Abnormal neuronal activity in Tourette syndrome and its modulation using deep brain stimulation

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Abstract

Tourette syndrome (TS) is a common childhood-onset disorder characterized by motor and vocal tics that are typically accompanied by a multitude of comorbid symptoms. Pharmacological treatment options are limited, which has led to the exploration of deep brain stimulation (DBS) as a possible treatment for severe cases. Multiple lines of evidence have linked TS with abnormalities in the motor and limbic cortico-basal ganglia (CBG) pathways. Neurophysiological data have only recently started to slowly accumulate from multiple sources: noninvasive imaging and electrophysiological techniques, invasive electrophysiological recordings in TS patients undergoing DBS implantation surgery and animal models of the disorder. These converging sources point to system level physiological changes throughout the CBG pathway including both general altered baseline neuronal activity patterns and specific tic related activity. DBS has been applied to different regions along the motor and limbic pathways, primarily to the globus pallidus internus, thalamic nuclei and nucleus accumbens. In line with the findings that also draw on the more abundant application of DBS to Parkinson’s disease, this stimulation is assumed to result in changes in the neuronal firing patterns and the passage of information through the stimulated nucleus. We present an overview of recent experimental findings on abnormal neuronal activity associated with TS and the changes in this activity following DBS. These findings are then discussed in the context of current models of CBG function in the normal state, during TS, and finally in the wider context of DBS in CBG-related disorders.

1. Introduction

1.1. Tourette syndrome

Georges Gilles de la Tourette first described patients suffering from the disorder which would later be named after him 130 years ago (Gilles de la Tourette, 1885). In his account of these patients he describes the key symptoms of this disorder including motor and vocal tics. Tics are currently defined as sudden, rapid, recurrent, non-rhythmic motor movements or vocalizations (DSM-V) (American Psychiatric Association, 2013). Tics range from simple motor tics that
involve only one or a few muscle groups, to complex motor or vocal tics that involve sequential
activation of several muscle groups. Tourette syndrome (TS) is defined as arising in childhood
(<18 years), having at least two types of motor tics and one type of vocal tic, lasting at least one
year and not arising as a side effect of a medication for other disorders (DSM-V). The disorder
typically appears in early childhood with a 0.8% prevalence of TS among children (Knight et al.,
2012). In adults, the prevalence of TS decreases dramatically with an 80-90% reduction in the
number of patients. Pharmacological interventions may reduce tics but rarely eliminate them.
The most effective and studied medications for TS are the D2 dopamine receptor antagonists
(antipsychotic drugs); however their use is restricted due to their side effects (Eddy et al., 2011).
α2 adrenergic receptor agonists have smaller tic-suppressing potency but also lower risk of
adverse reactions (Eddy et al., 2011). Other alternative medications are tetrabenazine, Δ9-
tetrahydrocannabinol and botulinum toxin (Botox) injections (Roessner et al., 2011). Tics are
typically associated with a premonitory urge which have been reported by >90% of the patients.
These patients typically report that the tics are (at least partially) voluntary responses to the
premonitory urge and are not an involuntary movement (Leckman et al., 1993). Tics are the
hallmark symptom of TS; however, they seldom appear by themselves. Over 90% of TS patients
suffer from additional comorbidities (Freeman et al., 2000). The most common comorbid
symptoms are attention deficit hyperactivity disorder (ADHD) and obsessive compulsive
disorder and behavior (OCD and OCB respectively) which affect over half of all TS patients
each. Thus, both the study of the underlying mechanism of TS and the clinical treatment of the
disorder need to take into account that tic-only TS patients comprise only a minority of the
overall TS patient group. The underlying mechanism of tic formation in TS is still largely
obscure but multiple lines of evidence have linked tics to malfunctions in the cortico-basal
ganglia (CBG) pathway (Singer and Minzer, 2003; Kalanithi et al., 2005).

1.2. The cortico-basal ganglia loop and its relation to TS

The basal ganglia (BG) comprise a group of interconnected sub-cortical nuclei involved in
motor, associative and limbic functions (Alexander et al., 1986). Information from multiple areas
of the cerebral cortex and thalamus is integrated in the BG and conveyed via the thalamus back
to frontal cortical areas, thus forming the CBG loop. The BG is composed of the striatum
(subdivided into the putamen, caudate and nucleus accumbens - NAc) the subthalamic nucleus
(STN), the globus pallidus external and internal segments (GPe and GPi respectively), and the substantia nigra pars compacta and pars reticulata (SNc and SNr respectively). Excitatory (glutamatergic) projections from the cerebral cortex and the centromedian and parafascicular thalamic nuclei (CM-PF complex) converge in the striatum and STN, the BG's input structures (Parent and Hazrati, 1995a, 1995b; Sadikot and Rymar, 2009). Dopaminergic input to the striatum is received through its reciprocal connections with neurons in the midbrain (SNc and ventral tegmental area) (Haber et al., 2000). Efferent projections from the BG's input structures induce opposing effects via the inhibitory (GABAergic) projections of the striatum and the excitatory projections of the STN (Smith and Parent, 1988; Tremblay and Filion, 1989).

Information from these input structures is transmitted, either directly or via the GPe, to the GPi and SNr, the BG's output structures. The output structures then send inhibitory (GABAergic) projections to the thalamus and brainstem. Multiple thalamic areas are innervated by the BG: the ventral anterior, ventral lateral, mediodorsal (MD) and the CM-Pf complex (Haber and McFarland, 2001; Sadikot and Rymar, 2009). These nuclei send excitatory projections to the cortex, completing the CBG partially closed loop (Tokuno et al., 1992; Hoover and Strick, 1993).

Cortical inputs are processed in the BG in multiple parallel, functionally defined, pathways including the motor, associative and limbic loops. Within each one of these pathways, partially segregated projections from functionally related cortical areas traverse discrete portions of the BG and thalamus. Thus, the pathways remain mostly specific throughout the CBG loop (Alexander et al., 1986; Parent and Hazrati, 1995b) despite some integrative projections (Draganski et al., 2008; Oguri et al., 2013). Sub-regions within the motor pathway are somatotopically organized throughout the different nuclei (Alexander and DeLong, 1985; DeLong et al., 1985). Information flows through the BG circuits in three feed-forward pathways, each of which has a different influence on the output nuclei (GPi/SNr) and thus affects cortical activity differentially. In the "direct pathway", striatal neurons project to the GPi/SNr, thereby decreasing their activity and facilitating cortical activation (Alexander and Crutcher, 1990). The other two pathways, the "indirect" and "hyperdirect" pathways, increase the GPi/SNr discharge and therefore suppress cortical activity. Striatal neurons in the "indirect pathway" inhibit the GPe, which then disinhibits the STN, causing an increase in GPi excitation (Alexander and Crutcher, 1990). In the "hyperdirect pathway", cortical projections reach the STN directly,
bypassing the striatal afferent and efferent fibers (Nambu et al., 2000) and excite the output nuclei. Dopaminergic projections modulate the CBG pathways by activating the D1 and D2 receptors in the striatum. Dopamine (DA) has opposing effects on these pathways by facilitating the "direct pathway" through the D1 receptors and inhibiting the "indirect pathway" through the D2 receptors expressed in neurons belonging to these pathways (Gerfen et al., 1990). Hence, higher levels of DA in the striatum increases cortical activation, whereas decreased DA levels suppress cortical activation (Albin et al., 1989; DeLong, 1990).

Striatal neurons can be divided into two populations: projection neurons and interneurons. GABAergic projection neurons comprise the vast majority (70-95%) of striatal neurons and are referred to as medium spiny neurons (MSNs) due to their morphological structure (Gerfen, 1988). MSN activity is mediated by axon collaterals of neighboring MSNs and feedforward interneuron inhibition (Tepper and Bolam, 2004). The remaining striatal neurons consist of several types of GABAergic interneurons and one type of cholinergic interneurons, classified based on their morphology, neurochemistry and physiology (Kawaguchi, 1993). Parvalbumin-positive interneurons are the best-characterized GABAergic interneurons in the striatum, exhibiting brief action potentials and a high discharge rate. They are referred to as fast spiking interneurons (FSIs). Individual FSIs innervate large populations of MSNs and can induce potent inhibition (Kita et al., 1990; Bennett and Bolam, 1994; Koós and Tepper, 1999). Cholinergic interneurons are characterized by their tonic discharge and are referred to as tonically active neurons (TANs) (Kimura et al., 1984). TANs activate GABAergic interneurons and therefore indirectly inhibit MSNs (English et al., 2011).

Behaviors associated with TS are generally attributed to malfunctions of the BG in general and specifically of the striatum. The activation of motor tics in TS is presumed to result from a malfunction of the motor pathway, whereas the premonitory urge is presumed to result from the limbic pathway. Functional and anatomical imaging studies of tic expression have reported aberrant activity in sensorimotor, associative and limbic circuits correlating tic severity with BG activation (Peterson et al., 1998; Stern et al., 2000; Baym et al., 2008; Wang et al., 2011). Structural abnormalities in the CBG loop measured by magnetic resonance imaging (MRI) present reduced caudate nucleus volumes in TS subjects regardless of age, whereas the volumes of the putamen and GP nuclei decreased mostly in adults with TS (Peterson et al., 2003). The
severity of tics in late adolescence and early adulthood were reported to be inversely correlated with caudate nucleus volumes in childhood (Bloch et al., 2005). Hinting at a system wide change, abnormalities were found in the CBG white matter pathways, and in particular exhibited an enhanced structural connectivity of the striatum and thalamus with the primary motor and sensory cortices, among other cortical areas (Worbe et al., 2015) and in thalamic and sensorimotor cortical volume (Sowell et al., 2008; Miller et al., 2010).

Multiple neuromodulator/neurotransmitter systems are altered in TS patients; most notably the dopaminergic and GABAergic systems. Improvements in tic expression after dopamine D2 antagonist treatment have suggested a super-sensitivity of dopaminergic receptors (Singer et al., 1982). Likewise, increased striatal expression of presynaptic dopamine carrier sites in postmortem brain tissue from TS patients have suggested enhanced dopamine innervation within the striatum (Singer et al., 1991). Consistent with these findings, neurochemical imaging studies have indicated abnormal dopaminergic innervation specifically in the ventral striatum (Albin et al., 2003; Cheon et al., 2004; Wong et al., 2008). Anomalies in the GABAergic system were found in post mortem studies of TS subjects, indicating a decreased number of the GABAergic parvalbumin positive (PV+) FSIs in the striatum (Kalanithi et al., 2005; Kataoka et al., 2010). This is complemented by significant changes in the PV+ projection neuron population in both parts of the GP: a decreased number in the GPe and an increased number in the GPi (Kalanithi et al., 2005). Decreased binding of GABA receptors in the ventral parts of the striatum and GP, as observed in neurochemical imaging studies, further emphasize the involvement of the BG GABAergic system, and its limbic pathway in particular, in TS (Lerner et al., 2012).

### 1.3. Animal models of Tourette syndrome and tic expression

Multiple animal models have been developed to address different properties of TS. Each one of these models focuses primarily on a single aspect of the disorder; i.e., motor tics, sensory motor gaiting deficits, comorbid symptoms or the heredity of genetic mutations. These models can be divided into two general categories based on the method used to generate the model: (1) models that use pharmacological manipulations, and (2) models that use genetic manipulations. Pharmacological animal models use systemic or localized administration of substances that affect different neurochemicals in the nervous system (for a detailed review see (Bronfeld et al., 2013a)). The most common targets are the neurotransmitter GABA and the neuromodulators
dopamine, serotonin and norepinephrine. The \textit{GABAergic} model uses focal injections of GABA$_A$ antagonists such as bicuculline and picrotoxin into motor regions of the striatum. These injections lead to the appearance of sudden, rapid and repetitive movements in both rodents and primates (Marsden et al., 1975; Crossman et al., 1988; McCairn et al., 2009; Bronfeld et al., 2013b) which resemble the simple motor tics of TS patients. Tics usually emerge within a few minutes following the injection, and last for up to two hours (Marsden et al., 1975; Tarsy et al., 1978; Patel and Slater, 1987; Crossman et al., 1988; McCairn et al., 2009; Bronfeld et al., 2013b). In monkeys, a minority of the injections led to abnormal sequential movements, which resembled complex motor tics. Similar injections that have been performed in different functional territories of the striatum and GPe have generated domain-specific behaviors similar to compulsive, hyperactive and/or attention deficit symptoms (Tarsy et al., 1978; François et al., 2004; Worbe et al., 2009; Bronfeld et al., 2010). Thus, indicating on the existence of a link between the generation of motor tics and their common comorbid disorders (OCD/OCB and ADHD). The presentation of an easily quantifiable motor symptom (simple motor tic) enables gaining insights into the additional limbic/associative disorders associated with the basal ganglia. This is beneficial as the direct study of such disorders typically presents a large challenge in the quantification of behavior.

The \textit{dopaminergic} models use systemic or focal administration of DA agonists such as amphetamine and apomorphine. Following the injection, the animal expresses stereotypic behaviors, such as sniffing, licking or biting (Randrup et al., 1963; Kelley et al., 1988) in addition to sensory motor gaiting deficits as assessed by the pre-pulse inhibition (PPI) paradigm (Mansbach et al., 1988; Wan and Swerdlow, 1996; Lind et al., 2004). Administration of DA agonists and the associated behaviors are not unique to modeling TS, and are frequently used to model other disorders such as schizophrenia, OCD and ADHD (Kokkinidis and Anisman, 1981; Weiss and Feldon, 2001; Geyer, 2006). Other models targeting the \textit{serotonergic} and the \textit{norepinephrine} neuromodulators use systemic administration of these drugs. The models display brief and repetitive movements (albeit not resembling tics) (Bedard and Pycock, 1977) and sensory motor gaiting deficits (Sipes and Geyer, 1994; Carasso et al., 1998).

Family studies of TS patients have indicated that genetic factors play a role in the manifestation of TS (Price et al., 1985). Several genes and chromosomal regions are considered likely
candidates in the TS etiology, but most are rare, and currently no gene is known to have a major
effect on TS etiology (Godar et al., 2014). Genetic animal models for TS can be divided into two
groups: (1) models that are based on mutant genes that were found in humans with TS and (2)
models based on mutations affecting the dopaminergic system. Models based on human TS
mutations mainly include the SLITRK1 (Abelson et al., 2005a; Verkerk et al., 2006; Fabbrini et
al., 2007), SAPAP3 (Crane et al., 2011) and HDC (histidine decarboxylase) (Ercan-Sencicek et
al., 2010) genes. The models related to the dopaminergic pathway mainly target the genes of D1
receptors (D1CT-7), D3 receptors and DAT. Currently, genetic animal models have not exhibited
the main characteristic of TS; i.e., motor tics. Rather, most animal models can successfully
produce a decrease in locomotion (SLITRK1 and HDC models) (Kubota et al., 2002; Katayama
et al., 2010), increased twitching (D1CT-7 model) (Nordstrom and Burton, 2002) or TS
comorbid symptoms such as OCB (SAPAP3, D1CT-7, DAT and HDC (following amphetamine
injection) models) (Campbell et al., 1999; Berridge et al., 2005; Welch et al., 2007; Castellan
Baldan et al., 2014), anxiety (SLITRK1 and SAPAP3 models) (Katayama et al., 2010; Welch et
al., 2007) and hyperactivity (D1CT-7 and non-functional D3 receptor models) (Accili et al.,
1996; Campbell et al., 1999).

Currently, each of the pharmacological and genetic TS animal models presents only a limited
subset of the complex set of properties associated with the disorder. Moreover, most of the
models are transient in nature and do not display the complex neurodevelopmental properties of
TS. Nonetheless, together these animal models provide unique and valuable insights into the
aberrant neural activity underlying the symptoms of TS.

2. Physiology of Tourette syndrome

The behavioral expression of TS symptoms has been studied for over a century; however, the
underlying neuronal abnormalities have only been studied extensively in the last two decades.
Physiological data which historically have been limited to non-invasive methods is currently
being augmented by invasive electrophysiological recordings in human patients undergoing
neurosurgery, and novel experimental animal models.

2.1. TS Physiology - human patients
Information regarding the underlying neurophysiology of TS in human patients is slowly accumulating through two complementary channels: (1) non-invasive methods such as functional magnetic resonance imaging (fMRI), positron emitting tomography (PET), electroencephalogram (EEG), magnetoencephalogram (MEG) and transcranial magnetic stimulation (TMS) and (2) invasive methods such as electrophysiological recordings of LFP and spiking activity from TS patients during and immediately following neurosurgery (Priori et al., 2013).

Non-invasive neurophysiological methods point to abnormal cortico-basal ganglia activity in TS both in the overall activity of specific brain regions and in the activity surrounding the timing of individual tics. (1) *Abnormal activity preceding the time of the tic*: An fMRI study reported the activation of limbic areas, such as the anterior cingulate (ACC) and insular cortex, and the supplementary motor area (SMA) preceding the tic, followed by the activation of sensorimotor areas with the tic onset (Bohlhalter et al., 2006). Activation of the SMA and M1 were observed up to 2 seconds prior to the tic onset (Neuner et al., 2014). A stronger and broader correlation between the SMA and M1 surrounding the time of the tic was shown using fMRI (Hampson et al., 2009). Increased coherence was also found using EEG between the sensorimotor, prefrontal and medial frontal areas during tic suppression (Serrien et al., 2005). Support for such findings comes from a PET study that found a correlation between the striatum, sensorimotor, associative and limbic cortices and tic occurrences (Stern et al., 2000). (2) *Abnormal baseline activity*: A study of tic suppression using fMRI revealed changes in basal ganglia and thalamic activation that correlated inversely with the severity of tic symptoms (Peterson et al., 1998). In line with these findings, a recent study found abnormal functional connectivity in the CBG pathway including the sensorimotor, premotor, parietal and cingulate cortices (Worbe et al., 2012). It showed that the tics were associated primarily with motor pathway abnormalities and OCD with associative and limbic pathways abnormalities. Increased activation was also observed throughout the direct pathway of the basal ganglia, as well as increased compensatory activation in the prefrontal cortex and the STN (Baym et al., 2008). A complementary study using TMS found abnormal cortical excitability in terms of a reduction in the cortical silent period in TS patients (Ziemann et al., 1997). Finally, while most studies have focused on activation levels, a MEG study revealed abnormalities in the beta band oscillatory activity of TS patients in the sensorimotor areas (Tinaz et al., 2014).
Invasive recordings in TS patients undergoing DBS implantation surgery have been performed in various nuclei of the thalamus and multiple locations within the GPi, both intra-operatively using micro-electrodes, and post-operatively through the stimulating electrode leads. *Tic related changes in neuronal activity* have primarily been studied in the period preceding the tic to avoid the large movement-related activity associated with the tic. Enhanced synchronization of cortical EEG with thalamic LFP recorded by the DBS electrode was observed up to 1.5 seconds prior to the tic onset (Bour et al., 2014). Tic-related neuronal activity was also observed in the ventralis oralis thalamic nucleus in one patient (Priori et al., 2013) but was not evident in the other cases since no tics occurred during the operation. GPi single neurons displayed tic-related neuronal activity preceding the tic by up to 2 seconds (Zhuang et al., 2009). *Changes to the baseline activity in TS patients* were observed in the GPi (Zhuang et al., 2009) revealing low firing rates comparable to dystonia patients (Vitek et al., 1999) but far below human Parkinson’s disease (PD) patients and normal non-human primates (Raz et al., 2000). Zhuang and colleagues also reported irregular GPi neuronal activity (coefficient of variation - CV>1) which was higher than the values observed in normal primates. Recordings in the ventralis oralis nucleus of the thalamus in TS patients under general anesthesia revealed neuronal bursting and LFP oscillations in the low frequency and alpha bands (3-13 Hz) (Marceglia et al., 2010). These recordings also exhibited decreased beta band oscillations contrary to the increased power in this band classically associated with PD (Stein and Bar-Gad, 2013). However, this type of oscillatory activity changes have been identified in patients under general anesthesia undergoing neurosurgery for other disorders and may thus be unrelated to TS.

### 2.2. TS Physiology - Animal models

Research using animal models of TS focused historically on behavioral properties and the effects of pharmacological agents on the expressed behaviors. Very few studies have attempted to explore the neurophysiological characteristics of the different models and their associated expressions of abnormal behaviors. Typically, existing animal models of TS focus on a small subset of the symptoms associated with the disorder and are based on transient deficits, in contrast to the neurodevelopmental nature of TS. However, these models provide a unique dataset, as the ability of examining the underlying neuronal activity in TS patient is severely limited. The dopaminergic animal model indicates changes in the baseline activity of neurons
along the CBG pathway following systemic or focal dopamine agonist, typically apomorphine, injection. The direct and most consistent effect is the inhibition of the TANs in the striatum and a reduction in their correlation (Fujita et al., 2013). Reports concerning changes in the mean firing rate of the projection neurons (MSNs) along the pathway are mixed: equal populations of striatal MSNs were found, which increased or decreased their rate as predicted by current theories on the function of the known dopamine receptor sub-types (Fujita et al., 2013). Mixed results were also observed in the GPe, in line with the division into two neuronal subtypes (Bergstrom et al., 1982; Kelland et al., 1995; Boraud et al., 2001). In the STN, the firing rate increased following the injection (Kreiss et al., 1996). Most studies have observed decreased firing rates in the output nuclei of the BG – the GPi and the SNr (Boraud et al., 2001; Nevet et al., 2004), but see the increased rates in an amphetamine study (Waszczak et al., 2001). To date, physiological recordings are not common in genetic models of TS. In a study performed on the genetic model of SAPAP3-knockout mice, an increased baseline firing rate was found in striatal MSNs (Burguière et al., 2013).

Unlike most current models, the striatal disinhibition animal model of TS enables the study of the underlying neuronal abnormalities associated specifically with tics. In this model, changes in neuronal activity synchronized with the tic expression were found in both individual neurons and larger populations, as reflected by LFP and EEG activity. Large transient deflections in cortical EEG activity (EEG spikes) and LFP throughout the BG and cerebellum (LFP spikes) were recorded from the ipsilateral hemisphere of the focal striatal injection (Tarsy et al., 1978; Muramatsu et al., 1990; Darbin and Wichmann, 2008; McCairn et al., 2013a; Pogorelov et al., 2015). The EEG spikes appeared shortly prior to the earliest observable tics. However, once initiated, the tics occurred concurrently with the EEG spikes (Tarsy et al., 1978; Muramatsu et al., 1990). The tic-related LFP spikes were stereotypic, lasted several hundred milliseconds and appeared synchronously with the tics (McCairn et al., 2009). Tic-related changes in the activity of individual neurons appeared throughout the CBG pathway. In the motor cortex, most of the recorded neurons fired abnormally, as they discharged in highly active bursts concurrently with the tics with little or no activity between tics (McCairn et al., 2009). In the striatum, an increase was found in the overall firing rate of MSN neurons during the tic period (Worbe et al., 2009). This results from the phasic firing rate modulations around tic onset time, as the neurons responded to tic expression with a brief burst of activity around the tic onset and nearly no
activity between tics (Bronfeld et al., 2011). MSN tic-related activity usually preceded both tic onset time and tic-related activity within the motor cortex (Bronfeld et al., 2011). Phasic firing rate modulations around tic onset were also found in striatal TANs composed of an increased and decreased phases of discharge rate around tic onset (Bronfeld et al., 2011). The MSNs and TANs that were locked to the tic time were found in the somatotopic region associated with the tic region within the striatum, while no tic-related changes were found in other regions within the striatum. In the GPe, the low frequency bursting (LFB) neurons displayed bursts of activity around tic onset and nearly no activity between tics (Bronfeld et al., 2011). The high frequency pauser (HFP) GPe neurons displayed both phasic increases and decreases in firing rate in relation to the tics, with most of the recorded neurons exhibiting excitation (McCairn et al., 2009). Complex response patterns were also found in the output nuclei of the BG; i.e., the GPi and the SNr. However, in these nuclei, most of the recorded neurons displayed transient decreases in firing rate in relation to the tics (Muramatsu et al., 1990; McCairn et al., 2009). In both segments of the GP, tic-related activity was distributed throughout the motor domain, regardless of the disinhibition region within the striatum and the location of the tics (Bronfeld et al., 2011). Consistent with the inhibitory response of the BG output nuclei, phasic excitations were found in the ventromedial nucleus of the thalamus in relation to the tics (Muramatsu et al., 1990). In the striatal disinhibition animal model, tic related neuronal activity changes were not unique to the CBG loop, in that tic-related responses were also found in the cerebellum prior to and during tic onset (McCairn et al., 2013a).

2.3. Relation to CBG theoretical models

These neurophysiological findings in TS human patients and in animal models of the disease may be assessed in the framework of some of the theoretical concepts dealing with the function of the CBG pathway in health and disease. Early studies utilized the mapping of pathways between the CBG components to put forward the box and arrow model (Albin et al., 1989; DeLong, 1990). In this model, each brain area is modeled as a single simplified unit (‘box’), which can either increase or decrease its overall activity depending on the activity of afferent brain areas and on the type of connection (‘arrow’). Thus, the CBG loop was perceived as a feedback loop with two competing elements: a positive feedback loop mediated by the direct pathway and a negative feedback loop mediated by the indirect pathway. The relative activity of
the two pathways is controlled by the dopaminergic signal which increases the activity of the
direct pathway and decreases the activity of the indirect pathway. Over the years, multiple
additions have been made to the original model to incorporate new anatomical and physiological
data, such as the hyperdirect pathway (Nambu et al., 2000), while maintaining the same basic
concept. According to the box and arrow model, hyperkinetic disorders in general, and TS
specifically, are expected to be associated with higher dopaminergic activity. This results in
enhanced activity in the direct pathway and reduced activity in the indirect pathway leading to
the inhibition of the output structures, which in turn results in disinhibition of the thalamus and
cortical targets, and enhances their overall activation.

Current data support the predictions of the box and arrow model for TS with regard to two key
features: changes in dopaminergic activity and increased cortical activity due to decreased basal
ganglia output (Table 1A). The supposition of hyper-dopaminergic activity is supported by the
success of dopamine antagonist treatment in handling the expression of tics (Jankovic, 2009).
Secondary support comes from the dopamine agonist models of TS which, despite not
demonstrating tics explicitly, express comorbid symptoms and secondary phenomena typical of
the disorder (Kelley et al., 1988; Mansbach et al., 1988). Direct support for the rate changes
predicted by the box and arrow model are provided by recordings in TS patients undergoing
surgery in which a lower baseline firing rate of the basal ganglia output, the GPi was observed
(Zhuang et al., 2009). This is also supported by fMRI studies that found increased activity in the
direct basal ganglia pathway (Baym et al., 2008) and increased cortical activity (Worbe et al.,
2012) and by the reduced silent period in the cortex following TMS (Ziemann et al., 1997).

A leading concept in CBG functionality is its central role in action selection models. These
models stress the role of the BG in choosing one or more actions out of a multitude presented to
the BG by the cortex (Mink, 1996). The models vary in the nature of the actions selected, which
range in their definition from low-level "simple" motor actions to high-level "complex"
behavioral schemes. The models also differ depending on whether the selection mechanism is
achieved using lateral or recurrent inhibition within the striatum (Wickens, 1993; Beiser and
Houk, 1998), or via feed-forward competition between the different pathways (Berns and
Sejnowski, 1998; Gurney et al., 2001). According to the action selection model, a malfunction of
the selection process, such as the one occurring following abnormal inhibition within the
striatum, will result in the expression of undesired actions that are not inhibited by the chosen action (Mink, 2001; Albin and Mink, 2006).

Indirect support for the action selection model and its malfunction in TS is provided by recordings in human TS patients undergoing surgery (Table 1B). These patients were seen to exhibit a burst of activity in the GPi prior to the tic (however, according to the model, a transient inhibition is expected) (Zhuang et al., 2009). Multiple fMRI and PET studies have reported transient cortical excitation prior to the tic, although it cannot be tied directly to the CBG pathway (Stern et al., 2000; Bohlhalter et al., 2006; Hampson et al., 2009; Neuner et al., 2014). More direct support for this concept is found in the striatal disinhibition animal model in which tic-related activity is expressed throughout the CBG pathway including a transient inhibition (tic release) in the basal ganglia output (GPi) (McCairn et al., 2009; Bronfeld et al., 2011) (Table 1B). Overall, although the physiological evidence is still sparse and may be affected by the comorbidities typical to TS, the vast majority of the data collected using diverse measures in human patients and animal models points to substantial changes occurring in neuronal activity throughout the CBG motor, associative and limbic pathways. The changes are not limited to a single brain region but rather represent a system-wide change in two main properties: the baseline firing rate and tic-related firing rate changes. These changes, which represent both temporally global changes (baseline rate) and temporally local changes (tic related), have been reported in multiple studies whereas other measures typical of other CBG disorders such as oscillatory and coherent activity do not appear to play a substantial role in TS physiology.

3. Deep brain stimulation

A novel approach to treating severe cases of TS which are non-responsive to behavioral and pharmacological treatments is a neurosurgical approach termed deep brain stimulation (DBS). This treatment, which has been previously applied successfully to multiple movement and psychiatric disorders, is used in an exploratory manner in TS.

3.1. Deep brain stimulation in movement disorders

The development of stereotaxic surgery enabled accurate access to deep brain structures for patients suffering from different disorders (Spiegel et al., 1947). This led to a proliferation of ablation surgeries during the 1950s and 60s targeting multiple brain structures, including the
basal ganglia for treating a multitude of movement disorders (Schwalb and Hamani, 2008). Some of these early studies used electrical stimulation as a means of identifying brain structures, thus paving the way for stimulation-based treatments which overcame the irreversibility of ablation-based treatments. In its current form, one or more DBS electrodes are chronically implanted and following surgery, continuous stimulation consisting of high frequency pulses is applied.

The vast majority of DBS surgeries for movement disorders are performed for treating Parkinson’s disease (PD). Multiple brain targets have been used for treating the symptoms of PD including the ventral intermediate (VIM) nucleus of the thalamus (Benabid et al., 1991), the GPi (Siegfried and Lippitz, 1994) and the STN (Limousin et al., 1995) (Table 2). Thalamic targets primarily provide relief to tremor but have limited effects on other motor symptoms while the GPi and the STN are used for more general treatment of the motor symptoms of PD. Each of these targets has a different effect on each of the motor symptoms and is associated with different side effects. Currently, bilateral implantation of electrodes in the STN is the de-facto standard, despite comparable results from GPi implantation, with both treatments providing immediate and long-lasting improvement for a wide variety of motor symptoms (Rodriguez-Oroz et al., 2005; Odekerken et al., 2013; Liu et al., 2014). In all cases, the implantation is targeted at the motor parts of the nucleus to avoid side effects arising from the stimulation of limbic pathways.

Dystonia is an additional movement disorder treated regularly with DBS. Multiple forms of dystonia exist, which are categorized as a function of anatomical distribution, age of onset, and division into primary and secondary. The most common form of dystonia treated with DBS is generalized primary dystonia but some other forms of dystonia respond well to DBS (Ostrem and Starr, 2008). The primary target representing the vast majority of the cases is the GPi (Guridi and Lozano, 1997) (Table 2). A very small minority of implantations were performed in the STN and thalamus, despite some successful results in these surgeries. Typically, unlike the immediate relief in symptoms occurring during DBS for PD, dystonia symptom reduction increases over weeks to months and lasts for prolonged periods.

3.2. Deep brain stimulation in obsessive-compulsive disorder
The effectiveness of DBS in treating movement disorders has led to its application in psychiatric conditions such as OCD. OCD is an anxiety disorder characterized by intrusive thoughts (obsessions) and repetitive or ritualistic actions (compulsions) and is a common comorbidity of TS. In severe cases, DBS in various targets associated with the limbic regions of the CBG circuit is used to ameliorate the symptoms of patients experiencing treatment-refractory OCD (Table 2).

Numerous clinical reports have stated that capsulotomy lesions placed in the anterior limbs of the internal capsules (ALIC) may alleviate patients' symptoms by interfering with reciprocal thalamocortical projections and over activation of the orbitofrontal cortex (Lippitz et al., 1999). Initially, DBS electrodes were implanted bilaterally in the ALIC, located based on anterior capsulotomy lesions (Nuttin et al., 1999, 2003; Abelson et al., 2005b). Symptom reduction appeared in most patients within a few weeks of treatment. In an attempt to improve results, more posterior sites were investigated, refining the target to the ventral ALIC and adjacent ventral striatum, targeting limbic CBG connections (Aouizerate et al., 2004; Greenberg et al., 2006, 2010; Goodman et al., 2010). DBS in the NAc also provides a partial reduction of OCD symptoms following both bilateral (Denys et al., 2010) and unilateral (Sturm et al., 2003) stimulation. Behavioral side-effects reported in PD patients who underwent STN DBS procedures have emphasized the role of the STN in behavioral integration, and led to the idea of stimulation in the limbic regions of the STN to treat non-motor symptoms. Although OCD symptoms attenuated, serious adverse events limit the usage of this nucleus as a DBS target (Mallet et al., 2008; Chabardès et al., 2013). Overall, although long term OCD DBS stimulation studies are still lacking, clinical outcomes of published short term studies indicate a significant symptom reduction lasting multiple years (Greenberg et al., 2006). This underscores the important therapeutic benefits of DBS in the psychopathology of severe and intractable OCD.

3.3. Deep brain stimulation in Tourette syndrome

The dramatic therapeutic benefits of DBS in movement disorder and early successes in psychiatric disorders paved the way for its implementation for treating severe cases of TS in which pharmacological and behavioral treatments were found to be inefficient. A growing number of TS DBS surgeries have been reported worldwide, recently exceeding 100 cases (for a detailed review see (Schrock et al., 2015)). Numerous surgical targets for TS DBS have been proposed, primarily within the CBG loop (Fig. 1; Table 2), in an attempt to select appropriate targets.
targets for the alleviation of both tics and comorbid symptoms. Regions of the medial thalamus
are the most commonly used targets due to their involvement in both motor and limbic pathways.
Preliminary studies of thalamic DBS were performed under the assumption that bilateral
stimulation in the CM-Pf complex would reduce the activity level of the dorsal (motor via CM)
and ventral (limbic via Pf) striatum (Vandewalle et al., 1999; Kim et al., 2013). These surgeries
resulted in partial tic reduction in both motor and vocal tics starting a week after surgery, with a
further decrease over longer follow-up periods (Visser-Vandewalle et al., 2003). Unilateral
stimulation was found to be ineffective compared to bilateral stimulation in a double blind study
(Maciunas et al., 2007). Findings from additional studies are consistent with these results, and
show a substantial reduction in tic severity following CM-Pf stimulation, with significant long
term improvement (Servello et al., 2008; Porta et al., 2009; Kaido et al., 2011; Maling et al.,
2012; Okun et al., 2013). The stimulation efficacy was confirmed by a prospective, randomized,
double-blinded study showing a significant improvement in tic severity during the on-stimulation
as compared with the off-stimulation state (Ackermans et al., 2011). However, the effect of
thalamic stimulation on comorbidities was conflicting; thus other targets involved in both motor
and limbic modulation were sought (Viswanathan et al., 2012).

Earlier successes of GPi stimulation in treating hyperkinetic disorders such as dystonia led to the
consideration of this region as a target for DBS in TS. Moreover, GPi stimulation affects both
motor and limbic pathways; thus, it is presumed to influence motor tics as well as psychiatric
comorbidities of TS (Viswanathan et al., 2012). Some procedures have targeted the
posteroventral GPi, the motor sub-region, leading to improvement in motor and vocal tics several
weeks after the operation, with a progressive improvement during a follow-up period, even to the
point of full tic remission (Diederich et al., 2005; Dehning et al., 2008; Zhang et al., 2014).
Others have found a greater improvement in stimulating the anteromedial GPi, the limbic sub-
region, given the involvement of the limbic loop in tic expression (Martinez-Fernandez et al.,
2011; Cannon et al., 2012). In the search for an optimal surgical target, several studies have
compared outcomes of stimulation in the limbic regions of the GPi and medial thalamus (Houeto
et al., 2005; Ackermans et al., 2006; Motlagh et al., 2013). Although both targets produced a
significant improvement in tic severity, a greater reduction of tics was obtained following the
pallidal stimulation (Welter et al., 2008). A recent double blind study of GPi DBS confirmed the
significant changes in tic severity (Kefalopoulou et al., 2015). Surprisingly, successful outcomes
were obtained in a case study of a patient who underwent DBS in the central GPe, an atypical
target for DBS (Piedimonte et al., 2013). Finally, a case study of a patient who suffered from
both TS and PD who underwent DBS in the STN, as typically targeted for treating PD, presented
an improvement in both tics and parkinsonian symptoms following stimulation (Martinez-Torres
et al., 2009).

The frequent association of TS and OCD/OCB is the rationale behind stimulating the ALIC and
NAc in treating TS patients' tics and comorbidities. Findings from these studies show a moderate
and sustained improvement in tic severity and a significant amelioration of OCD was observed
(Kuhn et al., 2007). However, tic reduction was lower compared to TS DBS in other locations, as
apparent in a case report of a patient whose symptoms improved after replacing the lead from the
ALIC to the CM-Pf complex (Flaherty et al., 2005; Shields et al., 2008). Moreover, while double
blind studies of thalamic (Ackermans et al., 2011) and pallidal (Kefalopoulou et al., 2015) DBS
have ruled out a placebo effect, such ALIC studies are still lacking.

Overall, target selections in TS DBS are multifaceted and patient specific, as both motor and
limbic aspects of the disorder, ameliorating motor and vocal tics as well as comorbid symptoms
need to be considered. Currently, three main targets are used: the CM-Pf complex of the
thalamus, the motor and limbic GPi and the ALIC and NAc (Fig. 1). In sharp contrast to the
immediate effects of DBS on PD symptoms, the symptomatic improvements following TS DBS
are delayed and gradual. A partial improvement of tic severity occurs in all these studies within a
few weeks following surgery, with further reduction occurring over longer periods of time.
Despite early successes showing the efficiency of DBS in treating the symptoms of TS,
additional progress in establishing the optimal target and stimulation parameters requires a better
assessment of the effects of DBS on the pathophysiology of TS.

4. Physiological effects of DBS

DBS surgery for different neurological disorders is a success story. However, despite its growing
popularity, its underlying mechanism in general and its specific neurophysiological effects on
each of the disorders remains obscure. A multitude of studies in human patients undergoing
surgery and in animal models have greatly improved our understanding of the mechanism over
the last decade. Only a very small fraction of these studies has been performed for TS; however,
the larger body of evidence from other CBG related disorders (such as PD) provides valuable information, and hints at its potential mechanism in TS.

4.1. Neurophysiological effect of DBS in PD

The mechanism of action of DBS has been studied most extensively in PD. This is a result of two main factors: the large number of PD patients who have undergone DBS implantation (currently around 150,000 worldwide) and successful animal models of the disorder, primarily MPTP treated primates and 6-OHDA treated rats. The mechanism hypothesized to be responsible for effect of DBS on PD symptom expression has changed dramatically over the years. Initially, the similarity in the effect of ablation and stimulation led to the assumption that the stimulation functions as a “temporary lesion” of the implanted nucleus, a concept supported by some early physiological studies (Boraud et al., 1996; Dostrovsky et al., 2000). Later studies however showed that the stimulation in either the STN or GPI does not inhibit the nuclei but rather leads to a partial temporal locking of neuronal activity to the stimulation pulses (Hashimoto et al., 2003; Bar-Gad et al., 2004). These conflicting results illustrate the dissociation between the inhibition of the stimulated nucleus and the locking of downstream targets via axonal activation, which was later confirmed in theoretical and experimental studies (McIntyre et al., 2004a; Miocinovic et al., 2006; Moran et al., 2011). The changes in the firing pattern associated with the stimulation leads to reduced oscillatory activity (Moran et al., 2012) and changes in the bursting activity of individual neurons (Hahn et al., 2008). This change in regularity was also assessed in some cases using measures associated with information theory such as the spike train entropy (Dorval et al., 2008). Overall, the stimulation functions to regularize single neuron activity by reducing the abnormal pattern transmission through the stimulated nucleus. In addition to changes in the activity of the neurons, the stimulation leads to changes in the interaction between neurons within the same nucleus as well as between nuclei. This is reflected in decreased coherence between neurons, both single units and multi-units, and larger neuronal populations as evidenced by the LFP (Brown et al., 2004; Meissner et al., 2005; Moran et al., 2012). This is consistent with theoretical models showing that a stimulation induced reduction in the oscillatory activity of the neurons in conjunction with reduced synchrony results in increased fidelity of the thalamo-cortical transmission, enabling information flow to the cortex (Rubin and Terman, 2004; Guo et al., 2008). Finally, the effect of the
stimulation is not static but rather evolves over time (Erez et al., 2009; McCairn and Turner, 2009; Moran et al., 2011) leading to decreased synaptic efficacy within the stimulated pathway. The diverse effects of the stimulation on the stimulated nucleus, its downstream targets and additional brain areas stem directly from the complex effect of the stimulation on multiple neuronal elements around the contacts of the electrodes including somas, efferent and afferent axons, and additional passing by axons (Lemon, 1984; McIntyre et al., 2004a, 2004b).

Attributing these different physiological and clinical changes to different elements has been a daunting task which is being addressed, at least partially, by optogenetic tools (Gradinaru et al., 2009).

4.2. Neurophysiological effect of DBS in TS

The vast majority of the 100+ reported cases of TS DBS has focused on the clinical outcomes and the effect of different stimulation targets, whereas only a few have examined the effect of DBS on neuronal activity. Stimulation in the thalamus was shown to modulate abnormal LFP oscillatory activity within the thalamus in a few (but not all) patients by decreasing the power in the low (≤10 Hz) frequencies (Bour et al., 2014) and increasing the power in higher (25-45 Hz) frequencies, which correlated to the improvement in the symptoms (Maling et al., 2012). These changes may be related to dopaminergic modulation, as demonstrated using PET, following thalamic stimulation (Kuhn et al., 2012). Stimulation in the GPi-homolog of anesthetized normal rats revealed similar results; namely, an increase in low gamma activity and a decrease in low beta band activity in both the M1 and the striatum (McCracken and Kiss, 2014). However, stimulation in an upstream nucleus, the NAc, of anesthetized normal rats resulted in enhanced beta and gamma band oscillations in the lateral orbitofrontal cortex, the medial prefrontal cortex and the MD thalamus (McCracken and Grace, 2009). It remains unclear whether persistent changes occur following DBS. A follow-up study on one patient found a long lasting effect of DBS, in that the clinical improvement remained present for 4 years after the stimulation was turned off (Dong et al., 2014). However, another study did not find changes in thalamic LFP oscillatory activity once the stimulator stopped working (Priori et al., 2013). A similar result was reported for PD patients undergoing STN DBS surgery (Giannicola et al., 2012), indicating that DBS may not necessarily induce persistent changes within the CBG loop.
Currently, primarily due to technical difficulties, there have been no studies of the effect of DBS on single neuronal activity in human patients. A small number of DBS studies have been conducted on animal models of TS. The mechanism of DBS that they revealed was generally consistent with the one observed in PD. Stimulation in the GPi results in a partial temporal locking of the neuronal responses to the stimulation pulses both in the stimulated nucleus and in the upstream nucleus – the GPe (McCairn et al., 2013b). This temporal locking abolishes the tic-related activity of the neurons, and for a short time period increases the overall firing rate of the nucleus (McCairn et al., 2012, 2013b). Thus, by influencing the firing patterns, the stimulation reduces the propagation of abnormal activity from the BG downstream to the thalamus and cortical areas. In addition, the neuronal activity response to the stimulation pulses was shown to be dynamic and evolved over time (McCairn et al., 2013b), indicating that short term plasticity plays a role in DBS function. Similar results were found in a GPi stimulation study in one normal primate (Bar-Gad and Turner, 2009), supporting the notion that the DBS mechanism is similar across clinical states. In addition, in a normal primate study it was found that the stimulation did not change task encoding neuronal activity. Thus, it enabled the flow of acute behavioral information throughout the BG, despite the changes that occurred in the neuronal activity patterns. In TS animal models, the stimulation induced significant neurophysiological changes, but did not cause major behavioral changes. Stimulation in the GPi did not reduce the sniffing (in the dopaminergic model) or the tic frequency (in the striatal disinhibition model), but decreased the magnitude of the tics and improved sensorimotor gating deficits (McCairn et al., 2012, 2013b; Posch et al., 2012). Behavioral effects were found immediately following STN stimulation in animals expressing stereotypic behaviors but not tics (Baup et al., 2008). The lack of immediate influence on tic frequency in animal models may be due to the short stimulation periods (seconds-minutes) that were used in these studies. This is in line with the reports that DBS stimulation in TS patients significantly reduced tic frequency with a latency of several months (Zhang et al., 2014). Studies of long term neurophysiological changes underlying the progressive effects of DBS in TS are still missing. Translational studies of long term DBS in animal models displaying chronic symptoms may provide new insights to this evolving therapeutic process.

Overall, studies have only started recently to address the mechanism of DBS on neuronal activity in TS. Although extensive studies are still needed, results from both human and animal models
are starting to accumulate. These results suggest that DBS alters the firing pattern, rather than the firing rate of neurons, in that neuronal activity has been found to be partially temporally locked to the stimulation pulses (Fig. 2). Thus, DBS exerts its effect by causing functional ablation, which reduces information flow through the stimulated nucleus. The similarity between findings on TS, PD and stimulation in normal animals support the notion that the mechanism of DBS is comparable regardless of the pathological state or region of stimulation.

5. Summary and conclusions

The growing popularity of DBS treatment as a therapeutic option for controlling the symptoms of different motor and psychiatric disorders, combined with the severe limitations of pharmaceutical therapies for TS, have led to an increasing number of exploratory DBS implantation surgeries. Targets for the DBS leads vary but are primarily situated in different targets along the CBG pathway: the GPi, thalamic nuclei and the NAc. These targets are part of either the motor pathway, presumably directly involved in tic generation, or the limbic pathway, presumably involved in the comorbidities and indirectly involved in tic generation via the premonitory urge. Early stimulation results show significant improvement in TS symptom expression following these surgeries. The improvements increase over the timeframe of weeks and months following the surgery and persist for years. Given this initial success, future progress will require further insights into the abnormal neuronal activity during TS and the ways in which this activity is modulated using DBS.

Physiological studies have reported system-wide changes throughout the CBG pathway, rather than focal neuronal abnormalities. These changes consist of an altered baseline level activity of individual neurons and whole nuclei, including changes to both firing rate and pattern. This is accompanied by abnormal interactions between cortical and thalamic areas with the basal ganglia. Finally, tic-related activity is expressed throughout the pathway, both preceding and following the expression of tics. While the converging experimental data are mostly coherent, it is crucial to bear in mind the limitations of the current dataset, which are primarily based on indirect non-invasive measures with only very few invasive recordings in human DBS patients and in only a small subset of the available animal models. Moreover, although a dataset is gradually building up on the neuronal abnormalities along the motor pathways related to tic
expression, little is currently known about the neuronal activity along the limbic pathways related to the premonitory urge. The modulation of this abnormal neuronal activity throughout the CBG pathway during DBS is complex and arises from the modulation of diverse neuronal populations. Most current thinking about this modulation comes indirectly from the more abundant recordings in PD patients as well as from studies in normal and disorder model animals. These studies emphasize that stimulation affects the firing pattern of individual neurons by partially entraining the neuronal firing to the stimulation pulses and a reduction in the transmission of the abnormal activity patterns, which is at least partially due to a depression of synaptic efficacy along the pathway. Moreover, the stimulation based modulation presumably functions on the correlated neuronal activity, hence reducing the loss-of-specificity induced by the striatal disinhibition.

The recent proliferation of new data stemming from both human patients and novel animal models have made the last decade a watershed in our understanding of TS pathophysiology. This novel physiological data constitute a crucial platform to advance stimulation based treatments from their current exploratory nature to standard clinical practice by supplying new measures of the neuronal modulation provided by DBS in TS.

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1. **DBS targets in TS.** Outline of the motor and limbic CBG pathways with the stimulation targets overlaid (stars) (pvGPi – posteroventral GPi, amGPi – anteromedial GPi).

2. **Tic encoding in the CBG pathway.** Schematic illustration of neuronal activity during (A) tic expression and (B) during DBS.
References


[Diagram of neuronal pathways]

A

Striatum → GPi → ? → CM-Pf → M1 → Tic

B

Striatum → GPi → ? → CM-Pf → M1 → No tic
(A) The box and arrow model

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(B) The action selection model

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Table 1: Neurophysiology of tics. Comparison between the predictions of theoretical TS models and experimental results from human patients and animal models of the disorder.

1 (Albin et al., 1989; DeLong, 1990) 2 (Jankovic, 2009) 3 (Kelley et al., 1988; Mansbach et al., 1988) 4 (Baym et al., 2008) 5 (Fujita et al., 2013) 6 (Zhuang et al., 2009) 7 (Boraud et al., 2001; Nevert et al., 2004) 8 (Ziemann et al., 1997) 9 (Mink, 2001; Albin and Mink, 2006) 10 (Stern et al., 2015) 11 (Bronfeld et al., 2011) 12 (McCairn et al., 2009) 13 (Bohlhalter et al., 2006; Neuner et al., 2014)
Table 2: DBS Targets. Comparison of DBS targets in TS and other CBG related disorders.

1(Schrock et al., 2015) 2(Siegfried and Lippitz, 1994) 3(Limousin et al., 1995) 4(Benabid et al., 1991) 5(Greenberg et al., 2010) 6(Mallet et al., 2008) 7(Guridi and Lozano, 1997)

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<td>+ 1</td>
<td>-</td>
<td>-</td>
<td>-</td>
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