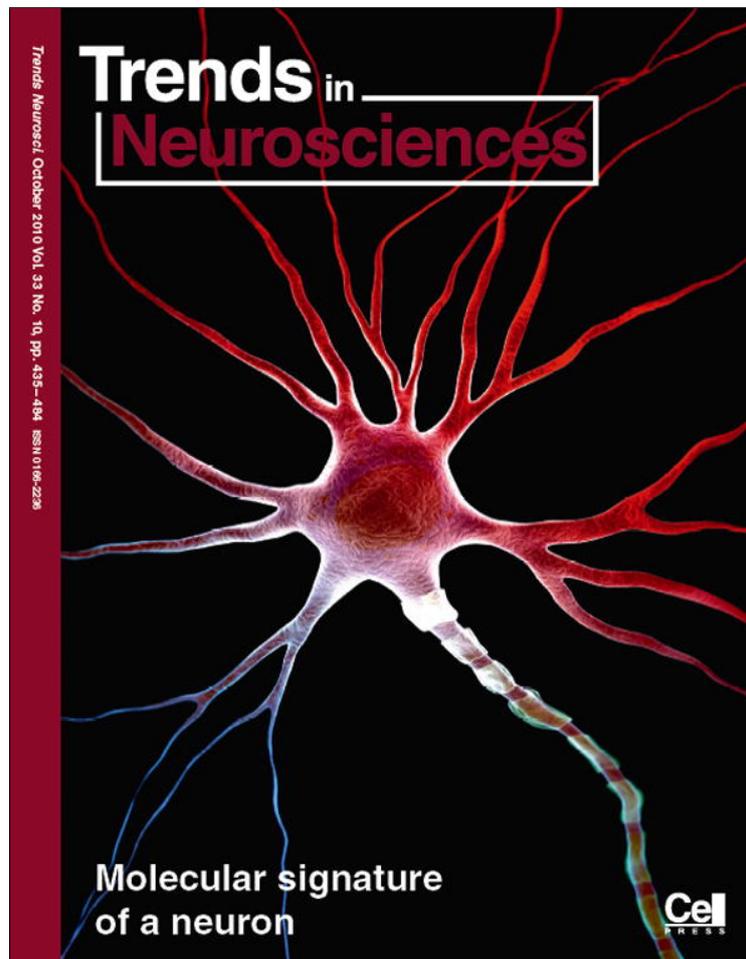


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Deep brain stimulation: from neurology to psychiatry?

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Functional stereotaxy was introduced in the late 1940s to reduce the morbidity of lobotomy in psychiatric disease by using more focal lesions. The advent of neuroleptics led to a drastic decline in psychosurgery for several decades. Functional stereotactic neurosurgery has recently been revitalized, starting with treatment of Parkinson's disease, in which deep brain stimulation (DBS) facilitates reversible focal neuromodulation of altered basal ganglia circuits. DBS is now being extended to treatment of neuropsychiatric conditions such as Gilles de la Tourette syndrome, obsessive-compulsive disorder, depression and addiction. In this review, we discuss the concept that dysfunction of motor, limbic and associative cortico-basal ganglia-thalamocortical loops underlies these various disorders, which might now be amenable to DBS treatment.

Introduction

Human stereotaxy was initially developed to treat psychiatric disease by targeting subcortical structures using circumscribed lesion or focal chronic electrical stimulation [1–6]. Owing to the demise of psychosurgery following the lobotomy era and abuses of early attempts at deep brain stimulation (DBS) techniques in psychiatric patients [7,8], and following the introduction of neuroleptic drugs, functional stereotaxy became limited to the treatment of Parkinson's disease (PD) and other movement disorders (torsion dystonia, action tremor). Such treatment mainly involved lesioning and occasionally DBS [9–12] of various thalamic subnuclei and basal ganglia structures (globus pallidus, subthalamic region).

Neuromodulation using DBS is a reversible method that re-emerged in the 1990s as a more lenient alternative to lesional surgery in advanced PD, especially in bilateral procedures and when targeting the subthalamic nucleus (STN). Choice of the STN as a target for PD arose from studies on the 1-methyl-4-phenyl-1,2,3,6-

tetrahydropyridine (MPTP) monkey model of PD, which showed increased neuronal activity in the STN [13] and marked amelioration of parkinsonian features following its lesion [14]. This antiparkinsonian effect could be reproduced with DBS of the STN in this model [15] and later in PD patients [16,17]. More recently, DBS has been introduced in the field of psychiatry to modulate neuronal activity in the same areas that were targeted for lesioning in the past [18,19]. Progress in functional neuroimaging and a better understanding of the pathophysiology of psychiatric disorders have contributed to renewed interest in surgical approaches to drug-resistant psychiatric diseases. In this regard, DBS offers several advantages. First, efficacy can be tested in randomized, double-blind, controlled clinical trials [20,21]. Second, DBS can be switched on and off, so that acute effects can be studied in humans [22,23]. Third, it can be coupled to functional neuroimaging studies [24,25]. Finally, implanted electrodes can be used to record neuronal activity within the brain while the patient performs cognitive, emotional or motor tasks [26]. Thus, DBS is not only a therapeutic technique, but also constitutes a powerful tool for the study of brain functions. In this review, we discuss how the observation of non-motor effects of DBS of the STN in both intact animals and parkinsonian patients contributed to the transfer of this technique to the treatment of psychiatric disorders. We propose that focal neuromodulation of corticobasal ganglia (BG)–thalamocortical loops involved in the control of behaviour and emotions might represent a new treatment option in psychiatry paralleling the effect of motor circuit modulation for the treatment of movement disorders.

Surgery for PD: lessons for psychiatry?

PD is both a motor and a neuropsychiatric illness [27]. Dopaminergic treatment reverses akinesia and apathy, but excessive and uncontrolled dopaminergic stimulation, as typically occurs in PD patients treated chronically with levodopa, can lead to motor, cognitive and emotional manifestations that are essentially the opposite of the

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Table 1. Mood, personality and behaviour in Parkinson's disease^a

Hypodopaminergic state	Hyperdopaminergic state
Parkinsonism, neuroleptics	L-Dopa, dopamine agonists
Motor loop	
Bradykinesia	Dyskinesia
Apathy (motor component)	Motor impulsivity
Associate loop	
Bradyphrenia	Cognitive impulsivity
Empty brain (absence of ideas)	Flight of ideas
Apathy (cognitive component)	Novelty seeking
Limbic loop	
Depression	Euphoria, mania
Apathy (emotional component)	Emotional impulsivity, behavioural addictions
Anhedonia	Hedonism, creativity, pleasure seeking
Anxiety, harm avoidance	Risk-taking behaviour
Drug withdrawal syndrome	Feeling 'on' or high

^aFor more details on the brain regions involved in the motor, associative and limbic loops, see Figure 1.

parkinsonian state (Table 1). Thus, the untreated and treated states of PD represent a model of opposite pathophysiological states linked to dysfunction in BG–thalamocortical loops (Figure 1) [28,29]. Different surgical targets exist for different parkinsonian signs (Table 2) [30,31]. For the purpose of this review, we focus on the STN, which has

become the main target, and DBS as the main surgical technique to improve motor symptoms and quality of life in PD [32,33]. In STN DBS for PD, the stimulating electrodes are aimed at the sensorimotor area of the STN to improve akinesia, rigidity and tremor. However, given the small volume of the STN (160 mm³ in humans) [34] and the tight intermingling and interactions of the different territories [35], diffusion of the electrical current to associative and limbic areas is common. Here, we review evidence indicating that diffusion of electricity to these areas [36] influences non-motor features of PD and can induce new behavioural or psychiatric symptoms.

The STN and impulsivity

In the 6-hydroxy-dopamine rat model of PD, lesion of the STN improved akinesia but induced impulsive behaviour [37], suggesting that STN manipulation could induce cognitive side effects. This finding led to studies investigating the role of STN in cognitive functions in the rat [38,39] in parallel with clinical studies assessing cognitive and non-motor functions in PD patients subjected to STN DBS [22,40–43]. An early imaging study of PD patients showed that STN DBS, performed during a motor task involving decision-making and motivational aspects, induced metabolic activation of the supplementary motor area, the dorsolateral prefrontal cortex and the anterior cingulate

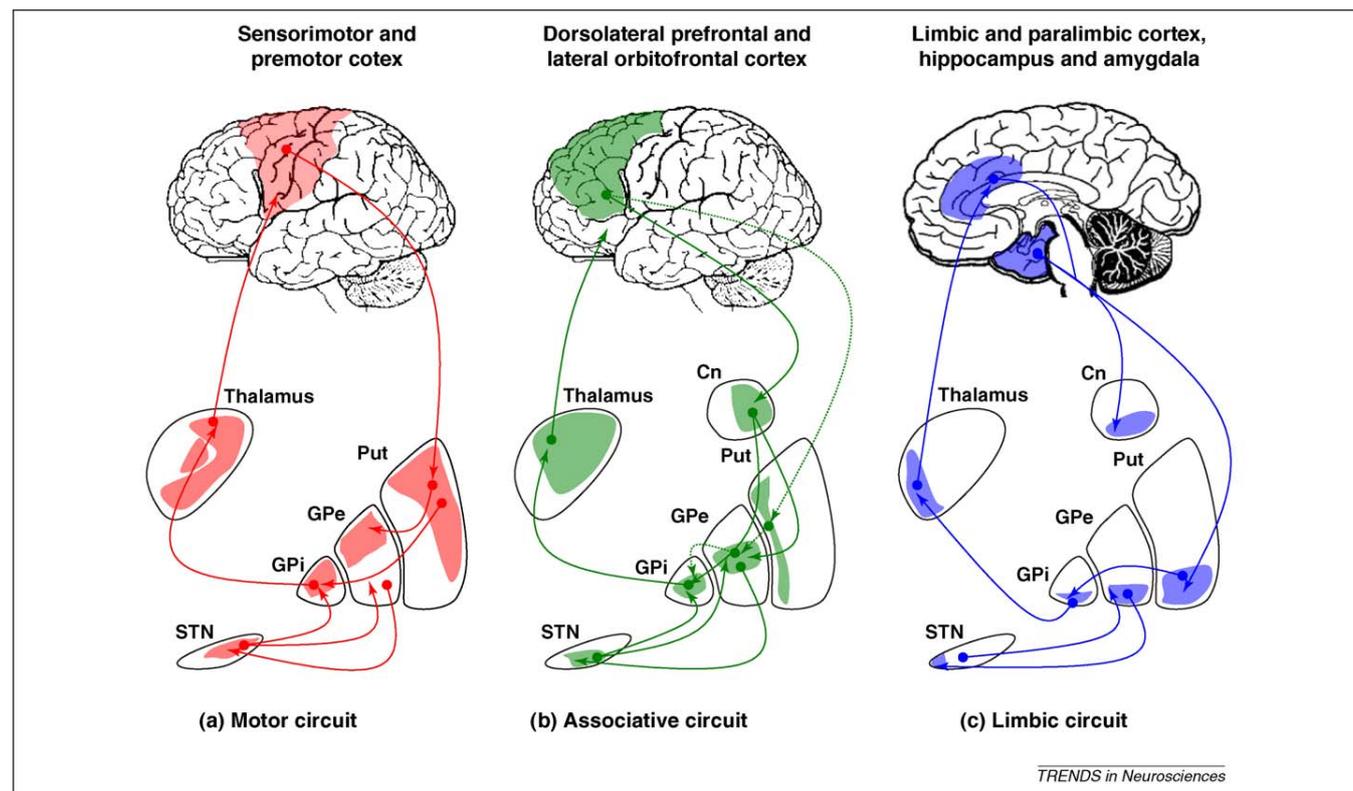


Figure 1. Schematic diagram illustrating the main cortico-basal ganglia–thalamocortical circuits within human brain. This figure shows a pseudo-anatomical arrangement of the motor, associative and limbic pathways. (a) Motor circuit. Neurons from the sensorimotor cortex project to the posterolateral putamen (Put). From the putamen there are two main projections topographically organized onto the posterolateral region of the target nuclei: (i) the direct circuit to the GPi and (ii) the indirect circuit connecting the posterior putamen to the globus pallidus pars externa (GPe), the STN and the GPi. The GPi is the primary output nucleus of the basal ganglia to the cortex via the ventrolateral thalamus. (b) Associative circuit. This circuit originates in the dorsolateral prefrontal and lateral orbitofrontal cortices, which project to the caudate nucleus (Cn) and anteromedial portion of the putamen. From the striatum (Cn + Put) it projects to the dorsomedial region of the GPi and anteromedial parts of the GPe and STN to converge onto the GPi and back to the cortex via the ventral anterior nuclei of the thalamus. (c) Limbic circuit. This loop starts in the hippocampus, amygdala and paralimbic and limbic cortices and projects to the ventral striatum (ventral portion of the caudate and putamen, including NAcc). The ventral striatum projects to the limbic portion of the GPe and medioventral STN and ventral GPi and to the cortex via the mediodorsal nucleus of the thalamus. Adapted, with permission, from Ref. [140].

Table 2. Interventions aimed at BG–thalamocortical loops in human patients^a

Neurological or psychiatric disorder	Cortex	Corticosubcortical projections	Basal ganglia	Basal ganglia projection	Thalamus
PD	Cortical stimulation, TMS, ECT	Pedunculotomy	Motor STN, motor GPi lesion or DBS	Ansotomy, zona incerta, subthalamic area (lesion or DBS)	Motor thalamus (Vim, Vop) lesion or DBS
OCD	Cingulotomy	Frontal leucotomy, anterior internal capsule lesion or DBS subcaudate tractotomy	Limbic STN DBS, NAcc, ventral striatum lesion or DBS	Inferior thalamic peduncle DBS	Medial thalamic lesion
GTS		Anterior internal capsule lesion or DBS	NAcc or GPi lesion or DBS (GPe or STN)	Lesions in subthalamic area or zona incerta	CMpf, Voi or dorsomedial thalamic nucleus lesion or DBS
Depression	Anterior or subgenual cingulotomy, ECT, TMS	Frontal leucotomy, subcaudate tractotomy, substantia innominata lesion, DBS of subgenual cingulate white matter close to Brodmann area 25	Ventral caudate or NAcc lesion or DBS; associative GPi-DBS	Lateral habenula DBS, inferior thalamic peduncle DBS	Medial thalamic lesion
Addiction	Anterior cingulotomy; insula ablation	Frontal leucotomy, substantia innominata lesion	NAcc lesion or DBS		

^aBeneficial outcome of interventional therapies aimed at different parts along these loops strongly argues in favour of the concept that these psychiatric disorders can indeed be conceived as being related to dysfunction of these loops. Abbreviations: ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation; GPe, globus pallidus externus; Vim, ventral intermediate thalamic nucleus; Vop, ventrooralis posterior thalamic nucleus. For reviews of ablative surgery in the field of psychiatry, see Refs. [99,111,112]. For further information, please refer to the main text and references within (as well Tables S1–S3 in the supplementary material online).

cortex [24]. This metabolic activation of cortical areas involved in motor, cognitive and motivational functions implies that STN DBS can affect all three functional loops.

Recordings of neuronal activity in PD patients and/or in animals have shown that the STN is involved not only in motor [44,45], but also in emotional [26] and motivational [46] processes. A classic paradigm for studying conflict is the Stroop word–colour interference task [47]. In this task, subjects are asked to indicate the typeface (ink) colour of a word that is also the name of a colour. When the ink colour and the word meaning are not the same, processing of the word meaning and the ink colour leads to different, incompatible responses, thereby slowing reaction times. This cognitive task requires both attention and impulse control. It activates the dorsolateral prefrontal cortex involved in conflict monitoring and the anterior cingulate cortex involved in conflict resolution [48]. Neuropsychological studies showed that switching on STN DBS speeded up responses in the Stroop task, but at the expense of an increase in self-recognized errors in the interference condition, which is compatible with increased impulsivity [40,49].

Case reports of PD patients with reversible changes in behaviour related to an acute increase in stimulation parameters comprise mirthful laughter [50], pathological crying [51], mania [25,52,53], aggressive behaviour [54] and acute dysphoria or depression [55,56]. Furthermore, STN DBS can contribute to certain impulsive behaviours during high-conflict decisions [57]. Functional imaging has revealed that the STN is involved in inhibition of an ongoing action [55]. It has also been suggested that modulation of STN hyperactivity on DBS might tend to favour the appearance of impulsive behaviour by acting on the gating mechanism involved in response initiation [56].

The STN and mood

Depression, apathy and anxiety can arise as complications after surgery [60–63] and rare cases of acute stimulation-induced depressed mood have been reported [57,58]. However, the vast majority of cases with an acute emotional response to STN DBS exhibit hypomania [50] or mania [25,52]. More importantly, a systematic study of a large number of PD patients revealed a mood effect of acute STN DBS that corresponds to subjective wellbeing or euphoria, and not depression [23,59]. Single case reports have also shown that dysphoria during the off-medication period is improved by STN DBS [60–62]. Accumulated data from the literature is confusing on first sight, because postoperative mood outcome is influenced not only by STN DBS itself, but also by a reduction in medication, occasionally leading to a dopamine withdrawal syndrome with increases in anxiety, apathy and depression [63,64]. A controlled study revealed that STN DBS improves anxiety in PD compared to the best medical treatment, with no changes in apathy or depression [42].

Mechanisms of action of DBS

Experience with DBS in PD patients indicates that the stimulation frequency is a key factor in determining clinical efficacy [65]. Stimulation starts to reduce tremor at a frequency of approximately 50 Hz and reaches a plateau at ~200 Hz. It is thought that low-frequency stimulation (LFS) activates neurons [66,67], whereas high-frequency stimulation (HFS) of the STN resulted in neuronal inhibition in experiments in the rat [68] and monkey [69], in agreement with observations in PD patients [70]. Thus, LFS and HFS can be used for neuromodulation with either activation or inhibition of neuronal networks. HFS also interferes with oscillatory activity (noisy signal

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hypothesis). The best-known example is the reduction of β band oscillation in the MPTP monkey model of PD [69] and in PD patients [71] on STN HFS. This suggests that the reduction in abnormally enhanced synchronization of basal ganglia output is an essential mechanism in the therapeutic effect of DBS in PD. By contrast, nucleus accumbens (NAcc) HFS increases rhythmicity in the cortex, which could be beneficial for the treatment of obsessive-compulsive disorder (OCD) and depression [72]. Other possible mechanisms of action for high-frequency DBS include local neuronal inhibition with concomitant activation of surrounding fibres, thus resulting in increased synaptic output [73] and activation of afferent axon terminals (e.g. the cortical inputs in the case of STN or NAcc HFS [73,74]; for a review, see [75]). The functional outcome of these complex putative mechanisms of action is uncertain and is probably variable, depending on the specific anatomophysiological arrangements of each target region.

The following observations should be considered to better understand the action of DBS: (i) HFS of sensory fibres or corticospinal motor fibres evokes continuous pain or muscle contractions [76] and (ii) the time course of the clinical effect of DBS differ, depending on the symptom targeted. Whereas the maximum beneficial effect on tremor and rigidity is reached within minutes, the delay for maximal improvement in akinesia is minutes to hours and the improvement in dystonia, OCD or depression gradually develops over several weeks [76–79]. It is thus possible that the latter cases are the result of plasticity changes in the

network affected by DBS, whereas the short-term improvements result from the immediate effect of DBS on the network. Finally, it is noteworthy that HFS mimics the outcome of a lesion in different target structures such as the STN, the internal segment of the globus pallidus (GPi), NAcc or white matter (anterior internal capsule or subgenual white matter). A hypothesis that takes into account all of these clinical observations is the hypothesis of jamming (i.e. overwriting of pathological activity by introducing a frequency that interferes with the pathological message), in line with the noisy signal hypothesis mentioned above.

DBS in psychiatry

Gilles de la Tourette syndrome

Gilles de la Tourette syndrome (GTS) is a neurodevelopmental disorder consisting of multiple motor and one or more vocal or phonic tics, with onset typically in early childhood. Comorbid neuropsychiatric symptoms occur in approximately 90% of patients; the most common of which are attention deficit hyperactivity disorder (ADHD) and OCD [80]. The ventral oral internus (Voi) and centromedial parafascicular (Cmpf) thalamic nuclei [18,81] were the first surgical target sites for stereotactic lesions performed in the 1970s. According to the literature, some 60 patients with GTS have been operated on, with stereotactic lesions targeting various thalamic regions, the subthalamic area, the cingulum and other parts of the limbic system and even the dentate nucleus [82]. The first target for DBS was also

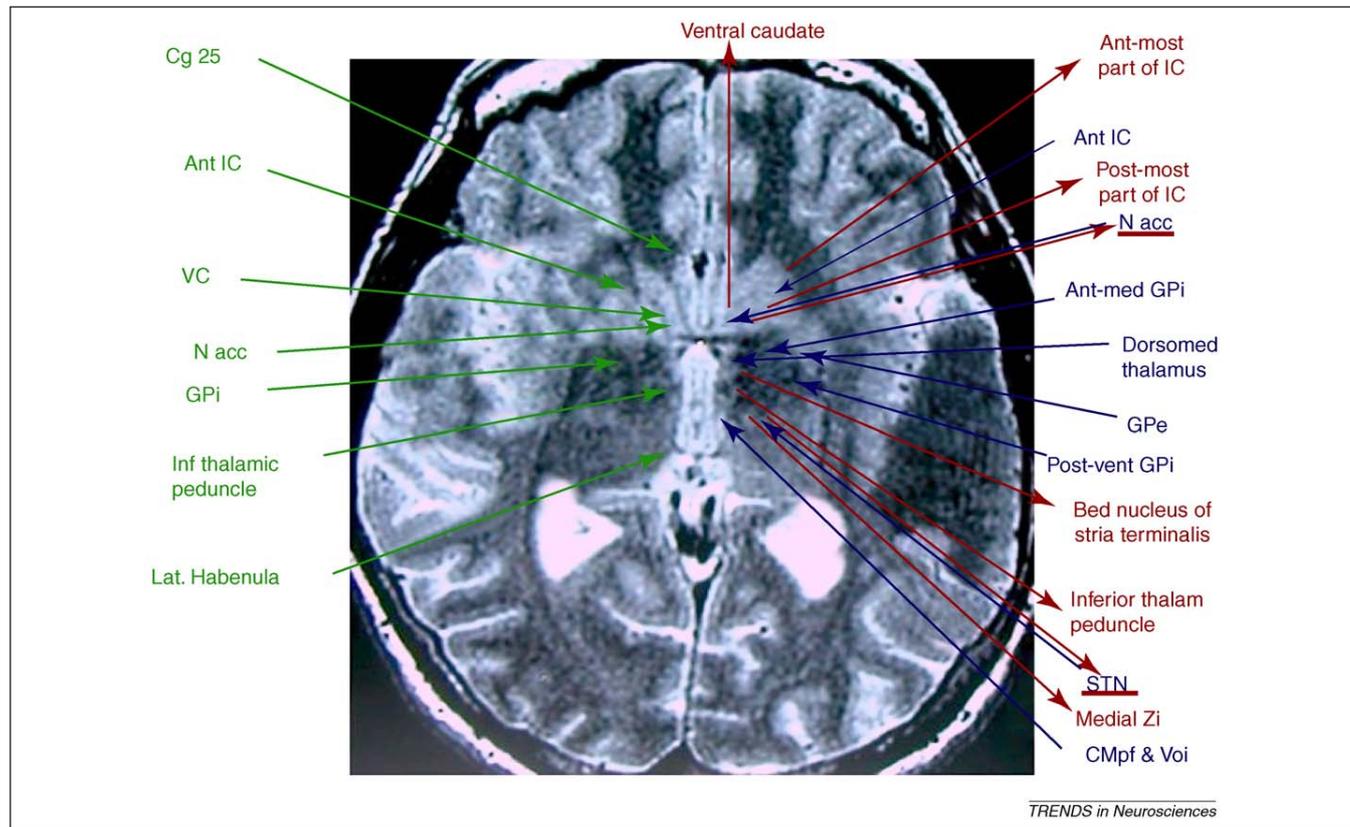


Figure 2. DBS targets for depression, OCD and GTS. Axial human brain magnetic resonance image (MRI) at the level of the anterior and posterior commissure showing the brain targets in which DBS has been applied to treat depression (green), OCD (red) and GTS (blue). Blue targets underlined in red are common to OCD and GTS. Cg 25, Brodmann area 25 of the subgenual cingulate cortex; Ant IC, anterior interior capsule (which can be targeted at its most anterior or most posterior part); GPi, globus pallidus internus; VC, ventral caudate; GPe, globus pallidus externus; Zi, zona incerta.

the thalamus in 1999 [18]. In the last 10 years, reports are available for some 50 patients treated with DBS applied to nine different brain targets (Figure 2, Table 2, Table S1 in the supplementary material online). The general rationale for modulating (or ablating) these areas is based on the assumption that tics and abnormal behaviour are associated with dysfunction of corticostriatal–thalamocortical circuitry involving frontal associative and limbic areas of the basal ganglia and thalamus (Table 2). Focal disruption of different functional striatal territories results in abnormal activation of neocortical motor and non-motor areas, producing repeated stereotypical movements and elaborated stereotypical behaviour, which supports the notion that both tics and OCD in GTS are related to BG–thalamocortical loop dysfunction [83–87]. Anecdotal improvements in GTS patients treated with DBS have been reported, but controlled studies currently include only very small numbers of patients [88,89]. Interpretation of results is complicated by a lack of adequate design and by uncontrolled variables, such as the electrical parameters for the current delivered to a particular brain region and how restricted the effect of DBS is for a given target (Figure 2, Table S1 in the supplementary material online). In addition, the phenotypic variability of GTS patients and various comorbidity patterns make it even more difficult to evaluate exactly what circuits should be modulated depending on the predominant clinical features. Despite all these confounding factors, results are encouraging regarding DBS of the CMpf [88] and anteromedial pallidum [89], and future studies are likely to clarify current uncertainties.

Obsessive–compulsive disorder

Severe OCD is characterized by intrusive anxious thoughts (obsessions) and repetitive ritualized behaviours (compulsions). It is one of the most disabling psychiatric disorders and has considerable repercussions on family relationships, social life and the ability to function at work [90]. Approximately 2% of the general population suffers from OCD [91] and 25–40% of patients are treatment-refractory [92]. Imaging studies of patients with OCD have revealed dysfunctional activity in the orbitofrontal and anterior cingulate cortex, the striatum and the thalamus. Hyperactivity in the orbitofrontal cortex correlates with the severity of OCD; it increases when OCD symptoms are present and decreases with successful medical or surgical treatment [93,94]. OCD has been called *folie du doute*, referring to pathological doubt. Typically, OCD patients suffer from pathological preoccupation with minute details. They feel that they have to get things just right and have to check to make sure. An imaging study revealed greater error-related activation of the rostral anterior cingulate [95], a structure involved in conflict resolution by top-down inhibition of the amygdala, where emotional conflict is generated [48]. Surgical ablation of the anterior cingulate, internal capsule, subcaudate tractotomy, rostral intralaminar and medial thalamic nuclei [96,97] can reduce OCD symptoms (Table 2). Taken together, these findings suggest that dysfunction of non-motor corticostriatal–thalamocortical loops occurs in OCD [96–98].

Historically, the first target for DBS in OCD was the white matter in the anterior limb of the internal capsule

based on therapeutic effects of ablative surgery (anterior capsulotomy) aimed at disrupting connexions between the prefrontal cortex and the dorsomedial thalamus [19,99–101]. Attempts to refine the optimal target for DBS have led to exploration of the NAcc, the ventral striatum and the bed nucleus of the stria terminalis (Figure 2) [101–103], with beneficial effects observed in all of these target regions (Table S2 in the supplementary material online). Serendipitous observations revealed that DBS in the STN had a beneficial effect on comorbid OCD symptoms in three PD patients [104,105]. This effect was the opposite to what would have been expected from animal experiments showing that STN inactivation led to impulse control disorder, which could be considered OCD-like behaviour [106]. The clinical observations in three PD patients prompted a crossover double-blind study of DBS in OCD that targeted the limbic-associative part of the STN [21]. In this trial, 16 patients were randomized and participated in two 3-month treatment phases, either active STN DBS or sham stimulation, separated by a washout period. The OCD severity was significantly lower after active STN DBS than after sham stimulation. Interestingly, STN DBS provoked reversible disinhibited behaviour that could be controlled by a decrease in stimulation intensity [21].

In OCD, switching from compulsive to normal behaviour is difficult or can become impossible because of recurrent obsessions. Unsuccessful resolution of an emotional conflict [48] is inhibiting or paralyzing to the patient, who can be in a frozen state similar to that of a PD patient with motor freezing. The mechanism of the improvement in OCD on STN DBS might be related to disinhibition that facilitates a switch from repetitive obsessive thoughts and obsessions to normal behaviour. This suggests that the inhibition of normal behaviour related to obsessions and compulsions on the one hand and impulsivity on the other might be on opposite sides of a behavioural spectrum. STN DBS in PD induces cognitive impulsivity, but at the same time improves cognitive flexibility [40,49] and speeds up decisions under high-conflict conditions [107], so we propose that cognitive–behavioural disinhibition might help in improving the incapacity to make a decision because of permanent doubt, which is a core feature of OCD. Although OCD seems as an area of high potential application of DBS, clinical trials are needed to reach conclusions regarding the best anatomical target site for this condition.

Refractory depression

Major depressive disorder is one of the most prevalent diseases, affecting 6.7% of the population annually [108] and 16.6% of people at some point in their life [91]. It is the leading cause of disability worldwide, as measured by years of life lived with a disability [109]. Some 20% of patients are refractory to the combination of behavioural, pharmacological and electroconvulsive therapy [110]. For these treatment-refractory patients, ablative stereotactic surgery has been proposed in the past, targeting limbic structures of the brain that are involved in the regulation of mood and affect. The classical targets for depression include the anterior cingulate cortex (cingulotomy), projections from the orbitofrontal and/or cingulate cortex to the basal ganglia and medial thalamus

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(capsulotomy, subcaudate tractotomy and lesions of the substantia innominata) or limbic leucotomy, which is a combination of cingulotomy and subcaudate tractotomy. The outcome of these surgical procedures suggested limbic dysfunction in depression (Table 2) [111,112]. More recently, functional imaging studies revealed decreases in metabolism in dorsal limbic (anterior and posterior cingulate) and neocortical regions (prefrontal, premotor, parietal cortex) and relative increases in ventral paralimbic areas (subgenual cingulate, anterior insula, hypothalamus and caudate) in depression. Based on these findings, a model of depression was proposed in which it was postulated that effective therapy requires inhibition of overactive ventral areas (including Brodmann area 25 in the subgenual cingulate cortex) with resulting disinhibition of underactive dorsal regions [113]. Integrity of the rostral cingulate, with its direct connections to these dorsal and ventral areas [113] and to the amygdala [48], also seems to be required for these adaptive responses. Based on this neurocircuitry model of depression, stimulation of the white matter in the subgenual cingulate cortex adjacent to Brodmann area 25 was tested in patients with treatment-refractory depression [79,114]. A positive clinical response was recorded in 60% of 20 patients at 6 months after surgery, and 35% met criteria for remission, benefits that were largely maintained at 12 months [114]. Furthermore, the antidepressant effect was associated with normalization of frontal brain metabolism, supporting the proposed model of depression [114]. Single case reports and open-label case series suggest that DBS of different targets located along a BG–thalamocortical loop (Table 2) is associated with antidepressant effects in depression (Table S3 in the supplementary material online, Figure 2). The most promising targets so far seem to be the subgenual cingulate cortex [79] and the ventral anterior limb of the internal capsule and/or the adjacent ventral striatum including the NAcc [78,115], with approximately 50% of subjects responding to

treatment. Although the internal capsule or ventral striatum target was chosen mainly based on experience with ablative surgery, the NAcc target was chosen based on theoretical considerations linking the NAcc to hedonic properties that are impaired in depression. It is important to note, however, that for improvements to be achieved, both these target areas require relatively high stimulation parameters. Furthermore, the stereotactic coordinates of the active electrodes used in both targets are identical in the internal capsule or ventral striatum [78] and the NAcc [115], indicating that the same target is probably involved (the NAcc is located within the ventral striatum).

Addiction

Drug addiction is a chronic relapsing disorder in which compulsive drug-seeking and drug-taking behaviour persists despite serious negative consequences. Lifetime prevalence of drug abuse is 8% in the US [91]. Addictive substances induce pleasant states (euphoria in the initiation phase) or relieve distress. Continued use induces adaptive changes in the central nervous system that lead to tolerance, physical dependence, sensitization, craving and relapse [116]. The neural basis of drug reward is linked to the mesocorticolimbic dopamine system (Box 1). All major drugs of abuse activate neuronal firing in the ventral tegmental area, resulting in increased extracellular dopamine concentrations in the NAcc shell, which causes the high or euphoria associated with drug-taking [117,118]. The drug craving that is critical for relapse after abstinence depends on the integrity of the NAcc core and its amygdala afferents [119]. Imaging studies point to a loss of control of the prefrontal cortex over the extended amygdala, attributing enhanced saliency to the drug of abuse and favouring the emergence of compulsive drug administration [117,118]. Compulsive behaviours, such as pathological gambling and binge eating leading to obesity, are also increasingly recognized and classified as behavioural addictions [120].

Box 1. Is DBS for drug addiction? Evidence based on animal studies

The neurobiological substrate of addiction has been extensively studied in animals [141]. Since the historical findings of Olds and Milner localizing reinforcing brain sites [142], the dopaminergic system (originating in the ventral tegmental area and innervating the NAcc and the prefrontal cortex) has been considered the key system for the biology of reward and motivation [143]. The dopaminergic system and the NAcc are involved in all forms of motivation, so one of the challenges in addiction treatment is to diminish or remove the motivation for the object of addiction without a general decrease in other forms of motivation. One interesting report showed that DBS of the NAcc shell could reduce cocaine reinstatement in rats with no effect on food reinstatement [144]; suggesting that DBS of this particular brain region could be an effective treatment strategy for cocaine addiction.

Although the STN has not been considered as an important structure in the context of motivation and addiction, animal data might provide support for reconsideration. It has been shown that bilateral lesions or DBS of the STN in rats can reduce the motivation for cocaine, but increase the motivation for food (without increasing food consumption) (Figure 1) [131,145]. These observations may position the STN as an interesting cerebral structure where dissociation between various forms of motivation could be made, especially since STN neurons are able to encode specific information regarding the value of the reward [46].

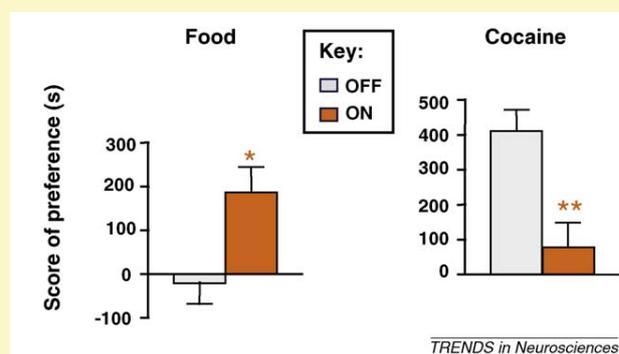


Figure 1. Effects of STN DBS on conditioned place preference for food (left) and for cocaine (right). In this test, animals are conditioned to associate an environment with a given reward (e.g. food or drug). A positive preference score indicates that the animals prefer to spend more time in the rewarding compared to the non-rewarding environment. The control rats with no DBS (OFF, grey bars) show no real preference for the environment paired with food, whereas the stimulated animals (ON, orange bars) show a significant preference for food. By contrast, whereas control animals exhibit a high score related to preference for the environment paired with cocaine, STN DBS reduces the preference for the cocaine-paired compartment. Differences between OFF and ON are significant (* $p < 0.05$, ** $p < 0.01$). Reproduced, with permission, from Ref. [131].

Functional stereotactic neurosurgery for addiction has been performed to ablate various brain areas of the limbic system, such as the anterior cingulum, substantia innominata and ventromedial hypothalamus [121]. More recently the NAcc, a critical structure of the reward system that is considered as the interface between motivation and action [122], was subjected to ablative surgery. In 28 opiate addicts, bilateral NAcc lesions reduced the quantity of drugs taken and drug cravings [123]. However, only 3 of the 17 patients with the longest follow-up (12–25 months) remained completely without relapse. Bilateral NAcc lesions were also induced in alcohol-dependent subjects. The severity of alcohol dependence and of alcohol cravings significantly decreased in this group. After a follow-up period of 6–27 months, only 2 of 12 patients had relapsed [124].

Fortuitous observations of improvements in alcoholism [125], nicotine [126–128] or food addiction [128] have been reported for patients treated with NAcc DBS for anxiety, OCD or GTS. Three patients were treated with NAcc DBS specifically for alcohol addiction. In all three patients, craving behaviour disappeared immediately after NAcc stimulation. Two of the patients remained completely abstinent in the 1-year follow-up period, and alcohol consumption was reduced considerably in the third patient [129,130].

Clearly, these few anecdotal reports on NAcc DBS for addiction in humans are very preliminary and caution is needed because the NAcc is involved in the general processing of reward, irrespective of the specific reward involved. Therefore, manipulation of the NAcc carries the risk of inducing anhedonia and an overall decrease in motivated behaviour. Interestingly, animal work has shown that STN DBS can treat cocaine addiction and craving in rats without diminishing the motivation for other more naturally rewarding activities (Box 1) [131]. In line with these findings, behavioural addictions and addiction to dopaminergic drugs in PD patients with a dopamine dysregulation syndrome can be improved by STN DBS, leading to marked decreases in dopaminergic medications [61–63].

Other indications

DBS is being investigated in a broad range of disorders such as chronic pain [132], epilepsy [133] and cluster headaches [134]. An interesting field of experimental clinical research relates to targeting a frontocortical–striatopallidal–thalamocortical mesocircuit that activates the frontal cortex, with the aim of improving consciousness, awareness or cognitive skills. HFS of the central thalamus [135] or LFS (activation) of the brainstem reticular formation in the pedunclopontine area [66] or the nucleus basalis Meynert [67] improved alertness and higher cognitive functions in single patients in blinded conditions. Aggressive behaviour related to schizophrenia or to mental retardation has been a classical indication for psychosurgery. Prefrontal leucotomy, amygdalotomy and lesions of the posteromedial hypothalamus have been effective in reducing aggressive behaviour [111,112,136]. DBS has been successfully applied to the posteromedial hypothalamus to treat aggressive behaviour in a few patients [137].

Conclusions

The main notion put forward here is that, just as in PD, in which dopamine depletion results in abnormal dysfunction of the motor circuit, psychiatric disorders such as GTS, OCD, depression and addiction are associated with dysfunction of non-motor cortical–BG loops. Thus, in the same manner as for movement disorders, surgery that targets the BG–thalamocortical loop can restore normal cortical activity associated with behavioural and mood disorders [24,114,138]. DBS for the treatment of psychiatric disease is compatible with the notion that neurological and psychiatric diseases share essential neurobiological mechanisms.

Although a better understanding of the biology of psychiatric disease is emerging, many patients with psychiatric disorders remain refractory to currently available medical and behavioural treatments. The limited application and success of DBS in psychiatry compared with its worldwide use for movement disorders is possibly related to a number of important factors. First, the pathophysiology of PD is better understood compared to psychiatric diseases. Furthermore, there are solid animal models providing a rationale for surgery in PD, whereas this is not the case for psychiatric illnesses. Second, the impact of surgery on motor symptoms is more predictable in PD and can be spectacular, with eradication of symptoms such as tremor, rigidity, levodopa-induced dyskinesias and dystonia. So far, DBS in psychiatry has been applied to a total of 17 brain targets in the treatment of GTS, OCD, depression and addiction. Although some reports of outcomes are encouraging, there has been no real breakthrough in terms of reliability and magnitude of the benefit. Third, surgery in PD addresses relatively simple and straightforward motor symptoms, whereas surgery in psychiatric illness targets rather complicated and multi-faceted mental symptoms with potential modification of personality, which raises ethical issues. Fourth, any surgery for a psychiatric illness is still overshadowed by the history of psychosurgery [7,139]. Therefore, applying DBS to the treatment of psychiatric diseases is inherently controversial, and will require not only well-founded scientific rationale, but also extreme caution and adherence to high ethical standards.

Finally, ethical issues need to be considered. DBS *per se*, notwithstanding its non-ablative character, is not

Box 2. Ethics and psychosurgery

“Model of a controlled trial: The basic problem of psychosurgery is psychiatric. Therefore, the initiative in considering surgical treatment must be taken by the psychiatrist. As soon as he is sure that conservative treatment by every available method cannot cure the patient, he should consult the neurosurgeon. Psychosurgery will remain experimental for years. Therefore, its use should be concentrated and restricted to psychosurgical research units having strong and intimate affiliation with scientists from many disciplines” – Lauri Laitinen [7].

Citation from Laitinen, who proposed a prospective randomized study to compare stereotactic surgery to the best psychiatric management, already 30 years ago [7]. In the same chapter, this pioneer functional neurosurgeon stated that it would even be possible to treat a patient with repeated stimulation without destroying tissue, showing that he was aware of the potential of DBS in surgical alleviation of psychiatric symptoms.

automatically ethical when applied to psychiatric illnesses. On the contrary, past history bears witness to the fact that DBS can be used for dubious aims and manipulations – rather than modulation– of brain circuitry in psychiatric patients and for questionable indications [7,8]. The ultimate aim of surgery for intractable psychiatric illnesses is the same as for neurological disorders: to improve the quality of life of patients and their families. This goal has mostly been reached in DBS for PD, tremor and dystonia, and surgery in disabling neurological disorders is an accepted treatment, despite surgical risks. DBS in psychiatry remains experimental and efforts need to be put into organizing controlled studies. However, this expanding and promising field requires ongoing input from, and interaction between, basic and clinical sciences (Box 2).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tins.2010.07.002](https://doi.org/10.1016/j.tins.2010.07.002).

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