Toward sophisiticated basal ganglia neuromodulation: review on basal gaglia deep brain stimulation

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Abstract

This review presents state-of-the-art knowledge about the roles of the basal ganglia (BG) in action-selection, cognition, and motivation, and how this knowledge has been used to improve deep brain stimulation (DBS) treatment of neurological and psychiatric disorders. Such pathological conditions include Parkinson's disease, Huntington's disease, Tourette syndrome, depression, and obsessive-compulsive disorder. The first section presents evidence supporting current hypotheses of how the cortico-BG circuitry works to select motor and emotional actions, and how defects in this circuitry can cause symptoms of the BG diseases. Emphasis is given to the role of striatal dopamine on motor performance, motivated behaviors and learning of procedural memories. Next, the use of cutting-edge electrochemical techniques in animal and human studies of BG functioning under normal and disease conditions is discussed. Finally, functional neuroimaging studies are reviewed; these works have shown the relationship between cortico-BG structures activated during DBS and improvement of disease symptoms.

Keywords

deep brain stimulation; striatum; subthalamic nucleus; globus pallidus; substantia nigra; electrochemistry; voltammetry; functional magnetic resonance imaging; pig; human

1. Introduction

Deep brain stimulation (DBS) of the basal ganglia (BG) is a well-established FDA-approved therapy for a variety of movement disorders such as Parkinson's disease (PD), essential tremor, and dystonia (Benabid, 1989, 1994, 2003, 2006; Lang and Lozano, 1998a). Additionally, it is an emerging therapy for several psychiatric and neurological conditions,

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including epilepsy, Tourette's syndrome (TS), major depression, and obsessive compulsive disorder (OCD) (Mayberg, 2005; Fisher et al., 2010). Despite its clinical success on these and other neurologic and psychiatric disorders, there is a limited understanding of the therapeutic mechanism behind DBS. In this review we discuss the current theories of DBS behind modulating BG dysfunction. Here, we explore current theories regarding BG dysfunction and the mechanisms underlying the associated motor deficit and neuropsychiatric symptoms in order to explore BG dysfunction improvement in response to DBS of cortico-BG targets.

A complete implanted DBS system consists of a pulse generator in the abdominal or infraclavicular region, which delivers the stimulation pulses via an intracerebrally implanted electrode. The stimulus is delivered via a clinical multi-contact electrode in which each contact is typically 1.5 mm in length and 1.27 mm in diameter (Godinho, 2006). The generator is connected to the electrode and battery powered. Stimulation parameters (pulse width, amplitude, frequency etc.) can be changed transdermally in order to optimize the therapeutic effects (Lyons, 2011).

There are several DBS targets within the basal ganglia (BG) that have been optimized to treat the aforementioned disorders. The subthalamic nucleus (STN) (Lyons, 2011 et al., 2006; Rodriguez-Oroz et al., 2005), internal part of the globus pallidum (GPi), or pedunculopontine tegmental nucleus (PPT) (Stefani et al., 2007) are shown to be effective in treating PD. To treat Huntington's disease and primary dystonia, GPi has been effectively targeted (Moreno et al., 2014; Vidailhet et al., 2013). The nucleus accumbens (NAc), cingulate cortex, and anterior limb of the internal capsule are targets to treat major depression (Kuhn et al., 2014; Schlaepfer et al., 2008; Lozano et al., 2008; Baker et al., 2007; Bewernick et al., 2010; Pandya et al., 2012). The anterior limb of the internal capsule is targeted to treat OCD (Greenberg et al., 2006). Finally, the internal capsule/NAc, centromedian/parafascicularis (CMPf) and the GPi are used to treat TS (Hariz and Robertson, 2010; Neuner et al., 2009; Saleh et al., 2012; Welter et al., 2008; Williams and Okun, 2013). Here, we will discuss the rationale and potential mechanism behind the effective treatment of the disorders associated with these BG DBS targets.

In this review, we explain how BG dysfunction is thought to give rise to an array of motor-related and neuropsychiatric disease states, and present the current theories surrounding how DBS of cortico-BG targets may lead to symptom relief. The BG has been proposed as a system to make selections: action-selection, reasoning/cognition related selections, and motivational state selections (Da Cunha et al., 2009, 2012; Redgrave et al., 2011). Understanding how the cortico-BG circuitry is suited for such computations is critical to understand how electrical stimulation of parts of this system can improve and/or motor and psychicatric functions. Here, we present new emerging theories pertaining to the diverse roles of the BG in action-selection, cognition, and motivation that support the notion that BG function is highly complex, and may therefore be sub-optimally controlled by simple continuous large area electrical stimulation. We go on to discuss potential avenues for increasing the sophistication of future BG neuromodulation techniques. Finally, we review new research approaches that may be critical to the development of such advances, including electrochemical monitoring of neurochemicals, functional neuroimaging, and new

large animal models of neuropsychiatric disorders. In summary, we emphasize that future research aimed at elucidating normal and pathological BG function, in combination with improved understanding of DBS mechanisms on a cellular and systems level, will open the door to more sophisticated and individualized DBS technologies.

2. BG cortico-thalamic loop

a. Circuits and connections

A growing body of evidence has shown that the BG forms a neural network dedicated to selection (Nicola, 2007; Redgrave et al., 2008, 2010; Da Cunha et al., 2009, 2012; Grillner et al., 2013). The strongest evidence is related to action-selection by the cortico-BG motor loop (Frank and Claus, 2006; Frank, 2011; Isoda and Hikosaka, 2011; Mink, 1996; Mogenson et al., 1980). In this loop, information from nearly all cortical and limbic subcortical areas flow into the BG input stations, including the dorsal striatum (Alexander et al., 1986) and STN (Nambu et al., 2002). The dorsal striatum also receives input from the thalamus (Parent and Hazrati, 1995a). More than 90% of the striatal neurons are GABAergic projection neurons named medium spiny neurons (MSNs) (Sesack and Grace, 2010). They compose two populations that make direct and indirect projections to the main output stations of the BG: the substantia nigra pars reticulata (SNr) and the GPi (Alexander et al., 1986). The external part of the globus pallidum (GPe) sends inhibitory projections to the SNr/GPi. Next, STN sends excitatory projections to the SNr/GPi (Alexander et al., 1986). The BG output stations (SNr/GPi) project mostly to motor areas of the thalamus (e.g., the ventrolateral thalamus), which in turn, project to motor areas of the neocortex (Alexander et al., 1986, Albin et al., 1989, Parent and Hazrati, 1995a,b). The inhibitory control of the BG over the thalamocortical neurons can be increased by the hyperdirect pathway formed by cortical projections that bypass the striatum by sending "hyperdirect" excitatory projections to the STN that stimulate the SNr/GPi (Nambu et al., 2002) (Figure 1). All BG nuclei are modulated by dopaminergic and GABAergic projections from the substantia nigra pars compacta (SNc), and by cholinergic, glutamatergic and, to a lesser extent, by GABAergic projections from the PPT (Parent and Hazrati, 1995b; Inglis and Winn, 1995).

b. Dopamine as the main modulator of the BG

In the dorsal striatum, both direct and indirect pathways are modulated by dopaminergic neurons. Dopamine (DA) is released in the dorsal and ventral striatum (which includes the NAc) by SNc and VTA neurons, respectively (Bjorklund and Dunnett, 2007). Population release of DA produces a slow time course of changes in extra-synaptic DA concentrations (Grace, 1991). Under this tonic release of DA, the extra-synaptic DA concentration in the striatum may be as low as 40 to 50 nanomolar (Sharp et al., 1986; Church et al., 1987). Short duration bursts of high-frequency firing of DA neurons cause transient increases in the extracellular DA concentration to micromolar levels, which have been labeled as phasic DA release. While changes in tonic DA do not seem to impact behavior, phasic DA is proposed to cause robust changes in behavior and to be involved in prediction-error encoding and reinforcement learning (Kuczenski and Segal, 1989; Kalivas and Duffy, 1990; Shultz, 1997).

DA receptors have been classified into two subtypes designated D1- and D2-like DA receptors (Richfield et al, 1989). Tonic levels of extracellular DA concentrations can activate high affinity D2 receptors. In contrast, phasic activity of DA neurons is needed to increase the extracellular DA to a concentration necessary to activate D1 receptors (Richfield et al, 1989; Grace 1995; Floresco et al., 2003). D1-like receptors (D1 and D5) stimulate Gs proteins; D2-like receptors (D2, D3 and D4) stimulate Go or Gi proteins (Neve et al. 2004). The result is stimulation or inhibition of the cyclic adenosine monophospate (cAMP) dependent protein kinase A (PKA) (Stoof and Kebabian 1984). PKA, in turn, phosphorylates voltage-dependent K^+ and Ca^{2+} channels, leading to changes in the resting potentials of pre- and post-synaptic membranes (Svenningsson et al. 2004). Although all five DA receptors are expressed in the striatum, D1 and D2 receptors are by far the most abundant (Surmeier et al. 1996). MSNs of the direct and indirect pathways (see Figure 1) express predominantly D1 and D2 DA receptors, respectively (Gerfen et al. 1990; Valjent et at al., 2009; Gertler et al., 2008; Hersch et al., 1995; Surmeier et al., 2007). D2 receptors are also expressed in the presynaptic terminals of nigral and VTA dopaminergic neurons (Benoit-Marand and Borrelli, 2001) and in the terminals of corticostriatal neurons (Wang and Pickel, 2002). As mentioned above, in the dorsal and ventral striatum, D1 and D2 receptors are mostly segregated into two populations of MSNs which send direct and indirect projections to the BG output stations (Robertson and Jian, 1995; Nicola, 2007). Although this has not been completely established, it has been proposed that MSNs in the NAc expressing predominantly D1 and D2 receptors are also segregated into two subpopulations of MSNs; both project to the ventral pallidum (the main output station of the ventral striatum) in a manner that might be equivalent to the direct and indirect pathways of the dorsal striatum (Nicola, 2007).

Striatal MSNs oscillate between the so-called down state (hyperpolarized) and up state (membrane potential closer to the depolarization threshold). MSNs fire in response to excitatory glutamatergic cortical and thalamic inputs only when they are in the up state and DA is released in a concentration enough to activate D1 receptors. Under these conditions activation of D1 receptors increase the likelihood of an MSN of the direct pathway to fire. In contrast, in the hyperpolarized down state activation of D1 receptors cause inhibition of MSNs (Flores-Barrera et al., 2011; for a review see Surmeier et al. 2011). This dual-condition mechanism probably works as a filter to increase the signal-to-noise ratio of corticostriatal neurotransmission. MSNs switch between down and up states depending on the activity of corticostriatal neurons. Stronger corticostriatal signals are supposed to encode relevant information for action-selection while weak signals are more likely to be irrelevant noise. This might increase the likelihood of the most proper action to be chosen by activation of specific MSNs. Activation of D2 receptors prevents the transition of MSNs from the down state to the up state (for a review see Surmeier et al., 2011).

3. Current theory of DBS on modulating BG dysfunction

a. DBS in Parkinson's disease (PD)

PD is one of the most common neurological movement disorders. It is characterized by a progressive loss of dopaminergic neurons in the SNc, leading to a massive reduction of

extracellular DA levels in the striatum (Lim and Lang, 2010; Wichmann and DeLong, 2011). This reduction prevents activation of both D1 and D2 dopaminergic post-synaptic receptors in the striatum that stimulate the direct and inhibit the indirect cortico-BG pathways. Thus, activity in the direct pathway is diminished and activity in the indirect pathway is increased (Alexander et al., 1986). High frequency neuronal discharges in GPi/SNr and STN and low frequency firing in the GPe are observed and this causes inhibition of motor nuclei in the thalamus (Bergman et al., 1994; Miller and DeLong, 1987; Soares et al., 2004; Wichmann et al., 1999) (Figure 2). The final result is the inhibition of movement initiation (akinesia) and increased inhibition of ongoing movements (muscular rigidity) (Okun, 2012).

DBS has grown considerably in the past decade as a therapeutic alternative for advanced PD and is considered an effective intervention to treat PD motor deficits (Wichmann and DeLong, 2011). The most common targets for this intervention include the motor portions of GPi or STN. In 2009, NIH COMPARE trial revealed no significant differences in STN or GPi DBS regarding motor deficit improvement (Williams and Okun, 2013). In addition, recent trials found comparable results for medication reduction, notably L-DOPA, in patients with STN or GPi DBS (Deuschl 2006; Okun 2012; Schuepbach et al., 2013; Odekerken et al., 2012; Follett, 2010). However, long-term cognitive problems have been reported in some STN DBS patients (Weaver, 2012). Hence, STN DBS is considered to be more suitable for patients with high dose medications and no significant cognitive deficits (Rodriguez-Oroz et al, 2004). GPi is a good target for patients with dyskinesia and/or preexisting cognitive issues (Williams and Okun, 2013). Thus, DBS in both STN and GPi significantly improves the quality of life for advanced PD patients, with consideration of psychiatric involvement, and is more effective than medication management (Weaver et al., 2009).

The mechanisms of action of DBS for motor improvement in PD patients are still unclear. In agreement with the hypothesis that DBS modulates neural activity, GPe and SNr neuronal firing records show that pathological low-frequency (~9 Hz) network oscillations are regularized by high-frequency STN DBS; and that neurons are entrained to fire at the stimulation frequency pattern (McConnel et al., 2012). In addition, STN DBS may inhibit STN neurons through activation of GABAergic neurons projecting from the GPe to directly activate axons of nearby neurons (McIntyre et al., 2004). Recent studies in rodents suggest that STN DBS influences cortical activity via antidromic activation of the hyperdirect pathway (Li et al., 2007; Gradinaru et al., 2009). In general terms, there are multiple putative mechanisms by which STN/GPi DBS may affect BG neural activity in a manner that improves PD motor deficits. DBS inhibits local neural firing while activating antidromic and orthodromic axonal conduction (Li et al., 2007; Dejean et al., 2009; Gradinaru et al., 2009). It alters concentrations of excitatory and inhibitory neurotransmitters, neural firing patterns, and may increase neurogenesis (Lee et al., 2009; Tye et al., 2009; Bourne et al., 2012). Thus, it appears that the multiple mechanisms of action of DBS in cortico-BG function culminate in the reinstatement of balance within BG connections (Wichmann and DeLong, 2011). One potential explanation for effective STN or GPi DBS is the idea that DBS normalizes inhibition from GPi to thalamus (Rubin et al., 2012).

A recent study investigated functional magnetic resonance imaging (fMRI) analysis of the effects of unilateral (single electrode) DBS of the STN and entopeduncular nucleus (EN), the non-primate analog of the primate GPi, in a normal large animal (swine). This study showed that STN and EN/GPi DBS significantly increased blood-oxygen-level dependent (BOLD) activation in the sensorimotor network (Min et al., 2012). Concomitant fMRI with DBS has also been described in rodents, revealing non-specific motor cortex BOLD increase (Lai et al., 2013; Younce et al., 2014). Finally, the network effects of DBS in nonhuman primates have been investigated, showing that STN DBS similarly increased BOLD activation in the sensorimotor cortex, supplementary motor area, caudate nucleus, PPT, cingulate, insular cortex and contralateral cerebellum. These results demonstrate that STN DBS evokes neural network grouping within the motor network and the BG (Min et al., 2014).

There is increasing evidence that DBS exerts both its therapeutic and adverse effects by modulating neural activity through anatomical and functional connections related to the target stimulation area and its surrounding structures (Chopra et al., 2011; Frankemolle et al., 2010; Kringelbach et al., 2007; Mallet et al., 2007; McIntyre and Hahn, 2010). The brain's dense wiring makes it challenging to characterize the effect of electrical stimulation on neuronal communication beyond a few synapses. Functional brain imaging has the advantage of providing global assessment of simultaneous neural activity. Much as we have found in swine and non-human primates, studies in PD patients during STN DBS show modulation of motor and non-motor areas including the primary sensorimotor cortex, premotor cortex, sensory motor area (SMA), dorsolateral prefrontal cortex, thalamus, BG, insular cortex and contralateral cerebellum (Asanuma et al., 2006; Grafton et al., 2006; Haslinger et al., 2003; Kahan et al., 2012; Phillips et al., 2006; Stefurak et al., 2003). Positron emission tomography (PET) studies have implicated parietal and temporal cortices classically defined as associative and limbic structures (Hershey et al., 2003; Le Jeune et al., 2010).

There are several clinical observations pointing toward an additional mechanism of action of STN DBS in PD involving the indirect activation of surviving nigrostriatal dopaminergic neurons. For example, STN DBS typically decreases or eliminates the need for L-Dopa (Moro et al., 1999; Molinuevo et al., 2000). It is most effective in PD patients who respond well to L-Dopa (Breit et al., 2004) and is contraindicated for those who do not respond to L-Dopa (Kern and Kumar, 2007). This suggests that therapeutic DBS requires endogenous DA production in the BG. DBS may even elicit dyskinesias that resemble those observed with increased L-Dopa dosage (Limousin et al., 1998) and impulsivity, a DA-related behavior (Frank et al., 2007). These clinical observations point toward the hypothesis that STN DBS may evoke DA release from surviving nigrostriatal dopaminergic neurons projecting to the BG to contribute to the therapeutic effects of STN DBS. They also elicit unwanted side effects when combined with inappropriately high doses of L-Dopa. Using *in vivo* electrochemical recording techniques, it has been shown that high-frequency stimulation of the STN is capable of evoking striatal DA release in the intact and 6-OHDA DA lesioned rat (Lee et al., 2006; Covey et al., 2008; Blaha et al., 2008). An important question for future investigation is whether STN DBS improves PD symptoms via the release of DA in the BG.

Another STN DBS mechanism may be stimulation-induced adenosine (ADO) release. This important, but understudied, endogenous neuromodulator is present in all cells and plays a role in the regulation of physiological activity in various tissues (Latini and Pedata, 2001). ADO has been shown to be released near the DBS electrode in the thalamus, and appears to be critical for tremor relief (Bekar et al., 2008). In the central nervous system, ADO regulates cerebral blood flow by signalling at A2A receptors, and to a lesser extent at A2B receptors (Cechova and Venton, 2008). As it is a product of ATP degradation, its release from cells is a sign of a high metabolic rate (Masino and Dulla, 2005). Thus, increases in extracellular ADO appear to match elevations in cerebral blood flow that result from increases in neural activity, directly amenable to measurement with fMRI (Phillips, 2004; Brundege and Dunwiddie, 1997). ADO A2A and DA D2 receptors are found on striatal GABAergic MSNs that comprise the indirect striatal output pathway, whereas ADO A1 and DA D1 receptors are found on GABAergic MSNs that form the direct striatal output pathway (Fredholm et al., 2005). In the striatum, cholinergic interneurons are one of the main sources of ADO (James and Richardson, 1993). Dopaminergic input from the SNc into the striatum inhibits the release of acetylcholine through D2 receptors and also stimulates its release through DA D1 receptors (Damsma et al., 1990; Bertorelli and Consolo, 1990). In this regard, it is of interest to note that at the circuit level, using fast scan cyclic voltammetry (FSCV) to measure ADO release several groups have demonstrated that high-frequency stimulation of the SNc elicits ADO release in the striatum of the rat and pig (Cechova and Venton, 2008; Shon et al., 2010a, 2010b).

Current DBS practice is based on the idea that high-frequency stimulation acts as a functional lesion by inhibiting or exciting specific brain regions. However, as our understanding of the mechanism behind DBS expands, we understand that there is substantial variability in its therapeutic effect. A recent study comparing pre- and postoperative diffusion tensor imaging in a PD patient undergoing bilateral STN DBS showed changes in structural connectivity before and after DBS. Using a computational model of spontaneous brain activity in this patient, van Hartevelt et al. found significant localized structural changes after long-term DBS in sensory-motor, prefrontal/limbic, and olfactory brain regions. This suggests that long-term DBS affects global structural and functional connectivity and changes in neural plasticity (van Hartevelt et al., 2014). Although our general understanding is improving, there are still large gaps of knowledge regarding neural plasticity changes from DBS in neurologic and neuropsychiatric disease.

b. DBS in Huntington's disease (HD)

HD is an autosomal dominant neurodegenerative disorder of striatal MSNs caused by the extensive repetition of the CAG sequence in the *huntingtin* gene (Sapp et al., 1997). The mutant form of the protein is responsible for dysfunctional cellular processes, such as gene transcription, protein trafficking, mitochondrial respiration, autophagy and calcium homeostasis (Eidelberg and Surmeier, 2011).

A predominant death of striatal MSNs in the indirect cortico-BG pathway is observed in HD (Reiner et al., 1988; Albin et al., 1989; Menalled et al., 2000; Raymond et al., 2011). Loss of this circuit leads to a condition where the 'break' provided by the indirect pathway is absent;

therefore, improper movements are no longer inhibited. This is proposed to be the cause of chorea, the main observed motor disability, characterized by spasmodic irregular movements in arms, legs, or in face muscles (Albin et al., 1990). Motor incoordination and cognitive deficits are also observed. In addition, other hyperkinetic (dystonia, myoclonia, tics) and hypokinetic dysfunctions (akinesia and muscular rigidity) are present. These motoric deficits are claimed to result from increased DA function in the early phase and decreased DA function in the late phase of HD (Raymond et al., 2011).

The preferential loss of indirect pathway MSNs reduces inhibitory GABAergic input to the GPe leading to an increase in GABAergic inhibition of the STN from the GPe. This inhibition is thought to lead to a decrease in STN glutamatergic excitatory drive on the GPi/SNr. In turn, GPi/SNr GABAergic inhibition of the thalamus is reduced, inducing an overflow of glutamate in motor areas of the cortex, and resultant hyperkinetic movements (Chevalier and Deniau, 1990; Raymond et al., 2011). Although much more is understood into the mechanism of DBS and PD, the documented increased firing rates in GPe and decreased firing rates in GPi observed in a HD patient strongly point toward a mechanism behind effective GPi DBS for motor deficits in HD patients (Figure 3) (Starr et al., 2008; Edwards et al., 2012).

c. DBS in obsessive compulsive disorder (OCD)

OCD is a type of anxiety disorder that happens when habits become compulsions. Obsessions are failures to inhibit invasive thoughts or images and compulsions are failures in inhibiting certain behaviors (Bourne et al., 2012). Disturbances in the cortico-BG limbic loop, especially the orbitofrontal cortex, anterior cingulate cortex, NAc, and mediodorsal thalamus have been reported (Bourne et al. 2012; Kopell and Greenberg, 2008).

Functional imaging studies report a significant dysfunction in the orbitofrontal cortex (Chamberlain et al., 2008) in OCD patients, whereby the orbitofrontal cortex and the basal ganglia are hyper-connected (Beucke et al., 2013). Distinct dysconnectivity has also been shown in the default mode network between the prefrontal cortex and BG (Anticevic et al., 2014). Additional studies investigating OCD in adolescent-patient populations has helped in disease prediction revealing that the caudate nucleus volume correlates significantly with the OCD symptoms in early adulthood (Bloch et al., 2005).

There is also a deficit of behavioral inhibition due to a misbalance between the direct and indirect BG pathways. Increase in the activity of the direct pathway, without the control of the indirect pathway, results in positive feedback where obsessive thoughts would permanently reverberate (Goodman et al., 2010) (Figure 4). Thus, abnormal activity in the amygdala and the hippocampus are linked to the anxiety generated by certain stimuli that often accompany the patient's urge to perform compulsive behaviors (Bourne et al., 2012; Koppel and Greenberg, 2008).

A number of DBS targets including the anterior limb of the internal capsule (Greenberg et al., 2006), ventral capsule/NAc (Do-Monte et al., 2013; Rodriguez-Romaguera et al., 2012), STN (Welter et al., 2011), and NAc (Denys et al., 2010) have been investigated for the treatment of OCD. DBS of the anterior limb of the internal capsule in OCD patients is

proposed to influence activity of the nearby NAc which, in turn, alters activity in other brain areas, predominantly in limbic areas of the cortex, BG and its projections to the thalamus (Nuttin et al., 2003; Rauch et al., 2006; Wichmann and DeLong, 2011; Okun et al., 2013). A double-blind cross-over study carried out by Denys et al. (2010) in which the NAc was targeted found a 25% improvement in OCD deficits and significant reductions in depression and anxiety. Interestingly, depression improved within seconds of stimulation, anxiety in minutes, obsessions in days and compulsions in months.

Some reports suggest that excessive connectivity between striatum and prefrontal cortex is normalized with NAc DBS (Figee et al., 2013, 2014). A relatively small number of clinical studies have investigated the efficacy of DBS for OCD. These do not permit a sufficiently detailed hypothesis of how DBS may work to improve OCD deficits. However, it has been proposed that the mechanisms of action behind the therapeutic effects of DBS in OCD result from a complex combination of effects on the cortico-BG circuit as proposed for the mechanisms of DBS in PD discussed above.

d. DBS in major depression

Major depression disorder is one of the most severe and prevalent neuropsychiatric disorders and the most common cause of disability. It is as debilitating as coronary heart disease and more debilitating as diabetes mellitus or arthritis (Prince et al., 2007). DBS might be of some help to treat the nearly 30% of major depression disorder patients who are unresponsive to traditional antidepressants, behavioral therapy, vagus nerve stimulation and electroconvulsive therapy (Rush et al., 2006). To date, there is no consensus on which brain regions are responsible for the major depression disorder deficits. However, ablation and imaging studies have indicated some structures that might be involved in the pathophysiology of the disease: the cingulate cortical area 25 (Dougherty et al., 2003; Mottaghy et al., 2002); the anterior limb of the internal capsule and the NAc (Malone et al., 2009; Hauptman et al., 2008); the inferior thalamic peduncle (Jimenez et al., 2005); and the lateral habenula (Sartorius et al., 2010). Improvement of depression deficits has been reported in patients receiving DBS in some of these brain areas. Decreased blood flow in the medial and frontal orbital areas and in the hypothalamus has been observed in major depression patients with DBS in cortical area 25 (Lozano et al., 2008). Stimulation of the anterior limb of the internal capsule has been shown to result in activational changes in the ipsilateral striatum, medial thalamus, anterior cingulate and contralateral cerebellum (Baker et al., 2007), while stimulation of the NAc decreased metabolism in orbitofrontal and dorsolateral prefrontal cortex and amygdala (Bewernick et al., 2010). Although the number of available up-to-date clinical studies is relatively small, it has been speculated that DBS of the targeted nuclei may lead to activation or deactivation of adjacent white matter projections in other cortical and subcortical areas involved in mood regulation, which includes the limbic loop of the BG (Pandya et al., 2012). Data from a recent fMRI study of NAc DBS in a large animal (swine) has shown alterations in the ipsilateral prefrontal cortex, insula, cingulate and bilateral parahippocampal gyrus along with a decreased BOLD signal in the ipsilateral dorsal region of the thalamus (Knight et al., 2013). This large animal model may offer a new and effective approach for identifying the cerebral nuclei and brain stuctures involved in DBS treatment of intractable drug-resistant depression.

e. DBS in Tourette syndrome (TS)

Tourette syndrome is a neuropsychiatric disorder with childhood onset that manifests itself in repetitive, stereotyped, involuntary movements and vocalizations called tics (Kuhn et al., 2011; Tye et al., 2009). These tics reach a peak in adolescence but tend to alleviate in adulthood (Wichmann and DeLong, 2011; Williams and Okun, 2013). Comorbidities can also be observed such as OCD, attention-deficit hyperactivity disorder, depression and psychosocial difficulties (Ludolph et al., 2012).

It has been postulated that an overactive thalamocortical system is responsible for TS deficits. However, the exact location within these pathways remains unclear (Singer and Minzer, 2003; Singer et al., 1993). Research has indicated that stimulation of various neural targets promotes amelioration of some of the deficits of Tourette syndrome, such as diminishing frequency of tics and improving comorbid psychiatric disorders. The main target areas proposed for DBS in TS are the thalamic centromedial/parafascicular nucleus (Savica et al., 2013), the motor and limbic portions of the GPi (Diederich et al., 2005; Ackermans et al., 2008), and the NAc (Kuhn et al., 2007).

A clinical study involving 18 refractory TS patients who underwent bilateral DBS in the thalamic centromedial/parafascicular nucleus reported decreased tics, self-injurious behaviors and anxiety (Servello et al. 2008). In this regard, a recent study investigating centromedial/parafascicular DBS in a large animal model supports that thalamic DBS has an inhibitory effect in regions that contribute to impaired sensory-motor and emotional processing (Kim et al., 2013). Only more recently the GPi has also been considered as a DBS target to treat Tourette syndrome. Some studies have shown great efficacy of GPi DBS in reducing motor tics and comorbid psychiatric deficits (Welter et al., 2008; Williams and Okun, 2013). Saleh et al. (2012) observed amelioration of hyperkinetic states in TS patients under GPi DBS. They proposed that this was a result of inhibition of thalamic neurons that project to motor areas of the cortex, as described in Figure 5.

4. Negative effects in DBS of the BG

DBS is an emerging treatment option to improve both motor disabilities and psychiatric symptoms observed in neuropsychological diseases, such as PD, OCD and depression. However, negative effects have been described following electrode implantation and/or after long-term stimulation which may directly worsen DBS outcome. Relative to pharmacological treatment, DBS is substantially more intrusive as is any surgical procedure where technical devices are implanted into the brain. Moreover, these devices are constantly active and may differentially affect brains regions as the disease progresses and the overall structure of the brain changes (Whoopen et al., 2013). Hence, DBS negative side effects may result from procedure-related complications, hardware implant and/or stimulation-related issues (Martinez-Ramires et al., 2014).

a. STN DBS and GPi DBS side effects in PD patients

Stimulation of the motor portions of the STN and GPi has near equivalent benefits in improving parkinsonian symptoms of PD patients. The site for DBS is therefore chosen based on clinical aspects, such as the intention to reduce medication intake (STN DBS) or

preexistence of dyskinesia or cognitive symptoms (GPi DBS), and the incidence of negative side effects associated to the stimulation of each of these targets (Williams and Okun, 2013). The most commom procedure-related complications found for STN and GPi DBS are psychiatric side effects, such as confusion and delirium. Moreover, these symptoms appear more prevalent in patients with STN DBS than GPi DBS (Videnovic and Metman, 2008). Also, surgical-site pain, low-risk intracerebral hemorrhaging (1–2%), and 10% risk of infection associated with the surgery or with the device have been reported for DBS regardless of the targeted nucleus (Weaver et al., 2010).

In a randomized controlled trial conducted by Weaver and co-workers (2010), patients undergoing DBS surgical intervention had a 3.8 times higher risk of experiencing serious side effects than patients on medical therapy. However, these serious side effects were resolved in 99% of cases by 6 months follow-up. They also reported other serious side effects that were device-related, such as lead migration and defective lead wire, and stimulation-related, such as delusions and hallucinations (Weaver et al., 2010).

Stimulation of the STN may produce weight-gain (Deuschl et al., 2006; Videnovic and Metman, 2008), cognitive side effects (e.g., reduced verbal fluency and deficits in executive functions) (Stefurak et al., 2003; Funkiewiez et al., 2004; Parsons et al., 2006), and psychiatric symptoms, such as depression (with suicide attempts or completed suicide), mania, anxiety and apathy (Bejjani et al., 1999; Stefurak et al., 2003; Funkiewiez et al., 2004; Anderson et al., 2005; Borgohaim et al., 2012). Adverse motor symptoms are also observed during STN stimulation adjustment or after long-term STN stimulation and include induction of paresthesias, severe dysarthria (Rodrigues-Oroz et al., 2004, Okun et al., 2013), and other parkinsonian-like effects, such as bradykinesia, rigidity, swallowing difficulties and worsening of gait or speech (Anderson et al., 2005).

GPi DBS presents relatively insignificant neuropsychiatric impairments compared to STN DBS (Borgohain et al., 2012). This is likely due to the more extensive separation of motor and non-motor functions in the GPi relative to the STN (Wichmann and DeLong, 2011). However, weigth gain, gait ignition failure, dysarthria (Videnovic and Metman, 2008), and mild visual field defects have been reported (Anderson et al., 2005). The apparent better "risk-benefit" of GPi DBS may lead this structure to be the preferred target to treat PD in the future.

b. GPi DBS side effects in HD patients

Stimulation of the GPi has been used to treat motoric symptoms in HD patients based on improvement of choreic dyskinesias of PD patients under GPi DBS (Anderson et al., 2005; Weaver et al., 2010). Although this improvement has been substantially observed, bradykinesia can be aggravated by GPi DBS depending on the stimulation frequency (Spielberger et al., 2012; Cislaghi et al., 2013; Gruber et al., 2014; Moro et al., 2004). Other motoric symptoms occasionally exacerbated in HD patients under GPi DBS are gait disturbance and dystonia of the feet (Gruber et al., 2014). Impairments in cognition (decline in executive functions and working memory) have been described, but they are likely related to disease progression, rather than from GPi stimulation solely (Fasano et al., 2008; Kang et al., 2010; Gruber et al., 2014). There are relatively few clinical data about the effects of GPi

DBS in HD and critical parameters such as patient selection criteria and stimulation settings need to be carefully considered (Chen et al., 2013).

c. Limbic targets - DBS side effects in OCD, depression and TS patients

Stimulation of limbic targets, such as the anterior limb of the internal capsule/ventral striatum, the NAc, the ventral NST and limbic portions of the GPi, has improved psychiatric symptoms of compulsion, obsession, depression, anxiety, and motor and vocal tics (Wichmann and DeLong, 2011). Nevertheless, DBS of the anterior limb of the internal capsule and the NAc have been shown to produce forgetfulness and word-finding difficulties (Mallet et al., 2008; Denys et al., 2010; Greenberg et al., 2013). In addition, several other psychiatric symptoms such as mania, fear, irritability, and anger may result from this DBS therapy (Shapira et al., 2006; Denys et al., 2010; Haq et al., 2010). Furthermore, the occurrence of suicidal feelings has been reported in some some patients with anxiety and depression under DBS treatment (Greenberg et al., 2013; Williams and Okun, 2013).

5. Emerging theories in BG mechanism

a. Role of the BG motor loop in action-selection

MSNs of the direct pathway are proposed to be in position to select actions encoded in the motor cortex, while MSNs of the indirect pathway can inhibit improper (e.g., concurrent) actions. A clear means of understanding this process is by the cortico-BG circuitry backwards:

i. Actions are encoded in motor areas of the cortex that include the area M1, the premotor cortex, and the supplementary motor cortex.

ii. Cortical neurons encoding an action are selectively activated by neurons of the motor thalamus.

iii. Thalamic neurons are under tonic inhibition of GABAergic neurons of the BG output stations, providing a distinct selective threshold prior to activation (e.g., the SNr/GPi).

iv. In order to trigger the onset of this action, selective striatal MSNs of the direct pathway disinhibit the thalamic neurons that project to the cortical neurons. At the same time, firing rates of a large number of MSNs of the indirect pathway and neurons of the hyperdirect pathway increase inhibition of the SNr/GPi on the other thalamocortical neurons, thus preventing initiation of the not selected actions.

Fundamentally, BG connectivity literature supports the model where activation of the direct pathway facilitates movements and activation of the hyperdirect and indirect pathways prevents movement (Nambu, 2011, Obeso et al., 2013). However, although there is extensive evidence that action-selection depends on the cortico-BG loop, such evidence is still insufficient to clearly support that action selection occurs as proposed above.

i. It is largely unknown how motor actions are encoded in motor areas of the cortex. Recent evidence suggests that it is not as simple as the selective control of all

muscles or joint movements as represented in Penfield's functional maps. Instead, it has been proposed that broader areas of the motor cortex encode stereotyped behaviors such as defensive movements of the arms or purposeful actions such as pointing to and reaching for a specific place (Schieber, 2001, Capaday et al., 2013).

ii. Tracing (Asanuma et al., 1983; Holsapple et al., 1991; Flaherty and Graybiel, 1993) and probabilistic tractography (Hyam et al., 2012) evidence have consistently shown that neurons of the motor thalamus (e.g., central anterior/ventrolateral thalamus) receive hyperdepolarizing inputs from GPi neurons (Hoover and Strick, 1993) and send projections that can activate motor areas of the cortex (primary motor cortex, premotor cortex, and supplementary motor area). Unitary cell recording studies in awake behaving monkeys show thalamocortical neurons presenting direction-related sustained change in activity during cue-guided motor action (Kurata, 2005), and before the onset of self-generated movements (van Donkelaar et al., 1999). This suggests that these neurons play a role in initiation and execution preparation of instructed and spontaneous motor actions. Studies have also revealed that the nucleus ventralis lateralis, pars oralis (VLo) which is a part of the motor thalamus that receives projections from the BG, is the thalamic region presenting the highest percentage of neurons responding to active movements and that these neurons are organized in a somatotopic manner (Vitek et al., 1994,1996). In addition, it has been shown that electrical microstimulation of the motor thalamus evokes movements in the contralateral limbs, trunk or face. Nearly 20% of the VLo neurons evoked movements when stimulated (Vitek et al., 1996). These findings are coherent with the hypothesis that activation of a subset of striato-thalamic neurons can selectively trigger motor actions carried out by specific body parts.

iii. The general model of the direct and indirect pathways controlling movement vs. non-movement predicts that when an animal is at rest the GPi/SNr neurons fire tonically at a high rate and that they decrease their activity just before a movement starts. It has been shown that in most monkeys GPi neurons present firing rates which vary from 20–140 spikes/sec (Filion and Temblay, 1991; Miller and DeLong, 1987); most of the time they present firing rates of approximately 60–80 spikes/sec (Delong, 1971; De long et al., 1985). A study by Oviedo et al. (2008) showed that electrical stimulation or infusion of glutamate into the dorsal striatum of rats produced a significant spike rate reduction in pallidal neurons. However, studies did not confirm the prediction that GPi neurons present a pause before the onset of a motor action. Instead, these studies have shown that most pallidal neurons alter their firing rate after the action was selected, i.e., after the firing rates of neurons in the primary motor cortex and supplementary motor area are increased (Crutcher and Alexander, 1990). In addition, most GPi neurons increased firing rate at movement onset (for a review see Goldberg and Bergman, 2011). This might be due to a subset of GPi neurons that pause to select a specific action while the majority increases firing to prevent concurrent actions. Indeed, most of the studies have shown movement related to decreased activity in a subpopulation of GPi neurons (Georgopoulos et al., 1983; Mitchell et al., 1987; Anderson and Horak,

1985; Turner and Anderson, 1997). Although less frequent, these studies report that a few GPi neurons fired before the movement onset. However, more problematic to the action-selection hypothesis is the finding that after inactivation of the GPi, as in pallidotomy or GPi DBS treatment of patients with Parkinson's disease, Huntington disease, or Tourette syndrome, patients maintain the ability to avoid improper actions (Turner and Desmurget, 2010).

iv. The Alexander et al. (1986) and Albin et al. (1989) general model of the BG circuitry predicts that activation of the direct (D1+) or indirect (D2+) pathway facilitates or inhibits movement, respectively. Such predictions have been confirmed by several approaches. In a study by Kravitz et al. (2010) optogenetic control of MSNs of the direct and indirect pathways of mice expressing Cre recombinase under control of regulatory elements for the DA D1 and D2 receptor was achieved through Cre-dependent viral expression of channelrhodopsin-2 (ChR2) in the striatum. Bilateral activation of the indirect pathway resulted in increased freezing, bradykinesia and decreased initiation of locomotor episodes. This picture is also seen in PD patients and in animal models of PD (DeLong, 1990). These motor deficits result from decreased striatal DA and, consequently, reduced activation of the direct pathway and reduced inhibition of the indirect pathway by D1 and D2 DA receptors, respectively. Conversely, optogenetic activation of direct pathway MSNs increased locomotion and rescued deficits in freezing, bradykinesia and akinesia in D2-Cre mice pre-treated with 6-OHDA (Kravitz et al., 2010). Coherently, unilateral activation of D2 receptors in hemiparkinsonian rats caused misbalanced locomotor activation in the contralateral side of the body causing turning behavior (Da Cunha et al., 2008; Dombrowki et al., 2010; Kravitz et al., 2010).

It is currently recognized that other important connections exist making the BG connectivity more complex than initially proposed. First, it is now understood that cortical neurons synapse onto not only the MSNs but also onto GABAergic interneurons in the striatum. Second, MSNs of the direct pathway are known to have branching collateral fibers that terminate in the GPe. Third, in addition to the striatum, cortical and subcortical inputs target the STN, which is now recognized as another important input station of the BG (see above hyperdirect pathway). Fourth, it is now recognized that the GPe projects not only to the STN but also sends branched collaterals to the GPi, SNr and SNc. Finally, instead of parallel cortico-BG loops, the striatum is now acknowledged to integrate functionally diverse information derived from cortex and subcortical areas (Bolam et al., 2000; Nambu et al., 2000; Miwa et al., 2001; Jaeger and Kita, 2011; Obeso et al., 2013; Surmeier, 2013; Ullsperger et al., 2014; Woolley et al., 2014).

There are, however, emerging pieces of evidence that challenge the general view that activation of the direct pathway promotes movement and activation of the indirect pathway inhibits movement. Contrary to this model, bilateral ablations of the main output station, the GPi, are not detrimental but rather therapeutic to action-selection in BG diseases such as PD and dystonia. Critics of the action-selection hypothesis for the BG function have been taking

this as evidence that the BG plays a role for the motor cortex areas responsible for action-selection (Turner and Desmurget, 2010).

The general model based on movement/non-movement mediated by the direct/indirect pathways has also been challenged by recent optogenetic studies and by studies based on optical fiber recordings. These studies have shown that while specific motor actions are carried out, both the direct and the indirect pathways are activated concomitantly (e.g., Cui et al., 2013).

Based on evidence that some MSNs of the primate putamen and rodent dorsolateral striatum are activated by sensory and motor stimulation of the same body part and that they increase their firing when an object projects to that body part (see below), it has been proposed in the mosaic of broken mirrors model (MBMM) that some MSNs can trigger movement of specific body parts towards specific objects and other MSNs can initiate locomotion to specific places (Figure 6) (Da Cunha et al., 2009). This means that all neurons of the direct or indirect pathway do not act as a switch between movement and non-movement. Rather, the MBMM considers that these neurons form an action-selection mechanism with a great number of channels, each being able to start or prevent specific actions. While interpreting the above-mentioned data under the logic of the MBMM, it is important to note that it does not predict activation of most MSNs of the direct pathway at the onset of a motor action as the general model of the BG does (Alexander et al., 1986). Instead, the MBMM predicts that selection of a motor action depends on activation of a few specific MSNs of the direct pathway, and inhibition of the few MSNs of the indirect pathway that inhibits that specific action. It also requires activation of a large number of MSNs of the indirect pathway that inhibit initiation of the concurrent actions. Such predictions are difficult to be tested because they require recording the activation of only a few neurons of the direct pathway among a huge population of the remaining neurons that remain silent.

Though collecting this type of evidence is difficult, there is some evidence that supports the MBMM. Optogenetic studies investigating D1-Cre and D2-Cre mice expressing ChR2 in the dorsolateral striatum showed that unilateral activation of D1+ MSNs at a decision-making point in a nose-poke reinforcement-learning task shifted the response toward the contralateral side while activation of D2+ MSNs shifted the response toward the ipsilateral side (Tai et al., 2012). Without activation the same mice presented right/left responses according to their previous reward history. These findings are in agreement with the MBMM in that selective MSNs of the direct pathway can trigger motor actions directed to specific places. An additional study revealed that stimulation of D1+ MSNs in the dorsomedial striatum promoted place preference, while stimulation of D2+ MSNs did not promote place preference or aversion (Kravitz et al., 2012).

A more recent study by Cui et al. (2013) challenged the general BG model prediction that the MSNs of the direct pathway are active just before movement initiation and the MSNs of the indirect pathway are active when movement stops. They used Cre-dependent viral expression of a calcium indicator in the dorsal striatum of D1-Cre and A2A-Cre to monitor neural activity in MSNs of the direct and indirect pathways, respectively. Time-correlated single-photon counting registered transient increases in activity of both direct and indirect

pathways just before initiation and with motor action. These results can be explained by the MBMM as reflecting the activation of a few MSNs of the direct pathway to choose and initiate motor action and activation of the MSNs of the indirect pathway to prevent the initiation of concurrent actions.

The MBMM is also supported by evidence correlating activation of MSNs in response to the approach and/or object touch in nonhuman primates (Graziano and Gross, 1993) and rats (West et al., 1990; Carelli and West, 1991). The same studies showed correlation between the firing of specific MSNs of the nonhuman primate putamen or the rat dorsolateral striatum and passive or self-generated movements of specific body parts.

Causal correlations between activation of MSNs in the dorsal striatum and motor action onset have been provided by old studies showing that electrical microstimulation in different regions of the nonhuman primate putamen evokes movement of specific body parts (Alexander and De Long, 1985a,b). These studies also suggest redundancy in the representation of body parts in the striatum as proposed by the MBMM, because they showed that stimulation at different depths of the putamen evoked movement of the same body part, as if MSNs encoding the same body part were organized in columns. The main problem with this evidence is that it does not discard the alternative explanation that such movements resulted from antidromic stimulation of the motor cortex neurons that project to the striatum. The same cannot be said about the evidence provided by Pisa (1988) showing that neurotoxic lesions of the rat lateral striatum caused severe and chronic impairment of tongue and forelimb reach movements.

b. Roles of the BG associative and limbic loops in cognition and affect

In addition to motor control regulation through the motor loop, the BG is also involved in some non-motor aspects of behavior (Leisman, 2014). There are other loops connecting cortical areas to function-related regions in the BG. More specifically, these loops involve the prefrontal and limbic cortices through which the BG is thought to play a role in cognitive and emotional function, respectively (Yin and Knowlton, 2006). The cortico-BG associative loop originates in the dorsolateral prefrontal cortex and projects to the head of the caudate nucleus and to the rostral part of the putamen anterior to the anterior commissure. This prefrontal territory in the striatum projects to the rostral GPe, to the dorsal parts of the caudal GPe and GPi, and to the rostromedial SNr. Projections from these structures have their terminals in the ventral anterior and medial dorsal thalamic nuclei, which in turn project back to the dorsolateral prefrontal cortex (Alexander et al., 1986; Voorn et al., 2004, Nambu, 2011, Leisman et al., 2014). This associative loop is implicated in "executive functions" that include attention, spatial orientation and in cognitive "working memory" tasks (Cagliori et al., 2013).

The selection of an action, among many possibilities stored along the frontal cortex, would be driven by the goal and/or by an intentional signal represented by prefrontal cortex projections to the striatum (Caligiori et al., 2013; Thill et al., 2013). Within the BG circuitry, information originating from various sources is somatotopically filtered and supported by prefrontal cortex signals in a way to properly select the correct action. Damage to areas forming this associative loop is associated with a variety of behavioral abnormalities related

to these cognitive functions, such as attention-deficit and hyperactivity disorder, OCD, schizophrenia and autism (Leisman et al., 2014).

The limbic loop has its origin in the pre-limbic, infra-limbic and lateral orbitofrontal cortices, along with the hippocampus and subcortical amygdala. Projections from these structures reach the ventromedial caudate nucleus, including the NAc, and the ventromedial part of the pre-commissural putamen. The ventral pallidum, the rostral part of GPe and the medial GPi/SNr receive those striatal projections and, in turn, project to the paramedian portion of the medial dorsal nucleus of the thalamus and then back to the limbic regions in the cortex (Haber et al., 1990; Ono et al., 2000; Nakano et al., 2000; Nambu, 2011).

Connectivity between the hippocampus and the NAc also provide some support for the MBMM hypothesis that "place-to-go" cells might exist in the NAc. The NAc receives afferents from the hippocampal formation, a region implicated in mapping the animal's location and in spatial memory (Groenewegen et al., 1987; van Groen and Wyss, 1990; Witter et al., 1990). In addition, the NAc receives a dopaminergic projection from the ventral tegmental area (VTA) which is known to carry information about motivational value and salience (Bromberg-Martin et al., 2010). Furthermore, the NAc projects to mesencephalic areas related to locomotor functions (Voorn et al., 2004). These connections put the NAc in a strategic position to select places to go based on expected outcomes (Redish and Touretzky, 1997).

The NAc is modulated by DA and is known as the main brain system that integrates emotional and cognitive information into behavioral actions known as motivated behaviors (Berridge and Robinson, 1998; Ono et al., 2000). In general, the limbic loop is involved in the selection of final reward-guided goals based on motivational aspects of the stimuli. Apathy, irritability, social and emotional inability, and lack of empathy are some of the symptoms present in neuropsychiatric disorders associated with damage to areas in the limbic loop, such as OCD and depression (Leisman et al., 2014).

The functionality of each of the three cortico-BG loops is given by a hierarchically-based flow of information according to their respective roles in the action-selection process (Yin and Knowlton, 2006). The sensorimotor loop controls motor actions oriented by decisions made in the current context of the animal. Associative loop-driven decisions are guided by motivational aspects of reward processed by the limbic loop. At the highest level, the NAc, enriched with motivational value information provided by other subcortical structures (e.g., amygdala, hippocampus), helps the limbic and the associative cortex to select the more biologically relevant goals. At the lowest level, the dorsolateral striatum selects the more adequate motor action encoded in the pre-motor and primary motor cortices (Haber et al., 2000; Cagliori et al., 2013). Such selection depends critically on DA alterations in the striatum as reviewed below.

c. Role of NAc DA in motivation

DA release in the NAc is related to motivation and drive states. It has been shown that high-arousal states are induced by DA release in the NAc shell/olfactory tubercle (Ikemoto and Panksepp, 1999; Hebb, 1955; Ikemoto, 2002, 2007). This state is particularly important to

an organism's survival because it promotes approach and avoidance behaviors to unconditioned stimuli (US) and conditioned stimuli (CS) (see section 4.d), depending on the reward or aversive nature of the stimulus (Parkinson et al., 1999). Such affective and drive states of mind/body interaction modulated by the NAc DA are referred to as "action-arousal." The limbic system supplies midbrain DA neurons with information about environmental stimuli that are important for self-preservation and procreation; this effects DA release in the NAc in a manner that motivates or "energizes" actions related to self-preservation (e.g., eating, drinking, mating, hiding from predators) (MacLean, 1990; Ikemoto, 2007). This DA system is sensitized by regulatory imbalances, such as hunger, and activated when animals detect incentive stimuli (Ikemoto, 2007). Another important function of DA release in the NAc shell/olfactory tubercle is acquisition and consolidation of stimulus-outcome associations (CS-US). When DA is released in the NAc core and lateral parts of the NAc shell/olfactory tubercle, the organism selects previously learned behaviors through CS-US associations (Ikemoto, 2007).

d. Role of striatal DA in associative learning

Subjects' motor behaviors are driven by changes in unconditioned responses (URs) to biologically relevant stimuli (i.e., USs such as food, sex, and painful or dangerous situations). Motor behavior is also driven by expectations about appetitive and aversive outcomes (USs) based on prediction cues (i.e., CSs). The predictive value of different CSs is learned through classic (Pavlovian) conditioning (Pavlov, 1927; Rescorla, 1988; Li et al., 2014). In addition, behavior is also driven by habitual (automatic) responses to neutral stimuli and by goal-directed actions, both learned through instrumental (operant) conditioning (Yin and Knowlton, 2006; Domjan, 2010). During instrumental conditioning learned under appetitive motivation, early responding appears to be goal-directed and slowly progresses to habitual responding (Mishkin et al., 1982; Knowlton et al. 1996; Packard and Knowlton, 2002). Conversely, during extinction (when a response is no longer rewarded), goal-directed responding of appetitive motivated actions rapidly fade while habitual responses persist for a relatively longer time (Devan and White, 1999; Yin et al., 2006; Balleine and O'Doherty, 2010).

An action is considered to be goal-directed if it is sensitive to outcome devaluation; for example, by pre-feeding the animal (Dickinson and Balleine, 1994). In contrast, stimulus-response (S-R) habits are considered to be insensitive to outcome devaluation, being performed not with an intended goal but as an automatic response to a stimulus that precedes the response's outcome (Yin et al., 2008). Therefore, the memory traces of habits are the S-R associations, meaning that, after a habit is acquired, the motor response is automatically triggered by the neutral stimulus, independent of the outcome. In contrast, the memory traces of goal-directed actions are the action-outcome (A-O) associations, meaning that goal-directed actions are selected based on expectation of a rewarding (e.g., appetitive) outcome (Dickinson and Balleine, 1994). Another relevant element in selection of motor responses is related to interaction between classical and instrumental conditioning. This association activates an emotional state that motivates the instrumental behavior where the emotional state is assumed to be either positive or negative in valence, depending on the hedonic property of the US. Conditioned cues that predict relevant stimuli can greatly

enhance instrumental responding. This process is known as Pavlovian-to-instrumental transfer (PIT) (Lovibond, 1983). PIT is highly influenced by DA activity (Dickinson et al., 2000; Wyvell and Berridge, 2000; Niv et al., 2006; Belin et al., 2009).

There is also compelling evidence that the striatum and other regions of the BG play a role in reward-motivated action selection learning (Schultz et al., 1997; Alderson et al., 2004; Yin et al., 2004, 2006; Da Cunha et al., 2009; Wilson at al., 2009; Haber and Knutson, 2010; Redgrave et al., 2010; Flagel et al., 2011; Da Cunha et al., 2012; Dezfouli and Balleine, 2012; Kravitz et al., 2012; Liljeholm and O'Doherty, 2012). In addition, the striatum and the other regions play a role in learning how to select responses instrumental to avoid aversive stimuli (Wadenberg et al., 2010; La Lumiere et al., 2005; Manago et al., 2009; Darvas et al., 2011; Dombrowski et al., 2013; Wendler et al., 2014). Striatal DA also plays a key role in associative learning (Schultz, 1997; Da Cunha et al., 2009; Niv, 2006; Bromberg-Martin et al., 2010; Da Cunha et al., 2012; Fiorillo et al., 2013; Schultz, 2013; Lak et al., 2014).

Strong evidence exists that acquisition of S-R and action-outcome (A-O) memory traces depend on strengthening synapses between cortical or limbic neurons with MSNs. These cortical neurons encode the stimulus or the outcome and the striatal MSNs trigger the proper motor response/motor action. Furthermore, many studies suggest that selection of USs occurs in the medial NAc shell, CRs in the NAc core, S-R habits in the dorsolateral striatum (putamen in primates), and goal-directed actions in the dorsomedial striatum (head of caudate nucleus in primates) (Wendler et al., 2014; for a review see Ikemoto 2007; Da Cunha et al., 2012). Subregions of the dorsal striatum and NAc are also known to play different roles in learning appetitive-motivated actions (Yin et al., 2004; Yin and Knowlton, 2006; Yin et al., 2006; Redgrave et al., 2010; Dezfouli and Balleine, 2012).

The dorsomedial striatum (DMS) and the dorsolateral striatum (DLS) of rodents are thought to be necessary for selection of goal-directed and S-R habits learned under appetitive reinforcement (Yin et al., 2006; Ikemoto, 2007). Although this is well established for appetitive motivated learning, it is not clear whether the same striatal regions play equivalent roles in aversively-motivated learning. There is also evidence that the NA core plays a role in Pavlovian conditioning (Riedel et al., 1997; Ikemoto and Panksepp, 1999; Berridge, 2012; Bossert et al., 2012; Klucken et al., 2012), but there is some uncertainty about the specific roles the NAc core and other limbic structures have in Pavlovian conditioning (for a review see Da Cunha et al., 2012).

Potentiation of corticostriatal synapses depends on three events happenning concomitantly: depolarization of the pre- and post-synaptic membranes of the involved neurons and phasic release of DA (for review see Da Cunha et al., 2009). Phasic release of DA is evoked by appetitive USs that are better than expected (positive prediction error), CSs that are predictive of appetitive USs and salient stimuli independent of their rewarding or aversive nature (Ramnani et al., 2004; Schultz, 2007; Bromberg-Martin et al., 2010; Berridge, 2012). Phasic DA drops in extracellular DA concentrations happen when something rewarding does not occur as expected and when something less rewarding than expected happens (negative prediction error) (Schultz et al., 1998; Tobler et al., 2003). Different subpopulations of midbrain DA neurons respond to aversive stimuli with phasic increases or phasic decreases

in DA release, respectively (Ljungberg et al., 1992; Mirenowicz and Schultz, 1996; Matsumoto and Hikosaka, 2009; Brischoux, et al., 2009; Budygin et al., 2012; Ilango et al., 2014). This supports the view that actions or responses to neutral stimuli that result in better than expected outcomes promote phasic release of DA that, in turn, strengthens the S-R and response outcome (R-O) memory traces. This increases the likelihood that a response will be selected as a result of coming in contact with the same stimulus or that an action will be selected. In contrast, phasic decrease of DA release is known to weaken the synapses between the cortical and striatal neurons encoding S-R and A-O associations. This drives avoidance behaviors in situations in which the same stimulus is presented or the subject wants to avoid an aversive outcome (for review see Da Cunha et al., 2009, 2012).

Strong evidence supports the view that activation of DA neurons in the VTA is critical for associative appetitive learning (Cheng et al., 2003; Nicola et al., 2005; Day et al., 2007; Ikemoto, 2007; Berridge and Kringelbach, 2013; Ouachikh et al., 2013; Steinberg et al., 2013;) Moreover, it has been shown that not only VTA, but also SNc DA neurons are implicated in unconditioned and conditioned responses to appetitive stimuli. Mice bar-press to stimulate either SNc DA neurons (Rossi et al., 2013) or dorsal striatum neurons expressing D1 receptors (Kravitz et al., 2012). This suggests that DA release in the dorsal striatum has reinforcing properties. A recent study presented strong evidence that DA neurons of the SNc are as critical to appetitive and aversive associative learning as the DA neurons of the VTA (Ilango et al., 2014). The latter study showed that optogenetic activation of DA neurons of the SNc sustains conditioned-place preference.

Aversive-driven learning has also been shown to depend on striatal DA. Optogenetic inactivation of DA neurons in the SNc or VTA induces conditioned-place aversion (Ilango and et al, 2014). Studies have demonstrated impaired conditioned-avoidance learning in rats with SNc lesions induced by MPTP (Da Cunha et al., 2001; Gevaerd et al., 2001a, b; Perry et al., 2004; Bortolanza et al., 2010) or 6-OHDA (Cooper et al., 1973) and in rats with dorsal striatum lesions (Wendler et al., 2014), dorsal striatum DA depletion (Rane and King, 2011), and intra-dorsolateral striatum infusion of D1 (Wietzikoski et al., 2012) and D2 DA receptor antagonists (Boschen et al., 2011). A recent microdialysis study by Dombrowski et al. (2013) found that during conditioned-avoidance learning, DA release in the striatum increased only in the first trials in which rats avoided footshocks but not after they had learned the task. However, no alteration in DA release was observed when the footshocks were presented in an unpredictable, unavoidable and inescapable manner. In contrast, MPTP-lesioned rats did not learn the task. Another recent study showed that inactivation of the tyrosine hydroxylase gene in the dorsal striatum, and consequent lack of DA synthesis, impaired the ability of mice to learn conditioned-avoidance responses (Darvas et al., 2011). Impairment in rats with these SNc lesions has also been observed in the cued- and working-memory version of the Morris Water maze (Bellissimo et al., 2004; Da Cunha et al., 2001; Ferro et al., 2005; Miyoshi et al., 2002).

The understanding that striatal DA is involved not only in motor control, but also in action-selection, learning and memory, and affective states is critical to explain and treat the non-motor symptoms of BG diseases such as PD (Conte et al., 2010), drug addiction (Rovinson et al., 2009; Wanat et al., 2009), bipolar disorder (Cousins et al., 2009), schizophrenia

(Carlsson et al., 2004), and attention deficit/hyperactive disorder (Del Campo et al., 2011), obsessive-compulsive disorder and Tourette syndrome. Deficits in aversive-driven learning related to the inability of striatal DA to encode negative-prediction errors may also explain why depression and gambling is much more prevalent in PD (Rosa et al., 2013).

6. New approaches for BG-DBS research

a. Electrophysiological signal as a feedback for DBS

The DBS field has advanced at a rapid pace and supporting technology to improve current use has evolved with it. Advanced DBS systems such as those that rely on real-time feedback from electrophysiological signals, provide the first generation of implantable devices that identify symptomatic and healthy brain states (Gunduz et al., 2014). These devices include the Medtronic Activa PC+S (Ryapolova-Webb et al., 2014) and Neuroscan RNS (Sun et al., 2008). With the understanding that changes in neuronal firing frequency occur in a pathogenic state, this approach shows potential in many disorders that are currently treated with DBS (Gunduz et al., 2014). Exaggerated beta band (8–35 Hz) synchrony in STN local field potentials occurs in PD patients, which is attenuated during therapeutic DBS, and returns when stimulation stops (Bronte-Stewart et al, 2009 Kuhn, 2008). Other studies have shown beta activity in the motor cortex (Whitmer et al., 2012), and phase-amplitude coupling (PAC) between beta and high gamma (>70 Hz), observed in PD, are also potential targets for closed-loop DBS (de Hemptinne et al., 2013). Electrophysiological measurements may also hold promise in DBS for the treatment of psychiatric disorders. For example, symptom provocation in the setting of OCD has been correlated with increased low frequency (2–5 Hz) activity over the frontal cortex (Pogarell et al., 2006), and DBS of the ventral striatum has been shown to attenuate these low frequency oscillations (Figee et al., 2013).

Although electrophysiological feedback is a promising modality for a closed-loop DBS device, it is important to acknowledge potential pitfalls as well. DBS has been shown to decrease beta synchrony in PD patients, but this has also been demonstrated during voluntary movements and during tremor. Despite its association with PD, PAC occurs during rest and also with voluntary movement (Miller et al., 2012; de Hemptinne et al., 2013). Additionally, frontal low frequency oscillations, while implicated in OCD, are correlated with normal goal-directed behavior (Knyazev, 2007). Preliminary trials will demonstrate the efficacy of these first generation neural stimulation feedback devices, which may provide direction in development of future generations of closed-loop DBS systems (Gunduz et al., 2014).

b. Electrochemical methods to determine neural circuitry underlying DBS

The use of *in vivo* electrochemical methods to investigate the neural circuitry underlying DBS makes it possible to circumvent the assumptions that are necessary with the use of alternative methods. The electrochemical procedures FSCV and fixed potential amperometry (FPA) offer the best temporal resolution of all *in vivo* electrochemical methods to date (5–10 samples/sec for FSCV; 10K samples/sec for FPA) (Kimble et al., 2009; Venton et al., 2002).

In Figure 7, FPA in combination with CFMs permitted quantitative detection of striatal DA overflow (efflux) evoked by electrical stimulation of excitatory inputs to DA cells in the SNc, such as those originating in the hindbrain PPT (Forster and Blaha, 2003). Overflow of a synaptic transmitter is referred to as "release" throughout this section. Dommett et al. (2005) have shown that FPA can be used to monitor striatal DA release in response to natural stimuli, such as light pulses. Visual stimuli evoked increases in striatal DA release via a direct input to the superior colliculus from the retina that, in turn, activated midbrain dopaminergic cells at a short latency. Collectively, these studies have confirmed the utility of fast electrochemical recording procedures to measure DA transmission driven by *polysynaptic* pathways, such as those we have proposed to mediate DBS-evoked DA neurotransmission (Lee et al., 2006, 2009; Shah et al., 2010).

With respect to quantifying glutamate release using FPA, recent development of enzyme-coated platinum microelectrodes based on work by Hu et al. (1994) have shown a high degree of reliability as a selective, sensitive and rapidly responding glutamate sensor *in vivo* (Wilson and Gifford, 2005). This glutamate sensor system provides an additional quantitative measure of potential glutamatergic transmission in the dorsal striatal complex circuitry interfacing with SNc DA cells. Our preliminary studies have shown that electrical stimulation can evoke frequency- and intensity-dependent increases in glutamate release recorded locally at the site of stimulation (STN) using these procedures (Figure 7B–E).

In agreement with the hypothesis that STN DBS improves motor symptoms of PD by striatal DA release, several animal studies have shown that STN DBS increases striatal DA levels. For example, *in vivo* microdialysis studies have shown that STN DBS increases the striatal DA metabolites (DOPAC and HVA) and tyrosine hydroxylase activity in normal and 6-OHDA lesioned rats (Meissner et al., 2001, 2002, 2003; Paul et al., 2000). With one exception (Bruet et al., 2001), STN DBS-evoked increases in striatal DA dialysate could not be detected without first inhibiting DA reuptake with nomifensine and stimulating for prolonged durations (20 mins) (Meissner et al., 2003). *In vivo* monitoring of slow (min-hrs) changes in DA release is easily accomplished using these conventional microdialysis techniques. However, analysis of more rapid changes in DA release in the absence of DA reuptake inhibition that may result from STN DBS requires an equally rapid 'real-time' detection and monitoring system, such as FSCV and FPA. For detection, sensitive carbon-fiber microelectrodes (CFM) and enzymatic sensors used with these methods permit submicromolar monitoring of central DA and glutamate release. As such, to establish the functional characteristics of the dorsal striatal complex circuitry, we have utilized electrochemical recording procedures established for reliable monitoring of DA and glutamate release and reuptake in dopaminergic and glutamatergic terminal sites in the brain *in vivo* (Blaha and Phillips, 1996; Michael and Wightman, 1999; Suaud-Chagny, 2004; Wilson and Gifford, 2005).

Our neurochemical studies have focused on determining the functional consequences of STN DBS in terms of rapid changes in striatal DA release elicited by relatively brief and prolonged electrical stimulation of the STN in the urethane anesthetized rat. Brief STN stimulation (15 pulses at 300 μA and 50 Hz) resulted in a stimulus time-locked increase in striatal DA release as measured by FPA in combination with CFMs (Figure 8). The

selectivity of the recording microelectrode to STN stimulation-evoked DA release was confirmed by systemic injection of the DA reuptake inhibitor nomifensine, which resulted in a significant increase in DA oxidation current, compared to serotonin (fluoxetine) and noradrenaline (desipramine) reuptake inhibitors, which did not alter the STN stimulation-evoked striatal response (Lee et al., 2006). These results support the hypothesis that STN DBS results in quantifiable striatal DA release. However, as these studies were performed in rats with intact SNc dopaminergic neurons, it is crucial to perform systematic measurements in an animal model of PD, such as 6-OHDA lesions, where the SNc neurons are selectively and partially destroyed.

In relation to an animal model of PD, our preliminary results have shown that, in combination with L-DOPA, repetitive stimulations in 6-OHDA lesioned rat are capable of facilitating DA release to levels comparable to that seen with stimulation in intact rats and are consistent with recent findings that high-frequency stimulations modulate the action of L-DOPA (Oueslati et al., 2007). Microinfusion of the neurotoxin 6-OHDA onto DA cell bodies in the SNc resulted in the selective degeneration of dopaminergic cells in that region (Ferro et al., 2005). As shown in Figure 9, compared to intact rats, 6-OHDA lesions resulted in rats exhibiting a marked, but clearly detectable, attenuation in medial forebrain bundle stimulation-evoked DA release in the striatum ($16.4\pm8.3\%$ of 100% intact responses) as monitored using FPA in combination with CFMs. Most significantly, compared to intact animals receiving a systemic injection of saline, systemic administration of a relatively low dose of L-DOPA to lesioned rats resulted in a near complete recovery in the magnitude of the evoked DA responses ($84.87\pm16.22\%$ of 100% intact responses at 30 min post-injection). Since L-DOPA increased the DA response in the lesioned animals to the statistical equivalent of the non-lesioned (saline-treated) animals, it can be inferred that on-line FPA or FSCV would be capable of (1) detecting depleted extracellular levels of DA in the striatum and (2) enhancing these levels in response to L-DOPA treatment across various dose ranges in PD patients (Blaha et al., 2008). These data highlight the relevance of monitoring dopaminergic transmission during STN DBS; these data also provide a framework for the development of a closed-loop neuroprosthesis with chemical sensing feedback and neuromodulation to maintain neurotransmitter levels consistent with optimal therapeutic efficacy.

Stimulation frequencies in the range of 37 to 75 Hz and current intensities in the range of 200–600 µA evoked maximal DA responses in the striatum (Figure 10A and B) (see Lee et al., 2006). More prolonged STN stimulation evoked a DA response that peaked within 15–20 applied pulses and fell off to ~30% of pre-stimulus baseline levels despite continuous stimulation. Stimulation dorsomedial to STN, corresponding to a portion of the medial forebrain bundle containing ascending nigrostriatal dopaminergic axons, resulted in an increase in striatal DA release that plateaued 5 sec into stimulation (Figure 10C). These results suggest that DBS in PD patients typically applied to the STN and adjacent regions increases brain extracellular DA levels, but also indicate that the pattern and magnitude of DA release varies significantly depending on the site and nature of stimulation. This latter finding has therapeutic implications for the site and pattern of stimulation in PD patients, which so far have not been fully explored.

We have demonstrated our ability to measure *in vivo* real-time oxygen, DA, ADO, histamine, and serotonin release with CFMs and glutamate release with an enzyme-linked biosensor during DBS (Lee et al., 2007; Agnesi et al., 2009; Bledsoe et al., 2009; Chang et al., 2012a; Shon et al., 2010a; 2010b). We have also shown that we can use the Mayo Clinic Engineering Department developed Wireless Instantaneous Neurotransmitter Concentration Sensing system (WINCS) to electrochemically codetect *in vivo* changes in ADO and DA concentrations in small and large animal models of DBS (Shon et al., 2010a). More importantly, our results (Shon et al., 2010b) have shown that STN DBS elicits DA and ADO release in the caudate nucleus of isoflurane anesthetized pigs. Additionally, we examined striatal DA release evoked by STN DBS in awake monkeys. We identified a site-dependency of DA release by stimulating at multiple points along a trajectory passing through the thalamus and STN. Greater DA release was observed when the stimulating electrode was within the dorsal region of the STN. Our results showed that the amount of DA release depends critically on the location of the stimulating electrode (Gale et al., 2013).

Our pig experiments have demonstrated that STN DBS elicits DA and ADO release distally in the caudate nucleus, shown in Figure 11 (see Shon et al., 2010b). For these experiments we implanted a single CFM into the caudate nucleus of isoflurane (1%) anesthetized pigs; FSCV recordings were taken during brief (2 sec) electrical stimulations of the human Medtronic 3389 DBS electrode implanted in the ipsilateral STN. With high-frequency stimulation (140 Hz), ADO and DA were clearly released (Figure 11A). The temporal patterns and magnitude of DA (black line) and ADO release (1st peak blue line and oxidation product 2nd peak red line) evoked by STN DBS are shown in Figure 11B. The voltammograms obtained with WINCS in the pig revealed one peak at +0.6 V for DA oxidation and two oxidation peaks for ADO (1st peak near +1.5 V and 2nd peak near +1.0 V), as shown in Figure 11C and D, respectively. Our now established pig model has permitted testing of our human neurochemical recording electrodes, as well as study of distal neurotransmitter release by STN DBS.

From knowledge and experience gained from tests conducted in our large animal (pig) experiments, we have successfully used WINCS to monitor DA and ADO release in the hippocampus of human patients undergoing resective surgery for medically intractable epilepsy (Van Gompel et al., 2014). A CFM was implanted 5 μm into the temporal lobe cortical surface of each patient for 15 min during intraoperative electrocorticography (ECoG) and 10 min of FSCV recordings prior to resection. One, out of ten patients tested, expressed a lateral neocortical seizure in which ADO release was observed and this was time-locked with the onset and termination of the seizure. These findings support a potential role of ADO in seizure termination during temporal lobe seizures.

In addition, WINCS-based FSCV measurements were taken in the thalamus of essential tremor patients during DBS neurosurgery (Figure 12); all the patients were awake during surgery. Arm and hand tremor were measured using a triaxial accelerometer which patients held in the hands opposite to the implanted hemisphere. Upon implantation of the DBS electrode, but prior to activation of the pulse generator, tremor amplitude was significantly reduced (n = 7; Figure 12A). Referred to as the microthalamotomy effect, symptom relief prior to neurostimulation has been observed in as many as 53% of patients undergoing DBS

surgery for essential tremor (Tasker, 1998). Our results showed that, as expected (Lakie et al., 1992), there was no change in tremor frequency, but average tremor amplitude was reduced by 61.2±13.7% upon DBS electrode insertion (n = 7 patients).

Coincident with tremor reduction, DBS electrode implantation evoked a large increase in the FSCV oxidation current peak at +1.45±0.03 V (n=7; Figure 12B). In four patients, this peak was followed by a second significantly smaller oxidation current peak at +1.19±0.06 V (white arrow in Figure 12B). Post-calibration analyses showed that the two oxidation current peaks recorded by FSCV matched those for authentic ADO and its oxidation byproduct (second peak). In accordance with post-calibration of the human CFM (see Chang et al., 2012b), the maximal increase in ADO at the first oxidation peak potential corresponded to an increase of 1.76±0.12 μM. These results demonstrate the first application of WINCS during DBS neurosurgery in patients (see Chang et al., 2012b; Kasasbeh et al., 2013).

To monitor real-time neurochemical changes associated with DBS, we performed similar FSCV measurements (−0.4 to +1.5 V every 100 ms) in the VIM of the thalamus of essential tremor patients during DBS neurosurgery using WINCS (Figure 13A–C). A FSCV color plot (Figure 13D) revealed that, during DBS, an oxidation peak current was detected at +1.4 V, corresponding to ADO oxidation (Swamy and Venton, 2007; Cechova and Venton, 2008; Pajski and Venton, 2010). Although a hand held accelerometer to measure tremor was not used in this patient shown in Figure 13, the rise in the ADO signal during and after DBS (Figure 13E) was visually observed to correlate with a marked reduction in tremor.

c. Translational importance on new large animal DBS models

Large animal models provide a necessary bridge between the fundamental discoveries made in small animal models and the translation into clinical practice. The preferred large animal model in neuroscience has been the non-human primate due to the higher cognitive function and behavioral similarities to the human. The rhesus macaque, for example, is a model with highly conserved when anatomy is compared to human. The Atlas of the Rhesus Monkey Brain (Saleem, 2007), combined with high-precision stereotactic head frame and high-resolution MRI coil allows translational DBS studies in this large animal model (Min et al., 2014).

There are also known similarities between porcine and human biology that have led to the proposal to use the porcine model as an excellent way to study human disease (Lind et al., 2007). Easy to get and maintain, the white domestic pig (*Sus scrofa*) is proving to be an economically viable alternative to the expensive non-human primate, and thus is becoming an increasingly popular animal for neuroscience research. Several characteristics make the pig an excellent model for mock human DBS surgery: (1) the pig has a gyrencephalic cortex, which is more similar to the human and non-human primate structure than that of commonly used lissencephalic rodent brains (Hofman, 1985, 1988); (2) the adult pig brain (~160 g) is comparable in size to that of the rhesus monkey (~100 g) and baboon (~140 g) and closer in size to the human brain (1300–1400g) than the rodent brain; (3) a high-resolution pig brain atlas is available allowing for precision DBS studies in pigs to advance our understanding of the underlying mechanism using functional imaging (Saikali et al., 2010); (4) pig brain development is complete by ~5 months (Dobbing, 1964), which enables

the use of younger pigs (20 – 50 kg) with adult-sized brains for easier mobilization and dissection during cranial surgery; (5) MPTP produces an effective pig PD model (Danielsen et al., 2000; Dall et al., 2002; Cumming et al., 2003); (6) several high-precision stereotactic head frames for pig neurosurgical studies have been developed establishing this system for DBS mechanistic studies (Bjarkam et al., 2009; Min et al., 2012); and (7) the pig genome has been decoded, which has revealed many key similarities between human and porcine genomes, further reinforcing the translational potential of this large animal model (Groenen et al., 2012). The advent of high-precision imaging tools such as functional magnetic resonance imaging (fMRI), combined with a recent increase in our understanding of cross-species neuroanatomical similarities among pig, human, and non-human primates highlight the potential of these large animal models to further our understanding of the mechanism behind DBS.

d. Use of functional neuroimaging in BG-DBS

Damage to the BG produces well-characterized changes that are related to movement disorders and motor deficits, including tremor, rigidity, and akinesia (Bhatia and Marsden, 1994; DeLong, 1983). Functional imaging is often used to indirectly monitor biochemical and anatomical changes within BG structures in movement and affective disorders due to its wide clinical availability and its global assessment of neural activity. Techniques including single photon emission computed tomography (SPECT), fMRI, and PET are used for this application. SPECT imaging has shown promise as a diagnostic tool for movement disorders revealing that changes in the caudate and putamen may help to differentiate early-stage PD from dystonia or essential tremor (Song et al., 2014). Other imaging studies, including PET, have been used to show decreased dopaminergic innervation within the BG in PD patients (Song et al., 2013). Longitudinal fMRI studies have also revealed heterogeneity in PD patients. These latter studies have shown differential changes in BG structures when patient populations are presented with motor tasks whether they are responding or not responding to pharmacological therapy (Holiga et al., 2013). In addition to movement disorders, BG dysfunction is now accepted as playing a role in a variety of neuropsychiatric diseases, including TS (DeLong and Wichmann, 2010).

When mapping this dysfunction, fMRI studies in TS patients have shown a relationship between tic onset and paralimbic and sensory-association areas (Bohlhalter et al., 2006). fMRI has also revealed a role for cortico-BG network dysfunction in TS (Peterson et al., 1998; Worbe et al., 2010; Worbe et al., 2012). Using diffusion tensor imaging (DTI), studies have also shown dysfunction in motor, associative, and limbic pathways (Neuner et al., 2009, 2010). Taken together, these studies show a role for neuroimaging in disease diagnosis and evaluating functionality of DBS for treating BG diseases.

As DBS is an effective treatment option for PD (Benabid, 1994, 2003, 2006), its application has now been applied to other neurological and psychiatric disorders (Mayberg et al., 2005). The incomplete understanding of the therapeutic mechanisms of DBS and lack of objective methods to measure its central global effects inhibit the advancement of a more individualized approach to DBS therapy. The brain's dense wiring makes characterizing the effect of electrical stimulation on neuronal communication beyond a few synapses extremely

challenging. Functional neuroimaging appears well suited to this task due to its wide clinical availability and its global assessment of neural activity. Many imaging studies in PD patients during STN DBS show modulation of motor and non-motor areas including the primary sensorimotor cortex, premotor cortex, SMA, dorsolateral prefrontal cortex, thalamus, BG, insular cortex, and contralateral cerebellum (Asanuma et al., 2006; Grafton et al., 2006; Haslinger et al., 2003; Kahan et al., 2012; Phillips et al., 2006; Stefurak et al., 2003). Other PET studies have implicated parietal and temporal cortices, classically defined as associative and limbic structures (Hersh et al., 2003; Le Jeune et al., 2010). These studies help to elucidate what makes DBS effective for treating motor and non-motor symptoms of PD.

Functional imaging studies of DBS have recently been aimed at identifying the circuitry elements that underlie effective, as opposed to ineffective, stimulation. For example, a recent tractography study of PD patients undergoing STN DBS identified a direct relationship between the positive clinical outcome and the targeting within white matter tracts that involve the cerebellum (Sweet et al., 2014). In a longitudinal SPECT study, a significant increase was shown in cerebral blood flow in the anterior cingulate/ supplementary motor cortex in PD patients who responded to STN DBS treatment (Antonini et al., 2003). PET has shown that long-term effective STN stimulation of PD patients increases frontal motor/associative area blood flow compared to baseline (Sestini et al., 2005). A regional cerebral blood flow (rCBF) SPECT study reported a correlation between improved motor scores and an increase in rCBF in the pre-SMA and primary motor cortex in PD patients receiving STN DBS treatment (Paschali et al., 2013). These studies suggest that neuroimaging biomarkers of effective DBS may exist for PD treatment.

Imaging has already identified structural and functional correlates of cognitive and affective deficits associated with PD (Kalbe et al., 2009; Kostic et al., 2010; Reijnders et al., 2010). In a case report in which STN DBS elicited several reproducible episodes of acute depressive dysphoria in PD patient, fMRI revealed increases in the superior prefrontal cortex, anterior cingulate, anterior thalamus, caudate and brainstem with widespread decreases in medial prefrontal cortex activation (Stefurak et al., 2003). Another case study identified STN DBS stimulation parameters which produced a hypomanic state in PD patient. A PET investigation showed involvement of limbic and association cortex, including areas of the anterior cingulate gyrus and the ventral anterior nucleus of the thalamus (Mallet et al., 2007). The fact that STN DBS can elicit cognitive and emotional side effects is unsurprising given our current understanding of the STN as a structure with anatomically-defined subregions which connect to motor, associative and limbic structures (Benarroch, 2009). A recent clinical report showed that using model-based optimization of DBS stimulation parameters to avoid the current spreading to non-motor areas reduced cognitive and cognitive-motor impairments while maintaining therapeutic motor benefits in STN DBS PD patients (Frankemolle et al., 2010). These data suggest that anatomical target-placement decisions during human DBS surgery could be augmented by structural and functional neuroimaging techniques which intraoperatively assess the motor and non-motor networks affected by STN DBS.

7. Concluding remarks

The last decade has held impressive developments in understanding the mechanism of BG function and how targeting different brain sites can improve motor, cognitive and motivional aspects of BG diseases. However, we are still far from having the ability to fundamentally describe the mechanism behind therapeutically effective DBS. Deepened understanding of BG connectivity and the resultant computational modeling of functional motor, motivational and cognitive processes have emerged in the last decade. However, these models are still insufficient to support the idea that different striatal-GPi/SNr-thalamus-motor cortex neurons can initiate or prevent a particular movement or a sequence of movements that compose specific actions. Additionally, these studies have revealed paradoxical challenges to the current BG action-selection hypothesis. DBS has indeed emerged as a therapy with wide applications expanding from STN DBS to treat PD, to cover many neurological and psychiatric diseases; however, our fundamental understanding of BG DBS is limited in its current state. A great deal of effort from the neuroscience community will be required to advance BG DBS to the proposed level of understanding and clinical application.

Acknowledgments

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Highlights

We review the circuits and connections of the basal ganglia cortico-thalamic loop.

Deep brain stimulation theories on modulating basal ganglia dysfunction are discussed.

We discuss new research approaches on basal ganglia-deep brain stimulation mechanisms.
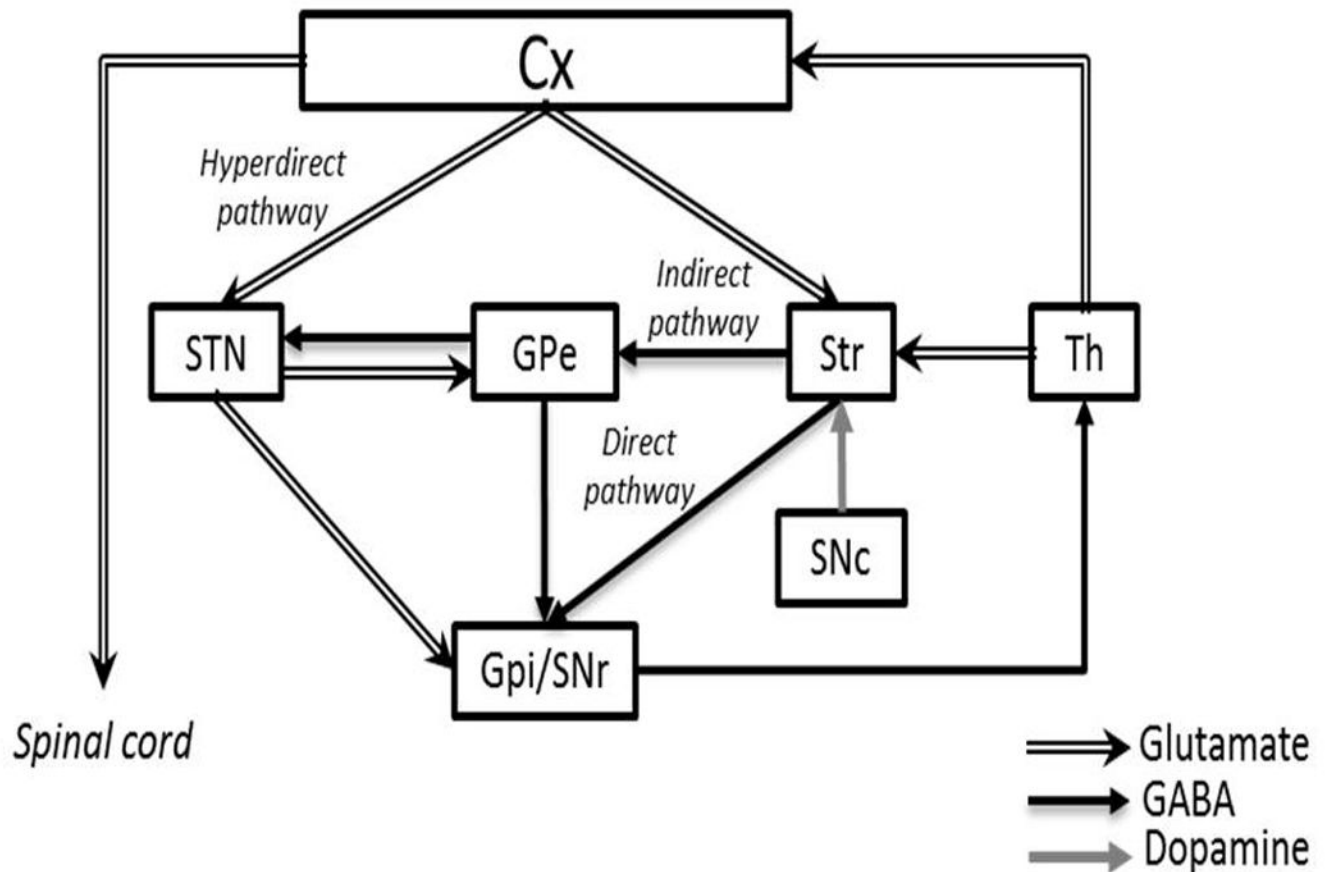
Figure 1.
Normal functioning of cortico-BG motor loop as proposed by Alexander, Delong and Strick (1986), Albin, Young, and Penney (1989) and Nambu (2002). Cx, cerebral cortex; GPe, external globus pallidum; GPi, internal globus pallidum; SNc, subtantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STN, subthalamic nucleus; Str, striatum; Th, thalamus. Illustration adapted with permission from Nambu (2011).
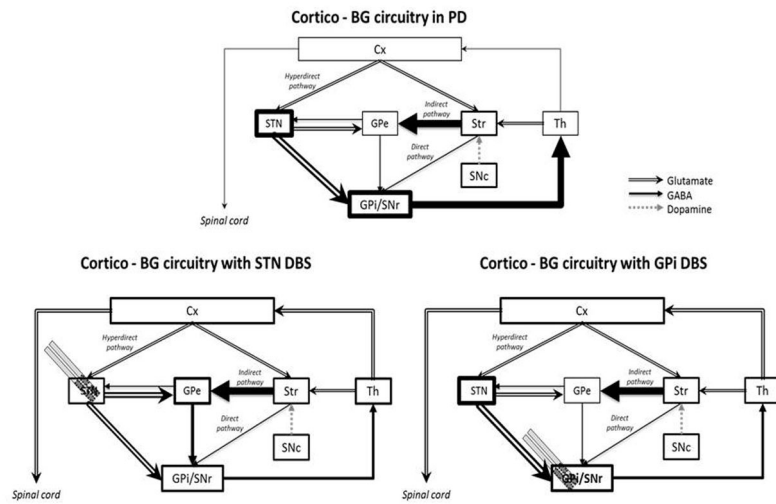
Figure 2.
Hypothetical cortico-BG circuitry functioning in Parkinson's disease (PD) before and after STN or GPi DBS. Cx, cerebral cortex; GPe, external globus pallidum; GPi, internal globus pallidum; SNc, subtantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STN, subthalamic nucleus; Str, striatum; Th, thalamus. Illustration adapted from Nambu (2011).
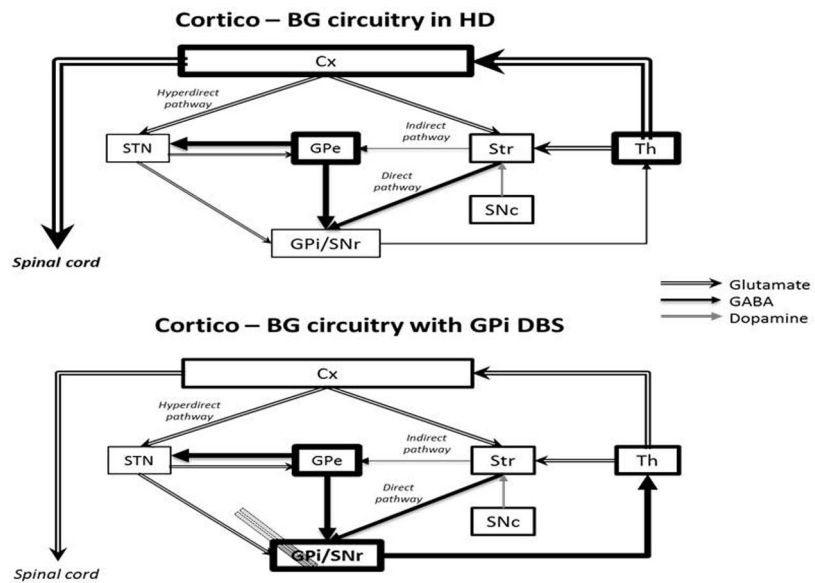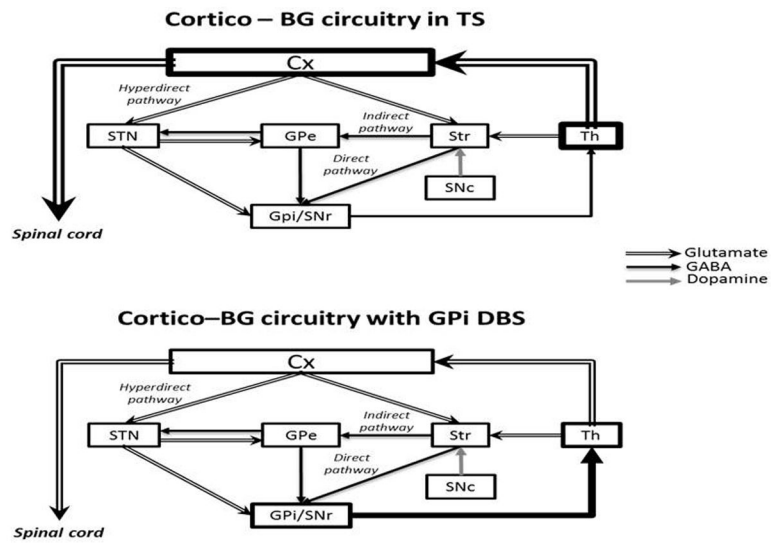
Figure 3.
Hypothetical cortico-BG functioning in Huntington's disease (HD) before and after GPi DBS. Cx, cerebral cortex; GPe, external globus pallidum; GPi, internal globus pallidum; SNc, subtantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STN, subthalamic nucleus; Str, striatum; Th, thalamus. Illustration adapted from Nambu (2011).
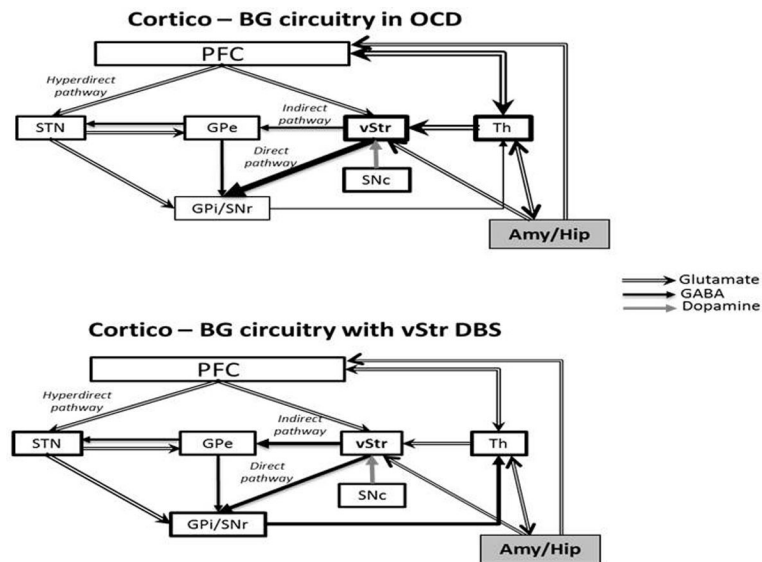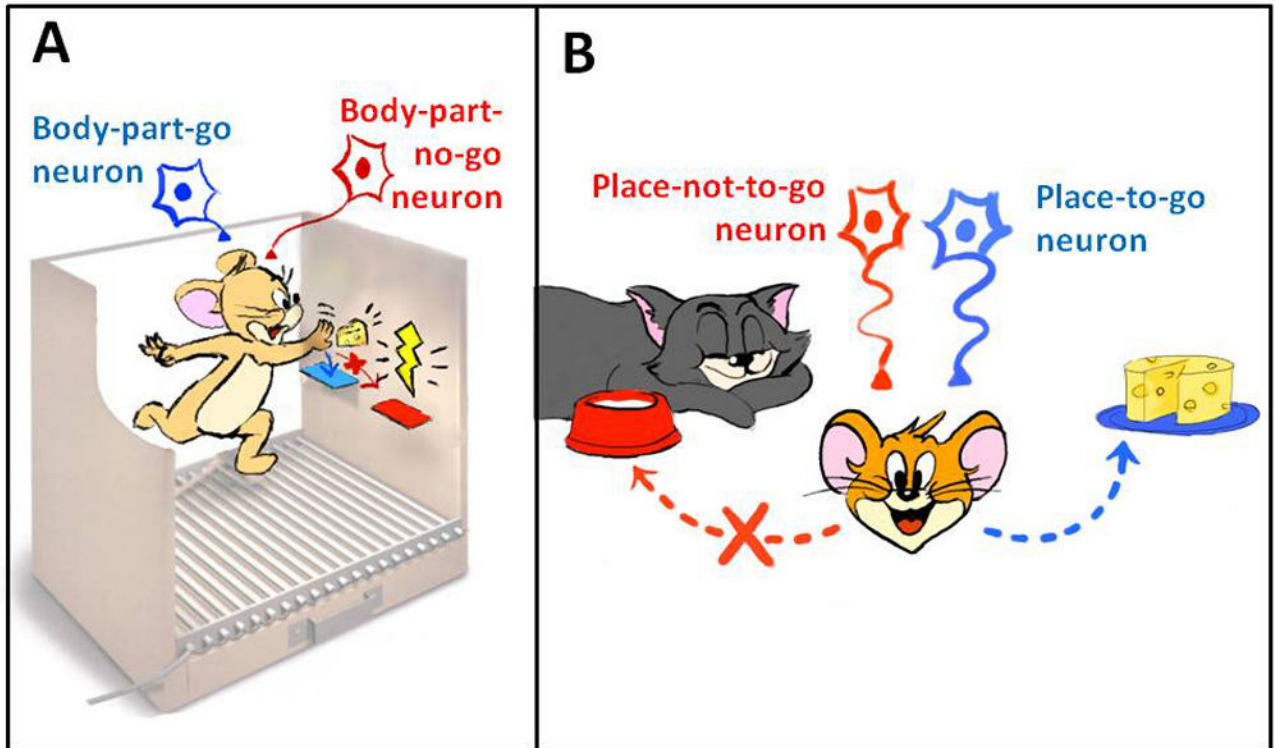
Figure 4.
Hypothetical cortico-BG circuitry functioning in obsessive compulsive disorder (OCD) before and after ventral striatum DBS. According to this model, obsessions would permanently reverberate in the loop formed by the stimulating activity of the Amy/Hip to Th and then to ventral striatum. The original emotional information would be transmitted through the overactive direct pathway back to Th where it could become a compulsion through thalamocortical activation or return to ventral striatum or Amy/Hip, closing the circuit. Amy, amygdala; GPe, external globus pallidum; GPi, internal globus pallidum; Hip, hippocampus; PFC, prefrontal cortex; SNc, subtantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STN, subthalamic nucleus; Str, striatum; vStr, ventral striatum (also as the nucleus accumbens); Th, thalamus. Illustration adapted from Nambu (2011).

Cortico — BG circuitry in TS

Cortico—BG circuitry with GPi DBS

Figure 5.
Hypothetical cortico-BG circuitry functioning in Tourette syndrome before and after GPi DBS. Cx, cerebral cortex; GPe, external globus pallidum; GPi, internal globus pallidum; SNc, subtantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STN, subthalamic nucleus; Str, striatum; Th, thalamus. Illustration adapted from Nambu (2011).

Figure 6.
Cartoon illustrating two postulates of the mosaic of broken mirrors model (MBMM). (A) Activation of a striatal "body-part-go cell" selects and initiates a motor action of a body part towards an object. (B) Activation of a striatal "place-to-go cell" selects and initiates the approach to a specific place; activation of a "place-not-to-go cell" prevents approaching to a place.
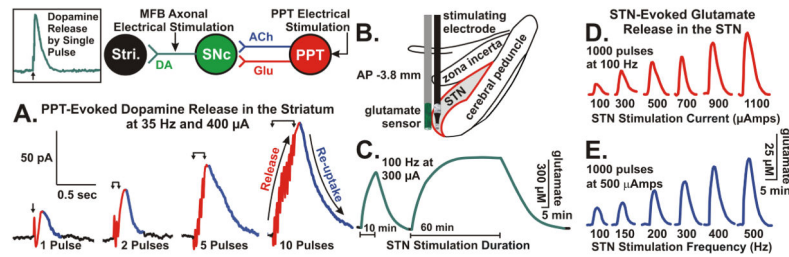
Figure 7.
(A.) DA release in the striatum (Stri.) of urethane anesthetized rats evoked by 1 to 10 pulses of electrical stimulation of pedunculopontine tegmental nucleus (PPT) glutamatergic and cholinergic projections to substantia nigra *pars compacta* (SNc) DA cells. Note that the increase in DA release is time locked to the stimulation (pulse artifacts are superimposed on the rising portion of the signal) and the recovery to baseline is a reflection of clearance of DA mainly via presynaptic re-uptake. INSET: rapid response of DA to stimulation of DA axons in the medial forebrain bundle (MFB) illustrating that the relatively slower PPT evoked response is trans-synaptically mediated. Glutamate release in the STN evoked by electrical stimulation of the STN at various durations (C.), intensities (D.), and frequencies (E.). (B.) Positioning of a glutamate sensor adjacent to a bipolar stimulating electrode in the STN (see Lee et al., 2007).
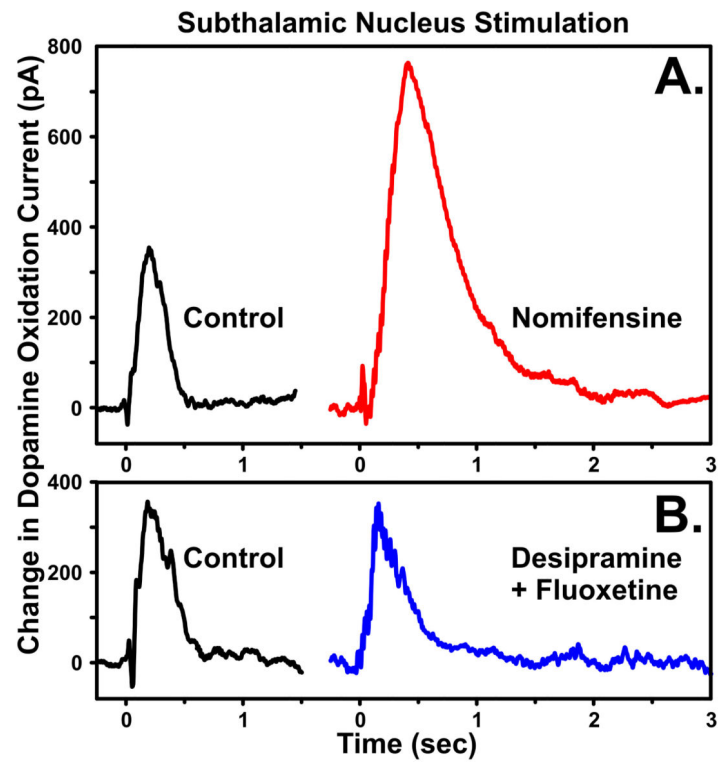
Figure 8.
Striatal DA is increased with brief STN stimulation. The selectivity of the response was confirmed by (A.) systemic injection of the DA reuptake inhibitor nomifensine (red line), which resulted in a significant increase in DA oxidation current, compared to (B.) serotonin (fluoxetine) and norepinephrine (desipramine) reuptake inhibitors (blue line) which did not significantly increase the STN stimulation-evoked response.
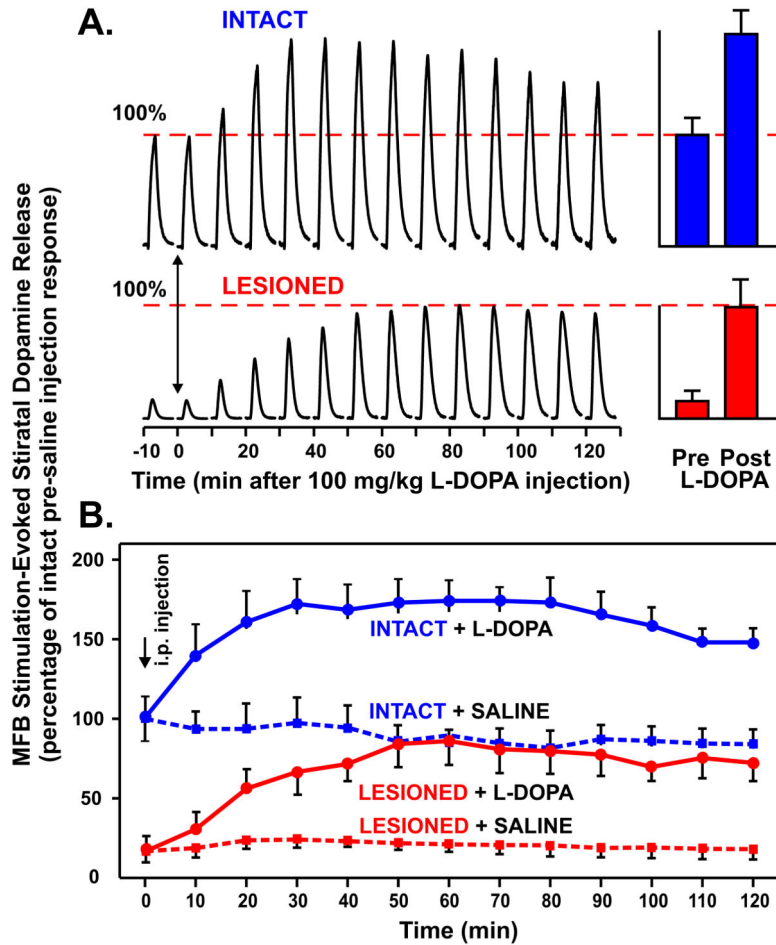
Figure 9.
(A.) Represetative example of medial forebrain bundle stimulation-evoked (20 pulses at 100 Hz applied every 10 min) striatal DA release in a urethane anesthetized intact rat and a rat sustaining neurotoxic 6-OHDA lesioning of the nigrostriatal dopaminergic pathway before and following systemic injection of L-DOPA (100 mg/kg i.p.). Note the recovery of stimulated DA release to 100% baseline levels of evoked striatal DA release following administration of L-DOPA in lesioned animals. (B.) Mean ± SEM time courses of effects of L-DOPA injections, compared to saline administration, on striatal DA release in intact and lesioned rats before and following systemic injection of L-DOPA. Solid and dashed blue lines: intact mice that received L-DOPA and saline, respectively. Percentage changes refer to intact pre-saline treated mice.
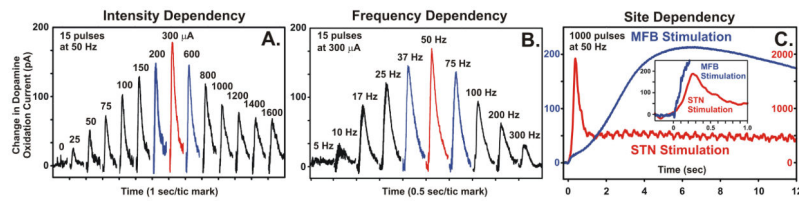
Figure 10.

Intensity, frequency, and site dependency of STN stimulation evoked striatal DA release of the urethane anesthetized rat. (A.) The optimal current intensity for STN stimulation was 300 μA, with the stimulation evoked DA response falling off at 600 μA and greater. (B.) The optimal frequency for STN stimulation was 50 Hz, with the stimulation evoked DA response falling off at 75 Hz and greater. (C.) Prolonged STN stimulation evoked a transient response that peaked within 20 applied pulses (red line), as compared to a 10-fold greater and more sustained DA response to stimulation of the medial forebrain bundle (MFB) (blue line). INSET: DA release evoked by stimulation of the MFB (blue line) was significantly faster at onset compared to STN stimulation when viewed on the same scale as the STN response (red line).
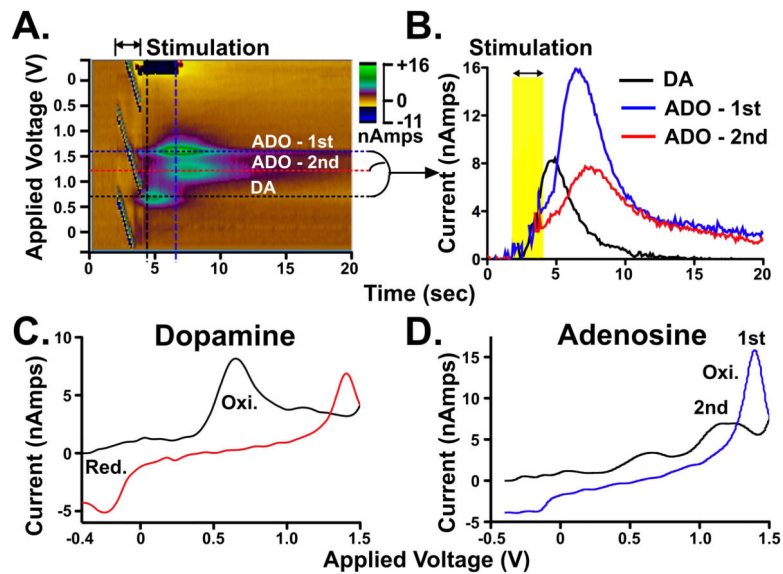
Figure 11.
In vivo dopamine (DA) and adenosine (ADO) release measured with WINCS-based FSCV at CFMs in the CN of the isoflurane anesthetized pig. (A.) Electrical stimulation (140 Hz, 0.5 ms- pulse width, for 2 sec) of the STN evoked both DA and adenosine release in the CN. The color plot shows the appearance of DA release immediately during and after stimulation, while the peak corresponding to adenosine release was delayed. (B.) Current versus time plot at +1.5V (blue), +1.0V (red), and +0.6V (black line) shows adenosine first and second oxidation (ADO - 1st, blue and ADO – 2nd, red) and DA (DA, black line) release following electrical stimulation (yellow box). (C.) and (D.) Background subtracted voltammograms for DA and adenosine, respectively, demonstrate simultaneous measurements of DA and adenosine releases (black and blue vertical dashed lines in A).
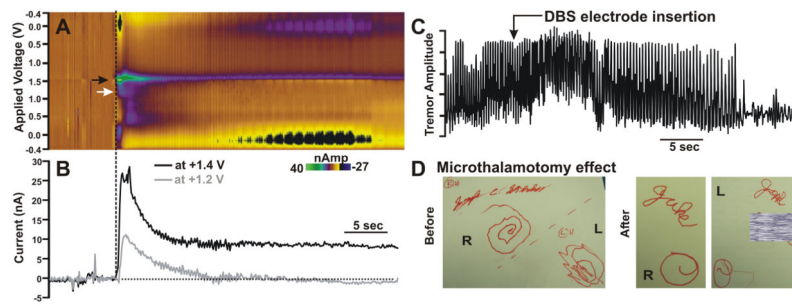
Figure 12.
Intraoperative FSCV recordings during monitoring of tremor in essential tremor patients. (A) FSCV color plot shows increases in oxidation current at +1.4 V (black arrow) and +1.2 V (white arrow) time-locked with the insertion of the DBS electrode into the ventral intermediate nucleus (VIM) of the thalamus (n = 7 patients). (B) Oxidation currents at +1.4 V (black) and +1.2 V (gray) plotted against time. (C) Representative tremor monitoring with a hand- held accelerometer shows tremor was decreased upon DBS electrode insertion. Time scale is the same as in (B). (D) Representative handwriting sample before and after DBS electrode implantation (L, left hand; R, right hand).
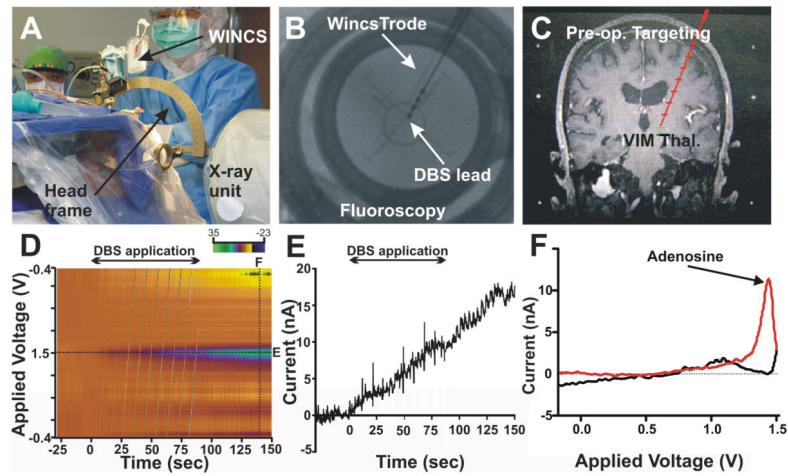
Figure 13.
Neurochemical changes evoked by DBS in the VIM of the thalamus in patients with essential tremor. (A) Surgical set-up. (B) X-ray of the position of the human CFM and DBS lead in patient's thalamus. (C) MR image of implantation trajectory. (D) Color plot shows the appearance of oxidation current at +1.4V immediately upon application of DBS (135 Hz, 60 μsec pulse width, 0.5–2.0 V, slowly increased). (E) Current versus time plot at +1.4V following DBS. (F) Background subtracted cyclic voltammogram shows the oxidation peak of adenosine at +1.4 V.