et al., 2014), which predicted the probability of a successful study outcome to be utmost 17.2%. This result raised the questions whether DBS is indeed the right treatment for TRD, and whether the SCC is the right target. However, Riva-Posse et al. (2014) used diffusion tensor imaging (DTI) to model white matter connections in the SCC in order to locate the optimal DBS target area individually. For each patient, activation volume around the contacts was modelled, and white matter tracts travelling through each activation volume were defined using probabilistic tractography in order to map patient-specific tracts. At 2-year follow-up, 12 out of 16 patients were classed as responders, and whole-brain activation volume tractography showed that all responders shared bilateral connections from their activation volumes to the mPFC, rostral and dorsal cingulate cortex and subcortical nuclei (VS, putamen, hypothalamus, and anterior thalamus). Non-responders did not show these pathways. Thus, patient-specific activation volume tractography modelling might be a valuable future method to identify patient-specific white matter targets for DBS.

The medial forebrain bundle (MFB) comprises ascending and descending dopaminergic fibres connecting the VTA with the NAc, and is considered to play a role in motivation and reward (Coenen, Panksepp, Hurwitz, Urbach, & Mädler, 2012). In an open-label TRD-DBS study by Schlaepfer and Bewernick (2013), the superolateral branch of the MFB (slMFB) was the target for the electrode. They used DTI to identify the slMFB, since these white matter fibres cannot be visualized with conventional MRI. Rapid antidepressant effects were observed in six out of seven TRD patients, and four patients were in full remission at last follow-up (between 12–33 weeks). In a recent interim analysis of an ongoing pilot study including 10 TRD patients, the results of four patients treated with DBS of the MFB were presented (Fenoy et al., 2016). During the sham phase, no significant changes in mood were observed. Seven days post-stimulation, three patients had >50% symptom decrease (on the Montgomery-Åsberg Depression

Rating Scale) and two out of three patients continued to have a > 80% symptom decrease at 26 weeks follow-up. Especially symptoms of anhedonia improved with DBS of the MFB. These results may provide hope for targeting DBS at specific symptoms of depression and their associated brain circuits, such as anhedonia and the motivational network. Two other potential DBS brain targets for the treatment of depression, described in case-reports, are the ITP (Jiminez et al., 2005) and the lateral habenula (Sartorius et al., 2010). The two patients in these case-reports achieved remission at 12 and 24 months, respectively.

Of note, one SCC DBS trial also included seven patients with a bipolar depression (Holtzheimer, 2012). No DBS-induced hypomanic episodes occurred in this study, and the observed anti-depressant effect was similar to in patients with unipolar depression. In line with these results, five additional studies with DBS targeted at the SCC, NAc, and MFB have included a total of five bipolar patients. All patients experienced a significant improvement of depressive symptoms following DBS (Gippert et al., 2016). DBS-induced hypomanic symptoms occurred in only one patient, which reversed rapidly when stimulation was stopped. However, it is important to note that transient hypomanic symptoms occur in OCD patients treated with DBS in the ALIC, NAc, and STN (Haq et al., 2010; Mallet et al., 2008), which still warrants caution with DBS for bipolar depression using these targets.

In summary, studies of DBS for mood disorders are predominantly open-label and small, and the only two published sham-controlled studies had conflicting results. These studies suggest efficacy of vALIC DBS for TRD. The MFB is a promising target, especially for anhedonia. Hopefully, more sham-controlled studies will follow in the future, potentially also using MDD sub-types and individualized targets, to expand the evidence for DBS in TRD.

Tourette's syndrome

Currently, TS is thought to be caused by a dysfunction of the CSTC circuit. This hypothesis is based on neuroimaging studies showing enhanced connectivity between the basal ganglia and cortex in TS patients (Cheng et al., 2014; Worbe et al., 2015), parallel to the neural substrates of OCD. A recent meta-analysis (Baldermann et al., 2015) including 57 articles, reported the results of a total of 150 patients treated with DBS for TS. Six of these patients were treated with stimulation of two different target areas.

Of these patients, 78 received DBS of the thalamus, 44 DBS of the anteromedial part of the globus pallidus internum (GPi-am), 20 DBS of the posteroventrolateral part of the GPi (GPi-pl), two DBS of the GPi with no further description and, two DBS of both the GPi-am and GPi-pl. Furthermore, nine patients were stimulated in the region of ALIC/NAc, and one patient received DBS of the STN and the globus pallidus externa (Gpe). The median symptom improvement of all patients was 52.68% ($p < 0.001$) reduction on the Yale Global Tic Severity Scale (YGTSS), with a median score declining from 83.0 to 35.0 at last follow-up (Baldermann et al., 2015). Eighty-one per cent of the TS patients showed at least a 25% reduction of the YGTSS and 54.0% improved by more than 50%. Vocal tics revealed a significantly greater mean reduction following DBS than motoric tics (50.72% vs 44.96% reduction; $p = 0.012$).

Compared to DBS for other psychiatric disorders, many target areas have been identified for DBS for TS. The reason for this might be that TS is a disorder with large phenotypic variability. The London TS group identified five phenotypes; (1) minimally affected class, (2) CMT (chronic motor tics) and OCD, (3) TS and OCD/OCB (obsessive-compulsive behaviour), (4) TS and OCD, and (5) TS and OCD and Attention-Deficit-Hyperactivity-Disorder (ADHD) (Grados & Mathews, 2008). Thus, in order to treat the entire spectrum of symptomatology, the target areas of DBS for TS might need to be chosen based on these phenotypes. For example, patients with mainly tic symptomatology and little co-morbidity might benefit from DBS of the thalamus, whereas patients with TS and symptoms of OCD may best be treated with vALIC DBS (Porta et al. 2016).

'Closed loop' stimulation is a novel development in DBS, suggested for application in movement disorders and OCD (Beuter, Lefaucheur, & Modolo, 2014). Neural recordings from the DBS electrodes such as abnormal electrographic discharges are used to augment parameter settings to optimally influence the symptoms. Closed loop DBS seems to be well-suited for TS, as symptoms usually present in a paroxysmal pattern with intermittent episodes of vocal and/or motoric tics and periodes with less symptoms. Low-frequency patterns have been shown to provide the most adequate biomarker of TS, but also of OCD, and brain–computer interface systems can use these patterns from the electrode recordings to regulate stimulation (Almeida et al. 2015). So far, no studies on

closed-loop stimulation for TS or OCD have been published.

Addiction

Various case-reports of DBS aimed at relieving other psychiatric symptoms have reported reversal of addictive behaviours after NAc DBS. For example, NAc DBS was associated with cessation of nicotine addiction in a patient with OCD (Kuhn et al., 2007; Mantione et al., 2010) and in three out of 10 patients with TS (Kuhn et al., 2009), and remission of alcohol dependency was reported following NAc DBS in a patient with panic disorder (Kuhn et al., 2007; Mantione et al., 2010). Animal studies support the potential of DBS as a treatment for addiction. For example, DBS targeted at the NAc and the lateral habenula reduced cocaine and sucrose seeking behaviour in mice (Friedman et al., 2010, 2011; Guercio, Schmidt, and Pierce, 2015). No controlled trials have been published yet, but several preliminary case-studies have shown beneficial effects of DBS as a treatment for addiction. Gonçalves-Ferreire et al. (2015) observed increased control over cocaine craving and intake that lasted at least 2.5 years in two patients following DBS of the NAc shell and bed nucleus stria terminalis (BNST). Three studies, two including one and one including two patients, reported successful abstinence of opioids following DBS of the NAc (Kuhn et al., 2014; Valencia-Alfonso et al., 2012; Zhou, Xu, and Jiang, 2011). A study including five alcohol addicted patients that were treated with DBS of the NAc showed significant improvement of craving in all patients, and two patients remained abstinent until 5 year follow-up (Voges, Müller, Bogerts, Münte, & Heinze, 2013). The same effect of NAc DBS was observed in a study including one patient with alcohol dependency (Kuhn et al., 2011).

The mechanism of NAc DBS for addiction remains unclear. Some DBS animal models suggest that attenuation of addictive behaviours depends on modulation of the NAc shell (Vassoler et al., 2013; Wilden et al., 2014), which is the part of the NAc that regulates reward perception and the hedonic effects of drugs. Addiction symptoms increase and decrease over time, and vulnerability for drug taking may last only a few hours or days and is influenced by anxiety, stress, or environmental factors. Therefore, patients with addiction might also benefit from closed-loop stimulation (see previous paragraph).

Although the evidence for DBS in addiction is promising, it is based on case-reports and small open studies only. Additional trials, preferably randomized and controlled, are required before definite conclusions can be drawn. However, the recruitment of patients with drug addiction for these trials remains a challenge. Luigjes, van den Brink, Schuurman, Kuhn, and Denys, (2015) reported having substantially more trouble including patients with substance use disorder for a DBS trial than with OCD, and another trial (Cologne, Germany) is currently experiencing similar problems recruiting patients (Luigjes et al., 2015). Despite these difficulties, DBS should be further considered as a treatment for treatment-refractory patients with severe addiction.

Anorexia nervosa

Multiple factors have led to the consideration of DBS as a treatment for refractory AN. AN is a disorder marked by compulsivity and impaired emotional processing, and functional imaging studies have revealed a strong involvement of corticolimbic networks (Lipsman & Lozano, 2014) that could serve as targets for DBS. Furthermore, DBS has previously been shown to improve symptoms of depression and anxiety (Denys et al., 2010; Greenberg et al., 2010) that are also prevalent in AN.

Only two case reports and two small case-series of DBS for AN have been published. The SCC is thought to play an important role in emotional processing, and, therefore, it might be an appropriate target for DBS in AN. Israel, Steiger, Kolivakis, McGregor, and Sadikot, (2010) reported remission of AN that lasted until at least 3 years following SCC DBS in one patient who was originally treated with DBS for TRD. Her score on the Eating Attitude Test (EAT-26) decreased from 41 to 18 following 2 months of treatment, which occurred partially independent of her improvement in depressive symptoms. In the first pilot trial of SCC DBS for AN, DBS was associated with a mean BMI increase of 12% along with a 40% reduction of depression scores (HDRS) in six treatment-refractory AN patients at 6 months follow-up (Lipsman & Lozano, 2014). At 9 months post-DBS, three of the six patients had substantially improved core symptoms of AN accompanied by weight gain and an increase in QoL. Four patients experienced improvements in mood, anxiety, affect regulation, and anorexia nervosa-related obsessions and compulsions. PET scans showed that DBS of the SCC led to increased activity in parietal regions, which are hypometabolic in AN patients, and decreased activity in the SCC and insula (Lipsman & Lozano, 2014).

Another possible target for DBS in AN is the NAc region. The NAc and vALIC have proven to be valid

DBS targets for OCD, and many parallels can be drawn between OCD and AN, for instance in terms of compulsive behaviours and underlying neurocircuitry (Oudijn, Storosum, Nelis, & Denys, 2013). One study examined the effects of stimulation of the NAc in four AN patients (Wu et al., 2013). At final follow-up (mean 3 years), all of the four patients experienced a substantial improvement in anorexia symptoms. Their weight exceeded 85% of the expected body weight and they, thus, no longer met the diagnostic criteria of AN. McLaughlin et al. (2013) described one patient who experienced a reduction of AN symptoms following DBS of the VC/VS for refractory OCD. Her BMI normalized from 17.4 kg/m^2 to 19.6 kg/m^2, and she was less distressed with regard to caloric intake and weight. Modulation of other areas associated with reward processing and compulsivity, such as the vALIC or MFB, might also be effective for refractory AN, but no studies have yet examined this hypothesis.

New psychiatric indications

Autism

Three case-reports of DBS in four patients with treatment-refractory autism spectrum disorder (ASD) have been published (Stocco & Baizabal-Carvallo, 2014; Sturm et al., 2012). Sturm et al. (2012) were the first to apply DBS to a patient with Kanner's autism and life-threatening self-injurious behaviour (SIB). The electrodes were placed in the basolateral nucleus of the amygdale (BLn) of a 13-year old boy. The amygdala was chosen by the authors because of its established role in rage, social processing, and fear, mental abilities that are thought to be impaired in autism. After 24 months, SIB and core symptoms of autism spectrum in emotional, social, and cognitive domains were improved, although the scores relied on subjective day-to-day reports by the boy's parents. Segar, Chodakiewitz, Torabi, and Cosgrove, (2015) also reported beneficial effects of BLn DBS for a 24-year old patient with severe autism and Kleefstra syndrome, a rare genetic condition with TS and OCD-like symptoms. Three years after placement of the DBS devices, the patient continued to show improvements in her coprolalia, the involuntary and uncontrollable use of obscene language, social behaviour, and also her TS and OCD-like symptoms. This case suggests that DBS may be an effective treatment for compulsivity in patients with ASD. Stocco and Baizabal-Carvallo (2014) examined the effects of DBS in two patients with severe stereotypies. The first patient was a 19-year old woman whom received DBS

at the GPi. At 13 months post-DBS, her score on the Hopkins motor stereotypy rating scale (JHMRS) was decreased by 91.3% (from 46 to 4). The second patient, an 18-year old man, showed an initial decrease of his JHMRS score from 67 to 19 at 3-months follow-up after DBS of both the ALIC and GPi; however, at 6 months post-surgery, his stereotypies gradually returned to baseline.

These cases illustrate that DBS may possibly be an effective treatment for patients with ASD. DBS of the amygdala might be more valuable for ASD patients with predominantly social dysfunctioning and SIB, whereas ASD patients with compulsive behaviours or stereotypies might benefit more from stimulation of striatal areas.

Schizophrenia

The first medical application of DBS in an experimental setting was in a patient with schizophrenia (Heath et al., 1955). It is, therefore, remarkable that, for over 50 years, no further research was conducted and only recently a single patient with schizophrenia has been treated with DBS (Corripio et al., 2016). With increasing knowledge of heterogeneous dysfunctions in brain networks attributed to schizophrenia, DBS targetted at these networks is reappearing as a treatment option. Current theories state that dopaminergic and glutamatergic impairments in the striatum attribute to symptoms of schizophrenia (Youngerman, Chan, Mikell, McKhann, & Sheth, 2016). High-frequency DBS in the NAc is thought to stabilize dopamine transmission in the midbrain, which may control symptoms of schizophrenia. DBS of the NAc or mPFC improved schizophrenia-like deficits in rats, such as impaired sensorimotor gating and attentional selectivity (Bikovsky et al., 2016). In addition to the ventral striatum, regions that are believed to drive striatal dopamine release are also suggested as potential DBS targets, i.e. the hippocampus, substantia nigra, and VTA (Youngerman et al., 2016).

Recently, a case of a patient with treatment-refractory schizophrenia treated with DBS of the NAc was published (Corripio et al., 2016). At 44 weeks follow-up she experienced remarkably less positive symptoms (61.54% reduction on the Positive and Negative Syndrome Scale [PANSS] positive factor from 13 to 5) and also less negative symptoms (33.4% reduction PANSS negative factor from 18 to 12). Her scores on the disorganized, excited, and depressed factors of the PANSS also declined. During the phase of optimizing parameter settings, the patient developed akathisia with bilateral stimulation, which was rapidly reversed

after changing the parameters to unilateral (left-sided) stimulation. So far this is the only known case of a patient treated with schizophrenia. However, a trial of DBS of the NAc or subgenual anterior cingulate for patients with treatment-resistant schizophrenia is ongoing (ClinicalTrials. Gov Identifier: CT02377505).

Anxiety disorders

Currently there is very little evidence for the use of DBS in the treatment of anxiety disorders. Nac DBS was not effective in one patient treated with Nac DBS for panic disorder (Kuhn et al., 2007). However, anxiety symptoms substantially and rapidly decrease in most patients treated with DBS for OCD (Abelson et al., 2005; Aouizerate, Cuny, et al., 2004; Denys et al., 2010; Greenberg et al., 2010). The Denys group (van Dijk et al., 2013) observed that, in patients treated with vALIC-DBS for OCD, reduction of anxiety especially encompassed the symptomatic fear associated with their obsessions and to a lesser extent general anxiety or unconditioned fear. Indeed, animal studies have demonstrated that active DBS of the dorsomedial VS (VC/VS homologue of rats) enhanced fear extinction recall relative to sham stimulation (Rodriguez-Romaguera et al., 2012). However, it was critical to administer DBS during fear extinction training, as only stimulation paired with extinction would improve maintenance. Furthermore, DBS of the dorsomedial VS increased the expression of a plasticity marker in areas known to be involved in extinction, such as the amygdala, the orbitofrontal cortex, the prelimbic and infralimbic prefrontal cortices, the central nucleus, and intercalated cells. A rodent study by van Dijk et al. (2013) revealed that stimulation of the ventral medial caudate nucleus in rats reduced both conditioned and unconditioned fear, whereas stimulation of the internal capsule only diminished conditioned anxiety.

Aberrant extinction of conditioned fear plays an important role in many anxiety disorders, especially in post-traumatic stress disorder (PTSD). PTSD has been associated with over-activity in the amygdala-hippocampus axis, explaining excessive autonomic fear responses (Taghva et al., 2013). In addition, the ventro-medial PFC (vmPFC), responsible for inhibiting the amygdala, is generally under-active in PTSD and, therefore, failing to regulate amygdala over-activity and extinction learning. DBS of the basolateral nucleus of the amygdala (BLn), the site of the amygdala that mediates extinction learning, may reduce the functional output of the amygdala and thereby compensate for ineffective vmPFC control. Indeed, a

recent case-report presented a patient with treatment-refractory PTSD that was successfully treated with DBS of the BLn (Langevin et al., 2015). After 8 months of treatment the patient experienced a 37,8% reduction on the Clinician-Administered PTSD Scale (CAPS), and also his functioning in daily life improved. It was observed that DBS in this PTSD patient first decreased emotional and physiologic hyperarousal, whereafter improvements in avoidance behaviour followed gradually. Thus, similar to striatal DBS, DBS of the BLn may create an emotional state in which re-exposure to the trigger could lead to extinction learning. Currently, an early-phase trial on DBS of the BLn for treatment-refractory combat PTSD is still recruiting patients (ClinicalTrials.gov Identifier: NCT02091843). For now, the evidence for DBS in PTSD and other disorders of fear conditioning and extinction is promising, but too limited to draw conclusions.

Conclusion

The application of DBS in psychiatry is progressing slowly but consistently. Efficacy of DBS is established for OCD, with more than 50% responders in severely ill and treatment-refractory patients. The effects of DBS for OCD seem to go beyond its classically defined symptoms. DBS targeted at the vALIC or ventral striatum improves quality-of-life independently of obsessive-compulsive symptoms, and is also able to improve mood, anxiety, and addiction. The heterogeneous effects of DBS might be explained by its restorative effects on frontostriatal networks for motivation and emotion regulation. Consistent with these effects in OCD, vALIC DBS was also shown to be efficacious for treatment-resistant depression, although results of other trials have been conflicting. Some studies suggest that specifically anhedonia symptoms might respond to DBS targeted at ventral striatal targets or the MFB. Overall, the studies reviewed here strongly indicate that DBS for psychiatric indications could progress by moving towards the selection of targets and primary outcomes based on transdiagnostic symptom domains and associated neural networks.

TS is also a very heterogeneous disorder, which is probably why DBS trials in TS, although often demonstrating positive results, have investigated a large variety of neuroanatomical targets. TS with predominantly tic-related symptoms might benefit from thalamus stimulation, whereas TS with compulsive symptoms might benefit more from DBS of the NAc. A transdiagnostic approach can also help expand psychiatric

indications for DBS. Like OCD and TS, addiction is characterized by compulsivity, and DBS of the NAc has been shown to attenuate alcohol and opioid addiction in small case-series. Compulsivity but also affective dysregulation are important aspects of the symptomatology of AN. Accordingly, DBS of the NAc, involved in compulsivity, and DBS of the SCC, involved in emotional processing, have been shown to reduce AN-symptoms in two small case-series.

Newer indications for DBS are autism, schizophrenia, and PTSD. For autism, preliminary data from case reports suggests that DBS in basal ganglia targets may improve compulsive and stereotypical behaviours, whereas DBS of the basolateral amygdala in one patient improved social impairment and aggression. DBS targeted at the NAc is presumed to stabilize striatal dopamine and, capitalizing on this idea, a case-study reported positive effects of NAc DBS in a patient with schizophrenia. A larger clinical trial is underway. Ventral striatal DBS enhanced extinction-based learning in animal models and in patients with OCD, which holds promise for the application of DBS in anxiety disorders and PTSD.

Future studies should focus on new techniques for personalizing DBS. Neuro-anatomic targeting with DTI to locate individual white matter connections has shown to be promising for DBS in depression targeted at the medial forebrain bundle or SCC. Closed-loop stimulation is another important development for psychiatry, as psychiatric symptoms generally fluctuate over time, which this experimental technique may be able to adjust for.

In conclusion, although efficacy of DBS is not yet established for most psychiatric disorders, the reviewed studies are promising for its future application in psychiatry. Investigation of the shared effects of DBS across a variety of psychiatric disorders and exploration of new stimulation techniques might contribute to the efficacy of DBS and its personalization to each patient's needs.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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