Deep Brain Stimulation for Psychiatric Disorders

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13.1 Introduction

The global burden of neuropsychiatric disease is substantial, and expected to rise significantly in the next few decades. The World Health Organization (WHO) estimates that one in four patients who seek medical help do so for a mental or behavioural illness, with major depressive disorder (MDD) ranking as the third most important cause of global disease burden (Kessler et al. 2003, 2005). As the population ages, and the prevalence of these conditions increases, there will be an urgent need to develop novel therapeutic interventions.

For patients with the most common forms of mental illness, including MDD and obsessive–compulsive disorder (OCD), some effective treatments are available, including pharmacological and psychotherapeutic options whether alone or in combination. For example, current guidelines for the management of MDD emphasize a stepwise, graded approach to medical management, which achieves a satisfactory clinical response in up to two-thirds of patients (Kennedy et al. 2009; Lam et al. 2009). Despite these and other available therapies, however, a substantial proportion of patients remain resistant to treatment (Giancobbe et al. 2009; Kennedy et al. 2009). For these patients neuromodulation may be an option.

Brain circuit-based neuromodulation for psychiatric illness is not new, and its history extends to the 1930s with the early development of electroconvulsive therapy (ECT). The idea that electrical currents can be used to 'reset' activity in pathological brain structures took hold early, and with significant advances in anaesthesia, patient monitoring, and psychopharmacology, ECT today is an important part of the treatment algorithm for several psychiatric conditions (Lipsman et al. 2013a). Other non-invasive approaches currently under active investigation include repetitive transcranial magnetic stimulation (rTMS), deep TMS and magnetic seizure therapy (MST).

Alternatives to non-invasive neuromodulation are invasive surgical procedures which can more directly target pathological circuits and structures. Early operations, such as limbic leucotomy, have now been supplanted by far more refined, safer and image-guided procedures. Deep brain stimulation (DBS) is one such procedure. The last 15 years have seen a surge of interest in DBS for psychiatric disorders, an interest that has been driven primarily by three factors:

1. Safety and efficacy: DBS is part of the standard treatment of patients with Parkinson's disease (PD), dystonia and essential tremor, with over 100,000 patients treated globally to date (Lozano et al. 2013). In properly selected patients, and guided by expert

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T. Itakura (ed.), *Deep Brain Stimulation for Neurological Disorders: Theoretical Background and Clinical Application*, DOI 10.1007/978-3-319-08476-3_13,

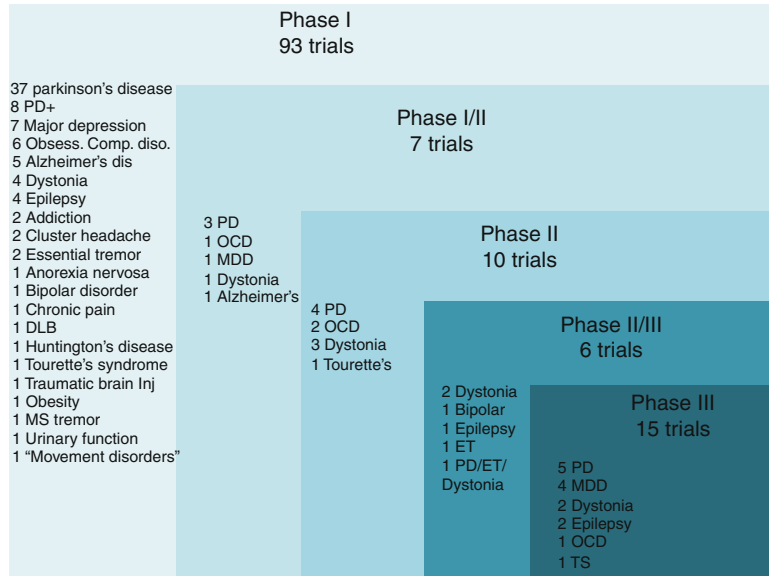

Fig. 13.1 Clinical trials in deep brain stimulation, according to the National Institute of Health (NIH) clinical trials registry (From Lozano and Lipsman (2013) with permission)

multi-disciplinary teams, DBS is effective in controlling symptoms and improving quality of life in these disorders. The ability of DBS to reversibly modulate activity in motor circuits has led to its investigation in other circuit-based conditions, including psychiatric disorders.

2. Neuroimaging: Advances in structural and functional neuroimaging are providing insights into the mechanisms of psychiatric conditions. Imaging studies have helped generate hypothesis-driven investigations of neural circuitry and suggested critical nodes within disrupted circuits that can be targeted with DBS.
3. Definition of treatment-resistance: Although pharmacological treatments are available for most psychiatric illnesses, a large minority of patients remains treatment-resistant. Specific approaches for these patients, who are susceptible to the effects of both polypharmacy and chronic mental illness, are required.

DBS is currently under investigations for a number of neurological and psychiatric conditions. A survey of the National Institutes of Health (NIH) clinical trial registry reveals that at least 21 distinct indications are now under Phase I, 'first-in-man', investigation (Fig. 13.1). Several of these, such as Parkinson's disease, epilepsy and depression, have progressed to Phase III, randomized controlled, multi-centre trials. It appears therefore that the fastest growing indications for investigative DBS are psychiatric, which as of today are among the strongest drivers of progress in DBS research. There are currently trials investigating DBS for major depression, bipolar disorder, OCD, Tourette's syndrome, anorexia nervosa, schizophrenia, obesity, Alzheimer's disease and addiction. This chapter will focus on two of the most common indications, MDD and OCD, and provide an overview of the circuitry of these conditions, the targets currently employed, and a summary of results to date. We also discuss some of the emerging indications in the last 5 years, and hypothesize about the future psychiatric DBS, and neuromodulation for these disorders.

13.2 MDD

13.2.1 Epidemiology and Phenomenology

MDD is among the most common psychiatric conditions, with a lifetime prevalence of up to 16 % in the general adult population (Kessler et al. 2003). The condition is highly

heterogeneous, and encompasses much more than just depressed mood. Patients often endorse varying degrees of amotivation, apathy, and anhedonia, as well as lack of energy, and sleep and appetite disturbances. The involvement of multiple 'systems' including mood, cognitive, perceptual and vegetative functions suggests broad circuit dysfunction involving several, primarily limbic, networks. It is not possible, therefore, to ascribe MDD to dysfunction of a specific structure, but instead MDD should be viewed as a network disorder, much like Parkinson's disease. Similarly, it is not possible to link MDD to dysfunction in one neurotransmitter system, such as serotonin. Indeed, neurobiological models suggest that dopaminergic and noradrenergic dysfunction contribute in important ways to MDD, as evidenced, in part, by the successful use of anti-depressants that target these systems (Lam et al. 2009). An improved understanding of MDD aetiology, and the development of novel therapies, would therefore need to account for its heterogeneous clinical and neurobiological picture.

13.2.2 Neurocircuitry

Much of the progress in elucidating MDD circuitry has been driven by advances in neuroimaging, and particularly functional imaging which permits a real-time view of the active brain. These studies have identified critical 'nodes' in primarily limbic circuits that are dysfunctional in the pathologically depressed state. For example, metabolic imaging with fluorodeoxyglucose (FDG)-PET has shown that the subcallosal cingulate (SCC) region is hyperactive in unmedicated depressed patients as well as in healthy subjects experiencing sadness (Kennedy et al. 2007; Mayberg 1997; Mayberg et al. 1999). This hyperactivity normalizes with remission of the depression following medical, psychotherapeutic or DBS treatment (Kennedy et al. 2001, 2007; Mayberg et al. 2005). Other regions implicated in depression include those involved in reward- and decision-making pathways, such as the nucleus accumbens and dorsolateral prefrontal cortex (DLPFC) (Price and Drevets 2010). Anhedonia, or the lack of pleasure in typically pleasurable activities, is a major component of depression, and has been linked to dysfunction in the nucleus accumbens (NAcc) in patients and pre-clinical models (Bewernick et al. 2010; Price and Drevets 2010). The DLPFC participates in decision-making and has reciprocal projections with both anterior cingulate and medial prefrontal cortical regions, which participate in affect- or reward-guided decisions, both dysfunctional in MDD. The DLPFC is also a TMS target in depression, where its modulation is linked to improvements in mood (Lipsman et al. 2013a). All of these structures, and the SCC in particular, project widely in the brain, along pathways subserving many of MDD's cardinal symptoms. The SCC, for example, projects to amygdala and the insula, which participate in vegetative and homeostatic control, as well as to the medial prefrontal and anterior cingulate region, which participate in decision-making (Hamani et al. 2011). In this way, dysfunction in SCC can be linked to several key MDD symptoms. More broadly, such work can identify specific regions for DBS targeting, which can further be tailored according to the predominant clinical picture.

13.2.3 DBS Targets

Several brain targets for the management of treatment-refractory MDD with DBS are currently under investigation. These include SCC, NAcc, ventral caudate/ventral striatum (VC/VS), inferior thalamic peduncle (ITP), lateral habenula (Hab), and medial forebrain bundle (MFB) (Table 13.1). Below we review the targets that have accumulated the most experience to date.

13.2.3.1 SCC

SCC (aka subgenual cingulate gyrus, 'Area 25') is a region below the genu of the corpus callosum that sits at the confluence of at least three white matter pathways. These pathways, projecting to orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC) and cingulate connect higher order, 'top-down' cortical structures with subcortical modulatory regions. As described above, the

Table 13.1 DBS studies for major depressive disorder

Study	Target	Number/type of patients	Outcome
Mayberg et al. (2005)	SCC	5 (MDD, one patient with bipolar II)	Follow-up 6 months. 4/6 responders, 2/6 remission as measured by HDRS
Jimenez et al. (2012)	ITP	1 (MDD with comorbid bulimia nervosa and borderline personality disorder)	Double-blind assessment protocol following initial period of 8 months with 'on' stimulation. No relapse of depressive symptoms with DBS turned off for 12 months. Sustained remission at 24 months with DBS on
Schlaepfer et al. (2008)	NAcc	3 (MDD)	Double-blind changes to stimulation parameters and assessment. HDRS scores decreased with stimulation and increased with stimulation off
Malone et al. (2009)	VC/VS	15 (MDD)	Follow-up from 6 to 51 months. 8/15 responders and 6/15 in remission at last follow-up measured by Montgomery-Asberg Depression Scale (MADRS)
Bewernick et al. (2010)	NAcc	10 (MDD)	At 12 months, 5/10 had achieved >50 % reduction in HDRS scores (i.e. responders). Antidepressant, antianhedonic, and antianxiety effects observed
Kennedy et al. (2011)	SCC	20 (MDD, one patients with bipolar II)	At last follow-up (3–6 years following implantation, mean = 3.5), response rate = 64.3 % and remission rate = 42.9 % (by HDRS). Considerable improvement in social functioning: 65 % of patients engaged in work-related activity at last follow-up compared to 10 % prior to DBS
Puigdemont et al. (2011)	SCC	8 (MDD)	Response and remission at 1 year, 62.5 and 50 %, respectively
Holtzheimer et al. (2012)	SCC	17 (10 MDD, 7 with bipolar II)	At 1 year follow-up, remission and response rate of 36 %. At 2 years, remission rate of 58 % and response rate of 92 %. Remission and response rates based on Hamilton Depression Rating Scale (HDRS). Efficacy similar for MDD and bipolar patients
Lozano et al. (2012)	SCC	21 (MDD)	At 6 months follow-up, response rate of 48 %; at 1-year follow-up, response rate of 29 %. Response measured by HDRS
Schlaepfer et al. (2013)	MFB	7 (MDD)	>50 % reduction in depression scores in most patients by day 7 post-op, at 12–33 weeks 6/7 responders, 4/7 in remission

SCC subcallosal cingulate, *MDD* major depressive disorder, *HDRS* Hamilton Depression Rating Scale, *ITP* inferior thalamic peduncle, *DBS* deep brain stimulation, *NAcc* nucleus accumbens, *VC/VS* ventral caudate/ventral striatum, *MFB* medial forebrain bundle

SCC has been functionally linked to a depressed state, and more broadly to the regulation of negative emotions. Currently, the most experience with MDD DBS worldwide is with the SCC target. The SCC DBS experience started in 2003 and published in 2005 in six patients with chronic, resistant disease (Mayberg et al. 2005). Four of these patients experienced a greater than 50 % reduction in depression scores (HAMD: Hamilton Depression Rating Scale), with two patients achieving a clinical remission. This patient group has since been expanded and data on 20 patients and followed for between 3 and 6 years have been presented (Kennedy et al. 2011). Response

and remission rates at last follow-up were 64 and 43 %, respectively. Two other groups have reported their series with SCC DBS and found similar results. In one paper, eight patients were followed to 1 year with the authors finding response and remission rates of 63 and 50 % (Puigdemont et al. 2011). Another group followed 17 patients (10 with MDD and 7 with bipolar depression), and found that at 2 years following surgery, 92 % were responders and 58 % were in remission (Holtzheimer et al. 2012). An additional multi-centre trial of SCC DBS found response rates of 48 % at 6 months and 29 % at 12 months (Lozano et al. 2012). Such results, in the context of severe, unremitting chronic depression, are promising and have led to the design of phase III, randomized controlled trials. The results of these trials will help establish whether DBS at this target should be an accepted treatment for this specific patient population.

13.2.3.2 NAcc and VC/VS

The prominence of anhedonia in MDD motivated the investigation of targets along reward pathways with DBS. NAcc is a grey matter region comprised of an anatomic core and shell and which exists at the ventral confluence of the caudate and putamen (hence, ventral striatum). Neurophysiological studies in animal and human models have directly linked neuronal firing in the NAcc to the receipt and expectation of reward, and imaging studies using both PET and fMRI have linked NAcc striatal dysfunction to MDD (Patel et al. 2012).

Several studies have investigated NAcc and VC/VS with DBS in open-label, prospective trials. Malone et al. (2009) operated on 15 patients using the VC/VS target and at between 6 and 51 months follow-up found that eight patients were treatment responders, and six were in remission. Bewernick et al. (2010, 2012) targeted the NAcc in ten patients and at 1 year had a 50 % response rate, with further significant effects on anhedonia, as well as on comorbid anxiety. The similar results in these studies, from different centres and employing slightly different targets is encouraging, suggesting that DBS of reward pathways can have relatively stereotypic and reproducible response rates. VC/VS has also been investigated in refractory OCD (see below) and the experience with depression arose from the observation of improved mood in OCD patients. Given the established role of NAcc in reward pathways, and the preclinical and imaging literature linking NAcc activity to reward, it may be that NAcc, and its afferent/efferent projections may be the preferred target for primarily anhedonic MDD.

13.2.3.3 MFB

Rather than targeting distinct nuclei, as is the case for motor-circuit conditions such as Parkinson's disease, DBS in depression often targets axonal pathways in an effort to broadly modulate network wide activity. A recent example is MFB, an axon pathway that is part of the dopaminergic mesolimbic system connecting the ventral tegmental area (VTA) with NAcc and other key subcortical structures. Schlaepfer et al. (2013) described their experience of MFB DBS in seven patients with treatment-refractory MDD, and found that stimulation was associated with robust, and rapid, remission of depression. The rapidity of the response, which occurred within hours and days, contrast the typical time to response with SCC and NAcc DBS. In addition, the effect was seen in virtually every patient implanted, with six of seven patients classified as treatment responders at 12–33 weeks follow-up. These results, which require further investigation and validation in larger, blinded trials, are intriguing and suggest a more 'direct' route to mood change than previously observed. Coupling MFB stimulation with neuroimaging, and particularly dopamine or FDG PET, would provide additional insights into the mechanisms of the clinical response.

13.3 OCD

13.3.1 Epidemiology and Phenomenology

OCD is among the most common anxiety disorders, with a population prevalence of up to 2–3 % (Lipsman et al. 2007). The condition is marked by obtrusive, repetitive and anxiogenic

thoughts (obsessions), as well as time-consuming, disproportionate, and anxiolytic behaviours (compulsions). Although obsessions and compulsions can occur in the same patient, some suffer only from obsessions or compulsions. For example, whereas some patients will have contamination obsessions and/or compulsions (i.e. 'washers') others will have compulsions to count (i.e. 'checkers'). Heterogeneity in OCD is the rule, although it appears that activation of fear and anxiety circuitry is a common thread.

OCD exists at the interface between psychiatry and neurology given the prominence of physical behaviours that patients believe are 'outside of their control'. Behaviours, or compulsions, that are meant to relieve anxiety become reinforcing, leading to a vicious cycle of thoughts and actions. Current treatment strategies include medications targeting primarily the serotonergic system, and psychotherapeutic treatments that attempt to break the cycle by altering pathological cognitions. As in depression, a substantial proportion of patients, often up to a third, remain significantly disabled, despite optimal guideline-concordant care. For these patients, novel treatment strategies, including neurosurgery, are being investigated.

13.3.2 Neurocircuitry

Similar to mood disorders, advances in neuroimaging have led to a better understanding of OCD circuitry. Such studies have implicated decision-making and fear circuitry, as well as pure motor pathways in the basal ganglia (Greenberg et al. 2010b). For example, among the most consistently activated structures is OFC that is known to participate heavily in judgement, executive functioning, impulse control and emotion-guided decision-making (Kent et al. 2003). Both fMRI and PET studies have further shown significant amygdalar activation in response to provocative, disease-relevant stimuli, as well as a failure of cortical structures, and OFC in particular, to downregulate activity within the amygdale (Saxena et al. 1999, 2004; Swedo et al. 1992). The argument for overlap between anxiety and motor circuitry is strengthened by the large number of patients with Tourette's syndrome who are diagnosed with comorbid OCD (Cummings and Frankel 1985). It is further not uncommon for patients with striatal and other basal-ganglia pathology to develop tic- and OCD-like behaviours (Cummings and Frankel 1985). Indeed, the complex regionalization of neuroanatomy, particularly within motor circuitry is now being recognized. The subthalamic nucleus, for example, a traditionally 'motor' structure is now known to have distinct associative and limbic components, with unique efferent and afferent projections. The existence of parallel, yet overlapping, circuits within the same 5-mm structure, highlights the intimate relationship between these pathways, and how dysfunction in one 'critical node' can have network wide influence, and lead to a broad constellation of symptoms.

13.3.3 DBS Targets

OCD was the first psychiatric condition to be investigated with DBS, in a report published in 1999 that described the anterior limb of the internal capsule (ALIC) as the target (Nuttin et al. 1999). Since then, several structures have been investigated, including the subthalamic nucleus (STN), VC/VS and ITP. Below we review the targets that have accumulated the most experience to date (Table 13.2).

13.3.3.1 ALIC

The ALIC is a projection pathway connecting cortical structures in the frontal and medial frontal lobe with subcortical structures and thalamus. The importance of the ALIC to disorders of mood and anxiety was recognized early, and severing this cortical–subcortical connection was the objective of initial attempts at psychiatric surgery with limbic leucotomy (Dax et al. 1948). Leucotomy has long been abandoned, replaced with stereotactic capsulotomy, a more precise and safe lesioning of the ALIC which for many years was the standard surgical approach for

Table 13.2 DBS studies for OCD

Study	Target	Patients	Outcomes
Nuttin et al. (1999)	ALIC	4	Three-quarters of patients had significant clinical benefit
Mallet et al. (2002)	STN	2	Comorbid PD and OCD; 58 and 64 % reduction in OCD scores after surgery
Anderson and Ahmed (2003)	ALIC	1	79 % reduction in YBOCS score at 3-month follow-up
Nuttin et al. (2003)	ALIC	6	Four patients had pre/post YBOCS assessments, and three-quarters showed >35 % reduction in YBOCS score
Sturm et al. (2003)	VC/VS	4	Three-quarters of patients had 'near total recovery' at 24–30 months follow-up
Aouizerate et al. (2004)	VC/VS	1	Comorbid OCD/MDD; remission of MDD at 6 months (HAM-D <7); remission of OCD after 12–15 months
Fontaine et al. (2004)	STN	1	Comorbid PD and OCD; YBOCS score reduced from 32 to 1 at 1-year follow-up
Abelson et al. (2005)	ALIC	4	Randomization to 3-week blocks of on- and off-stimulation. one patient had reduction >35 % in YBOCS score during the double-blind period
Greenberg et al. (2006)	VC/VS	10	Eight patients followed for 3 years; 50 % had >35 % reduction in YBOCS score
Mallet et al. (2008)	STN	16	Randomized, double-blind design; eight patients assigned to sham and eight to active stimulation. Twelve of 16 had >25 % reduction in YBOCS score
Plewnia et al. (2008)	VC/VS	1	YBOCS score reduced from 40 to 22 at 6-month and 1-year follow-up
Jimenez-Ponce et al. (2009)	ITP	5	49 % reduction in YBOCS at 12 months Heterogeneous patient group (schizoid, addiction, etc.)
Denys et al. (2010)	VC/VS	16	46 % reduction in YBOCS score at 8 months in open-label phase and 25 % difference in YBOCS score between active and sham stimulated patients in blinded phase; nine patients classified as clinical responders
Franzini et al. (2010)	VC/VS	2	Clinically beneficial response in 2 of 2 patients, with YBOCS score decreasing to 22 (from 38) and 20 (from 30) at 12 and 22 months, respectively
Goodman et al. (2010)	VC/VS	6	Four of 6 patients had >35 % reduction in YBOCS score at 36 months
Tsai et al. (2012)	VC/VS	4	At 15 m follow-up, 33 % reduction in mean YBOCS score, 32 % reduction in HAMD, 31 % improvement in global assessment of functioning

ALIC anterior limb of internal capsule, *OCD* obsessive–compulsive disorder, *STN* subthalamic nucleus, *YBOCS* Yale-Brown Obsessive Compulsive Scale, *VC/VS* ventral caudate/ventral striatum, *HAMD* Hamilton Depression Rating Scale, *MDD* major depressive disorder, *PD* Parkinson's disease, *ITP* inferior thalamic peduncle

treatment-refractory anxiety and mood disorders. The development of DBS permitted implantation of electrodes at the capsulotomy target without causing a lesion. Nuttin et al. (1999) described their experience with ALIC DBS in OCD in two publications, their initial experience in 1999 in four patients and a subsequent publication in 2003 in six patients (Nuttin et al. 1999). Of the patients who had pre- and post-operative assessments with the Yale-Brown Obsessive Compulsive Scale (YBOCS), 75 % saw a reduction in scores of greater than 35 %, indicating a clinically meaningful response. Abelson et al. (2005) also performed a double-blind, sham stimulation study in four patients who underwent ALIC DBS and found that one patient saw a greater than 35 % YBOCS reduction during the double-blind period.

13.3.3.2 STN

The STN is an ovoid grey matter structure that is a component of the 'indirect' motor pathway. STN receives largely inhibitory input from the globus pallidus externus (GPe) and excitatory input directly from the motor cortex, and sends excitatory output to the globus pallidus internus (GPi) and substantia nigra reticulata (SNr).

The STN is a major DBS target for patients with disabling PD, and it was in the course of PD surgery that its putative role in OCD was hypothesized. Mallet et al. (2002) reported their experience of STN DBS in two patients with comorbid PD and OCD, and found that in addition to improvements in motor scores, patients experienced significant reductions in OCD scores post-operatively. This work led to a randomized, double-blind trial of STN DBS for OCD, wherein 16 patients underwent the procedure of which 12 saw at least a 25 % reduction in YBOCS scores (Mallet et al. 2008).

13.3.3.3 VC/VS

The DBS target with the most experience to date in OCD is the VC/VS. Anatomically, the VC/VS is closely related to the NAcc which exists at the ventral interface of caudate and putamen. Sturm et al. (2003) initially reported that three out of four patients who underwent VC/VS DBS for OCD saw 'near total recovery' at 24–30 months follow-up, although no YBOCS data were provided (Greenberg et al. 2010a; Greenberg et al. 2006) operated on ten patients with severe OCD using the same target, and found that of eight patients who were followed to 3 years, 50 % had a greater than 35 % reduction in YBOCS scores, indicating a treatment response. Such results are similar to those reported by Denys et al. (2010), who found 9 of 16 patients were responders at 8 months follow-up, with a mean YBOCS reduction of 46 % in open-label follow-up. Most recently, Tsai et al. (2012) reported their experience with VC/VS stimulation in four severe OCD patients and found that at 15-month follow-up, there was a mean 31 % reduction in YBOCS scores as well as 32 % reduction in depression ratings. Such results provide further support for the role of VC/VS in both mood and anxiety pathways.

13.3.3.4 ITP

The ITP consists of a relatively small bundle of projection fibres connecting OFC with the thalamus. ITP stimulation has been proposed for both refractory OCD and MDD, and a small experience with this target is accumulating. Jimenez-Ponce et al. reported the initial experience with ITP stimulation in five patients with OCD finding a mean 49 % reduction in YBOCS scores at 12-month follow-up (Jimenez-Ponce et al. 2009). The patient group, however, was highly heterogeneous and included some with comorbid schizophrenia and addiction. Larger studies, in more homogeneous cohorts will provide additional data about this target, but such results do to confirm earlier case reports that described the safety and efficacy of ITP stimulation (Jimenez et al. 2007).

13.4 Other Emerging Indications

All psychiatric indications for DBS are currently investigational. Although a Food & Drug Administration (FDA) humanitarian device exemption (HDE) exists for the use of DBS in OCD in the United States, DBS is not yet a standard of care for any psychiatric condition. However, the early promise of DBS in psychiatry has motivated its investigation in other circuit-based disorders, such as Alzheimer's disease and anorexia nervosa.

13.4.1 Alzheimer's Disease (AD)

AD is a neurodegenerative condition marked by severe memory and cognitive impairments. Given its relationship to advancing age and associated significant disability, demographic changes in the years to come will lead to an exponential rise in cases. The societal and public health costs will be enormous, and compounded by the abject lack of any effective treatments, despite decades of intense research (Laxton et al. 2013; Laxton and Lozano 2013).

It is becoming clear that AD is a disorder of brain networks, similar to PD and other

Table 13.3 DBS studies in Alzheimer's disease and dementia

Study	Target	No. of patients	Results
Turnbull et al. (1985)	NBM	1	No significant clinical response at 8 months following surgery, but increase in temporo-parietal metabolic activity
Freund et al. (2009)	NBM	1 (PD dementia)	Improvements in neuropsychological function at 2 months. Subsequent significant decline following deactivation of device and then recovery of previous gains with activation
Laxton et al. (2010)	Fornix	6	Two of six patients saw stabilization of MMSE scores, increased metabolic activity in temporo-parietal regions
Fontaine et al. (2013)	Fornix	1	At 12 months, MMSE scores stabilized compared to baseline, increase in mesial temporal metabolism

NBM nucleus basalis of meynert, *MMSE* mini-mental status examination

neurodegenerative disorders. Focal disturbances lead to local disruption of neuronal activity, which is then propagated to synaptically connected structures within a functional network (Smith et al. 2012). By focally targeting disrupted networks, DBS has been proposed as a means of modulating activity in these circuits thereby restoring function. To date, two targets have been proposed for DBS in AD (Table 13.3), the fornix and the nucleus basalis of meynert (NBM). As part of Papez Circuit, the fornix is the principle outflow tract from the hippocampus and projects to the mammillary bodies via post-commissural fibres. A case report in 2008 described stimulation of the hypothalamic fornix in a case of severe obesity, which instead of curbing appetite led to significant improvements in verbal memory as well as spontaneous recall of autobiographical events (Hamani et al. 2008). This motivated a pilot trial of fornix DBS in six patients with mild AD, which found a significant slowing or stabilization of disease in two patients, with concomitant increases in cerebral glucose utilization in key memory circuits, including the default mode network (Laxton et al. 2010). An additional case report of fornix DBS in a patient with AD also found stabilization of memory scores at 12 months following stimulation (Fontaine et al. 2013). A large, multi-centre phase II/III trial is now being conducted to study the potential of this approach.

The NBM is a prime source of cholinergic transmission, and projects widely to key memory-related structures. Two case reports have described NBM DBS in patients with dementia, one with Alzheimer's type and the other with Parkinson's (Freund et al. 2009; Turnbull et al. 1985). The AD saw little clinical improvement but significant changes in glucose utilization on PET scan. The PD patient did see significant cognitive improvements following stimulation. The entorhinal cortex (EC) has also been explored as a stimulation target for memory enhancement. To date, however, this work has been limited to patients without preexisting memory disturbance, and exclusively tested in patients undergoing epilepsy surgery (Suthana et al. 2012, 2013). In these patients, who had hippocampal depth electrodes in place for seizure localization, researchers were able to demonstrate significant improvements in spatial memory with EC stimulation; an intriguing result that requires additional investigation.

13.4.2 Anorexia Nervosa (AN)

AN is a psychiatric condition marked by severe disturbances in weight, body- and self-perception. A common condition, with a lifetime general population prevalence of between 0.3 and 0.9 % anorexia nervosa is approximately ten times more common in females than in males (Bulik et al. 2005; Smink et al. 2012). The most obvious and striking feature of AN is a severe state of emaciation and malnourishment. As a result of chronic starvation patients are at risk for serious medical and metabolic complications that can affect virtually any body system. AN has the highest mortality rate of any psychiatric disease

with mortality rates ranging from 5 to 15 % (Attia 2010; Hoek 2006; Morris and Twaddle 2007).

The imaging and anatomic literatures suggest that dysfunction in emotional circuits contribute to AN, as well as subsequent related dysfunctions in reward, perception and body-homeostatic control. Evidence is also emerging that depression, anxiety and dysregulated emotional processing impede effective therapies and lead to worse clinical outcomes (Kaye and Bailer 2011; Kaye et al. 2009). Circuit models have linked AN symptoms to interconnected regions and structures, such as the parietal lobe, insula and SCC. DBS, by intervening in a critical node in the AN circuit, may influence both core pathology and the symptoms that impede effective treatment. For these reasons, DBS for treatment-refractory AN has been proposed.

There are several published case reports and series' investigating DBS in AN. Two case reports evaluated DBS of the SCC and NAcc in patients with comorbid AN/MDD and AN/OCD, respectively (Israel et al. 2010; McLaughlin et al. 2012). In both cases, long-term follow-up was associated with improvements in weight, and in the OCD case, improvements in anxiety. One case series evaluated NAcc DBS in four adolescent females with acute AN (average illness duration 18 m), and found at mean 38 m follow-up, a mean 65 % increase in body mass index (Wu et al. 2012). A pilot trial investigating SCC DBS in six patients with chronic, refractory AN showed that at 6–9 months follow-up, four patients were at BMIs significantly higher than baseline, with five patients showing significant improvements in mood and/or anxiety (Lipsman et al. 2013c). At 6 months, DBS was also associated with significant changes in cerebral glucose metabolism on PET scans compared to baseline, most notably showing a reversal of known parietal hypometabolism. With the psychometric results preceding changes in weight, such results suggest that DBS may be influencing the most common obstacles to enduring behaviour change in these patients. Additional, larger trials, utilizing sham stimulation control, are now required to validate these results.

13.5 Future Directions

The future of DBS in psychiatry will see both technical and conceptual advances. The former will see smaller, rechargeable batteries make the procedure safer and the clinical benefits longer lasting. Improved imaging will allow more accurate targeting, as advances in tractography will permit placement of stimulating electrodes at key junctional pathways that maximize the modulatory effect. One key area of interest will be elucidating biomarkers for psychiatric conditions as well as predictors of treatment response. Recent work in MDD has shown, for example, that glucose utilization patterns in the insula, can predict response to a first-line depression treatment (McGrath et al. 2013). Similarly, work done using EEG has shown that preoperative power in specific frequency bands can predict outcomes following SCC DBS in depression (Broadway et al. 2012). Such work can help elucidate the characteristics of patients that do and do not respond to stimulation. It may also be that in the future, emerging technologies such as radiofrequency-guided nanotechnology and focused ultrasound will obviate the need for cranial access (Lipsman et al. 2013b; Stanley et al. 2012).

The number of indications for DBS in psychiatry will also continue to expand. Changes in the Diagnostic and Statistical Manual (DSM), such as a shift away from categorical labels and towards classification of broad behaviours and cognitions, will help tailor treatments to specific dysfunctional circuits. Improving our understanding of the neural circuitry maintaining these disorders will help to further define the role of DBS in their management.

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