
Review | Disorders of the Nervous System

Subthalamic Nucleus Deep Brain Stimulation: Basic Concepts and Novel Perspectives

Perspectives on STN DBS

Clement Hamani^{1,2,4}, Gerson Florence⁴, Helmut Heinsen^{3,9}, Birgit R. Plantinga^{5,6}, Yasin Temel^{6,7}, Kamil Uludag⁸, Eduardo Alho⁴, Manoel J. Teixeira⁴, Edson Amaro³ and Erich T. Fonoff^{4,10}

¹*Division of Neurosurgery, Sunnybrook Health Sciences Center, Sunnybrook Research Institute, University of Toronto*

²*Division of Neuroimaging Centre for Addiction and Mental Health, University of São Paulo Medical School, São Paulo, Brazil*

³*Department of Radiology, University of São Paulo Medical School, São Paulo, Brazil*

⁴*Division of Neurosurgery Department of Neurology, University of São Paulo Medical School, São Paulo, Brazil*

⁵*Department of Biomedical Image Analysis, Eindhoven University of Technology, Eindhoven, Netherlands*

⁶*Department of Neuroscience, Maastricht University, Maastricht, Netherlands*

⁷*Department of Neurosurgery, Maastricht University Medical Center, Maastricht, Netherlands*

⁸*Department of Cognitive Neuroscience, Maastricht University, Maastricht, Netherlands*

⁹*Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Clinic of Würzburg, Germany Würzburg*

¹⁰*Instituto De Ensino e Pesquisa Hospital Sírio-Libanês, São Paulo, Brazil*

DOI: 10.1523/ENEURO.0140-17.2017

Received: 21 April 2017

Revised: 7 July 2017

Accepted: 6 August 2017

Published: 13 September 2017

Author contributions: All authors have contributed with the writing of the manuscript.

Funding: None

Conflict of Interest: CH received honoraria from Medtronic and St Jude Medical. The other authors report no conflicts of interest.

Research was supported in part with funds from Fundação de Amparo à Pesquisa do Estado de São Paulo - FAPESP and Projeto PROADI SUS - IEP Hospital Sírio-Libanês.

Corresponding author: Clement Hamani, Sunnybrook Research Institute, 2075 Bayview Ave, S wing room S126, Toronto, ON M4N 3M5, Canada. Phone: (1)(416)4806100 ext 3318; Email: c.hamani@utoronto.ca

Cite as: eNeuro 2017; 10.1523/ENEURO.0140-17.2017

Alerts: Sign up at eneuro.org/alerts to receive customized email alerts when the fully formatted version of this article is published.

Accepted manuscripts are peer-reviewed but have not been through the copyediting, formatting, or proofreading process.

Copyright © 2017 Hamani et al.

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license, which permits unrestricted use, distribution and reproduction in any medium provided that the original work is properly attributed.

1 **1. Title:** Subthalamic nucleus deep brain stimulation: Basic concepts and novel
2 perspectives

3 **2. Abbreviated Title:** Perspectives on STN DBS

4 **3. Authors:** Clement Hamani MD, PhD ^{1,2,4}, Gerson Florence PhD ⁴, Helmut Heinsen PhD
5 ^{3,9}, Birgit R. Plantinga PhD ^{5,6}, Yasin Temel MD PhD ^{6,7}, Kamil Uludag PhD ⁸, Eduardo Alho
6 MD ⁴, Manoel J. Teixeira MD, PhD ⁴, Edson Amaro MD ³, Erich T. Fonoff MD, PhD ^{4,10}

7 1.Division of Neurosurgery, Sunnybrook Health Sciences Center, Sunnybrook Research
8 Institute, University of Toronto

9 2.Division of Neuroimaging, Centre for Addiction and Mental Health

10 3.Department of Radiology, University of São Paulo Medical School, São Paulo, Brazil.

11 4.Division of Neurosurgery, Department of Neurology, University of São Paulo Medical
12 School, São Paulo, Brazil.

13 5.Department of Biomedical Image Analysis, Eindhoven University of Technology,
14 Eindhoven, Netherlands

15 6.Department of Neuroscience, Maastricht University, Maastricht, Netherlands

16 7.Department of Neurosurgery, Maastricht University Medical Center, Maastricht,
17 Netherlands

18 8.Department of Cognitive Neuroscience, Maastricht University, Maastricht, Netherlands

19 9.Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental
20 Health, University Clinic of Würzburg, Würzburg, Germany

21 10. Instituto de Ensino e Pesquisa Hospital Sírio-Libanês, São Paulo, Brazil

22

23 **4. Author contributions:** All authors have contributed with the writing of the
24 manuscript.

25

26 **5. Corresponding author:** Clement Hamani

27 Sunnybrook Research Institute

28 2075 Bayview Ave, S wing room S126

29 Toronto, ON M4N 3M5, Canada

30 Phone: (1)(416)4806100 ext 3318

31 Email: c.hamani@utoronto.ca

32

33 **6. Number of Figures:** 4

34 **7. Number of Tables:** 0

35 **8. Number of Multimedia:** 0

36 **9. Number of words for Abstract:** 147

37 **10. Number of words for Significance Statement:** 118

38 **11 and 12. Number of words in the text:** 4411

39 **13. Acknowledgements:** None

40 **14. Conflict of Interest:** CH received honoraria from Medtronic and St Jude Medical.

41 The other authors report no conflicts of interest.

42 **15. Funding Sources:** Research was supported in part with funds from Fundação de

43 Amparo à Pesquisa do Estado de São Paulo - FAPESP and Projeto PROADI SUS - IEP

44 Hospital Sírio-Libanês.

45

46 **Abstract**

47 Over the last decades, extensive basic and clinical knowledge has been acquired on the

48 use of subthalamic nucleus (STN) deep brain stimulation (DBS) for Parkinson's disease

49 (PD). It is now clear that mechanisms involved in the effects of this therapy are far more

50 complex than previously anticipated. At frequencies commonly used in clinical practice,

51 neural elements may be excited or inhibited and novel dynamic states of equilibrium are

52 reached. Electrode contacts used for chronic DBS in Parkinson's disease are placed near

53 the dorsal border of the nucleus, a highly cellular region. DBS may thus exert its effects

54 by modulating these cells, hyperdirect projections from motor cortical areas, afferent

55 and efferent fibers to the motor STN. Advancements in neuroimaging techniques may

56 allow us to identify these neural elements, optimizing surgical targeting. In this review

57 we provide an update on mechanisms and the neural elements modulated by STN DBS.

58 **Key words:** Subthalamic nucleus; deep brain stimulation; mechanisms; plasticity;

59 anatomy; physiology; neuroimaging

60

61

62 **Significance Statement**

63 Over the last decades, extensive basic and clinical knowledge has been acquired on the
64 use of subthalamic nucleus (STN) deep brain stimulation (DBS) for Parkinson's disease
65 (PD). It is becoming clear that DBS exerts its effects through several mechanisms and
66 influences various neural structures and circuits. In this article, we discuss
67 electrophysiological findings suggesting that stimulation not only modulates activity of
68 neural elements but also leads to novel dynamic states of equilibrium. We also present
69 anatomical data showing that the STN is not a homogeneous structure and review fiber
70 pathways and regions of the nucleus potentially modulated by DBS. Finally, we discuss
71 novel neuroimaging modalities and how these may be used to optimize technical aspects
72 of the surgery.

73

74

75 **Introduction**

76 From its origins to clinical approval, the history of subthalamic nucleus (STN) deep
77 brain stimulation (DBS) for Parkinson's disease (PD) has been one of extreme success. In
78 the late 80s, thalamic stimulation was proposed as an alternative to ablative procedures
79 for treating patients with tremor (Benabid et al., 1991). In 1-methyl-4-phenyl-1,2,3,6-
80 tetrahydropyridine (MPTP)-treated non-human primates, both STN lesions (Bergman et
81 al., 1990) and stimulation (Benazzouz et al., 1993) were shown to improve parkinsonian
82 features. Soon after, a series of PD patients was successfully treated with STN DBS
83 (Limousin et al., 1995). To date, over 120,000 patients worldwide have been implanted
84 with DBS systems. In PD, marked improvements have been reported in motor symptoms
85 and levodopa-induced involuntary movements (Deuschl et al., 2006; Weaver et al.,
86 2009a).

87 Aside from impacting patient care, investigational data from preclinical models
88 and surgical candidates have yielded significant advancements in our understanding of
89 the physiology and pathophysiology of the basal ganglia. Despite this fact and the 30
90 years of experience with DBS, its mechanisms of action are still not fully understood.

91 In this review we provide an update on mechanisms and the neural elements
92 modulated by STN stimulation. We discuss the complexity of DBS and the fact that
93 neural elements may be excited or inhibited, reaching novel dynamic states of
94 equilibrium. We also review neuroanatomical substrates modulated by DBS in the
95 region of the STN. Finally, we examine how advancements in neuroimaging techniques
96 may allow us to identify specific STN regions, so that this therapy may be optimized.

97

98 **Anatomical aspects of the STN and nearby fiber structures**

99 The subthalamic nucleus is a lens-shaped densely populated structure, with
100 extensive membrane apposition between the cell bodies, dendrites, and proximal axonal
101 segments (Chang et al., 1983; Afsharpour, 1985; Hamani et al., 2004). It is
102 predominantly composed of glutamatergic projection neurons with 7.5% of cells in
103 humans being identified as GABAergic interneurons (Hamani et al., 2004; Levesque and
104 Parent, 2005). In primates, the STN has been subdivided in a tripartite arrangement
105 based on physiological characteristics and the distribution of efferent/afferent
106 projections (Alexander et al., 1990; Parent and Hazrati, 1993, 1995b, a; Hamani et al.,
107 2004; Krack et al., 2010) (Figure 1). The limbic STN and part of the associative territory
108 lie in medial-rostral portions of the nucleus. The ventral-lateral-rostral portion
109 comprises the remainder of the associative region. The dorsolateral aspects of the
110 rostral STN and the caudal third of the nucleus are associated with motor circuits
111 (Parent and Hazrati, 1995a; Shink et al., 1996; Hamani et al., 2004).

112 **Fiber systems**

113 One of the characteristics of the STN is that it is enveloped by fibers, including the
114 internal capsule, pallidofugal system and medial lemniscus.

115 *Pallidofugal systems:* The ansa (AL) and fasciulus lenticularis (FL) are largely comprised
116 by globus pallidus internus (GPi)-thalamic projections. In primates, the former was
117 thought to originate largely from the lateral GPi (Kuo and Carpenter, 1973; Kim et al.,
118 1976), sweeping around the internal capsule and curving posteriorly to reach the H
119 Field of Forel (Figure 2). The FL (H2 Field of Forel) was believed to arise from the medial
120 GPi (Kuo and Carpenter, 1973; Kim et al., 1976), perforate the internal capsule and form
121 a bundle ventral to the zona incerta. In contrast to this classical view, however, recent

122 studies suggest that the AL and FL should be considered as ventral and dorsal portions
123 of a morphological continuum that harbors pallidofugal axons arising from all sectors of
124 the GPi (Parent and Parent, 2004). Independent of the origin of pallidothalamic
125 projections, the lenticular fasciculus joins the ansa along with fibers from the superior
126 cerebellar peduncle and brainstem in the H Field of Forel, forming the thalamic
127 fasciculus (H1 Field of Forel) (Hamani et al., 2004; Parent and Parent, 2004). An
128 important aspect to be noticed in non-human primates is that a substantial portion of
129 pallidofugal fibers seems to run anterior to the motor STN (Figure 3).

130 **Afferent and efferent STN projections**

131 *STN-Basal Ganglia:* Projections from the basal ganglia to the STN derive largely from the
132 globus pallidus externus (GPe) via the subthalamic fasciculus, a fibre bundle that
133 enters/departs the STN from its inferolateral border and crosses the internal capsule.
134 Efferents from the STN to the basal ganglia comprise glutamatergic projections that
135 innervate the globus pallidus, substantia nigra and striatum. Though most STN-nigral
136 projections innervate the pars reticulata (SNr), fibers to the pars compacta (SNc) have
137 received considerable attention as a substrate capable of regulating dopamine release
138 (Smith et al., 1990; Parent and Hazrati, 1995a; Rodriguez et al., 1998). Overall, STN-basal
139 ganglia projections seem to follow the tripartite distribution (Figure 1) (Parent and
140 Hazrati, 1995a; Shink et al., 1996; Hamani et al., 2004; Krack et al., 2010).

141 *STN-cerebral cortex:* The hyperdirect pathway is comprised of motor and premotor
142 cortical fibers that travel through the internal capsule and directly innervate the STN. The
143 former innervates the dorsal STN and arises from the primary motor cortex,
144 supplementary motor area (SMA), pre-SMA, as well as the dorsal and ventral pre-motor
145 cortices (Nambu et al., 1996; Nambu et al., 1997; Nambu et al., 2000). Ventromedial

146 portions of the nucleus receive afferents from the frontal and supplementary frontal eye
147 fields and are involved in circuits related to eye movements (Matsumura et al., 1992).
148 Prefrontal cortical afferents from areas the dorsolateral prefrontal cortex and anterior
149 cingulate cortex terminate in ventromedial and medial regions of the STN, respectively
150 (Haynes and Haber, 2013).

151 *Thalamus and Brainstem:* The main projections from the thalamus to the STN originate
152 from the parafascicular (Pf) and centromedian nuclei (CM) (Sadikot et al., 1992; Hamani
153 et al., 2004). Brainstem projections arise from various nuclei and involve multiple
154 neurotransmitter systems. These include dopaminergic fibers from the SNc (Lavoie et
155 al., 1989; Francois et al., 2000; Hamani et al., 2004), cholinergic and non-cholinergic
156 projections from the pedunculopontine nucleus and laterodorsal tegmental nuclei
157 (Carpenter et al., 1981; Mesulam et al., 1992; Lavoie and Parent, 1994), noradrenergic
158 fibers from the locus ceruleus (Carpenter et al., 1981), and serotonergic fibers likely
159 from the raphe (Parent et al., 2011).

160

161 **Physiological properties of the STN and oscillatory activity**

162 STN cells in non-human primates fire at 18 ± 25 Hz, mostly in irregular but also
163 regular and bursty patterns (Wichmann et al., 1994a; Hamani et al., 2004). In
164 parkinsonian states, the STN fires more irregularly at higher rates, ultimately disrupting
165 the functioning of downstream basal ganglia structures (Robledo and Feger, 1990;
166 Bergman et al., 1994; Hassani et al., 1996; Hutchison et al., 1998). Also abnormal in PD
167 are cortico-basal ganglia oscillations. STN cells oscillating at frequencies below 10 Hz are
168 sometimes related to parkinsonian tremor (Levy et al., 2000; Magarinos-Ascone et al.,
169 2000). Oscillations in the 70-85 Hz range occur during movement or treatment with

170 dopaminergic agonists (Magill et al., 2001; Levy et al., 2002; Hamani et al., 2004).
171 Oscillations in the beta range (15-30Hz) are prominent in sensorimotor regions of the
172 basal ganglia and cortex (Bergman et al., 1994; Brown et al., 2001; Mallet et al., 2008c).
173 These in fact seem to entrain spiking activity in the STN, striatal cholinergic
174 interneurons and basal ganglia downstream structures (Deffains et al., 2016).

175 In the clinic, while treatment-induced reductions in bradykinesia and rigidity
176 correlate with decreases in beta (Brown et al., 2001; Kuhn et al., 2008; Ray et al., 2008;
177 Kuhn et al., 2009), STN stimulation at beta frequencies may worsen bradykinesia (Chen
178 et al., 2007; Eusebio et al., 2008). These same results have not been observed in drug-
179 naïve non-human primates, which have been shown to develop dystonia and myoclonia
180 but no bradykinesia following STN stimulation (Syed et al., 2012). The actual role of beta
181 oscillations on mechanisms of bradykinesia remains disputed.

182 Also characteristic of PD are altered cross-frequency interactions (CFI) (Lopez-
183 Azcarate et al., 2010; Shimamoto et al., 2013; de Hemptinne et al., 2015). These are often
184 appreciated when a more complex analysis of interactions between different frequency
185 bands is conducted (Canolty and Knight, 2010). Similar to beta oscillations, CFIs
186 correlate with motor symptoms and may be reversed by the administration of
187 dopaminergic medications (Lopez-Azcarate et al., 2010).

188

189 **Behavioural effects of STN stimulation**

190 In rodents, focal injections of GABAergic antagonists into the STN induce postural
191 asymmetry and abnormal movements (Dybdal and Gale, 2000; Perier et al., 2000).
192 Similar to the clinical scenario (Dewey and Jankovic, 1989; Lee and Marsden, 1994),

193 both lesions and the focal inactivation of the STN in non-human primates induce ballism,
194 choreic and dyskinetic movements (Hammond et al., 1979; Crossman et al., 1980;
195 Hamada and DeLong, 1992; Beurrier et al., 1997). STN DBS delivered to otherwise naïve
196 non-human primates may induce dyskinesias and abnormal movements, particularly
197 when applied at relatively high currents (Beurrier et al., 1997; Hamani et al., 2004). In
198 parkinsonian rodents and primates, STN lesions or high frequency stimulation (HFS)
199 mitigate motor deficits, bradykinesia, rigidity and tremor (whenever this is present)
200 (Bergman et al., 1990; Aziz et al., 1992; Benazzouz et al., 1993; Wichmann et al., 1994b;
201 Carvalho and Nikkhah, 2001; Darbaky et al., 2003; Hamani et al., 2004).

202 In addition to motor effects, clinical studies suggest that STN DBS may be
203 associated with impulsivity, cognitive and psychiatric adverse events (Rodriguez-Oroz et
204 al., 2005; Frank et al., 2007; Halbig et al., 2009; Okun et al., 2009; Weaver et al., 2009b;
205 Follett et al., 2010; Bronstein et al., 2011; Rothlind et al., 2015). As patients receiving
206 DBS often have Parkinson's disease and are under pharmacological treatment, the
207 physiological role of the STN in non-motor behaviour may be better appraised in
208 preclinical models (Hamani and Temel, 2012).

209 In animals, some of the most commonly investigated non-motor behaviours are
210 impulsivity, compulsivity, drug and reward consumption (Hamani and Temel, 2012).
211 Impulsivity can be broadly defined as acting or making decisions without appropriate
212 forethought (Winstanley, 2011). Overall, impulsive behaviour encompasses multiple
213 facets, from motor disinhibition to maladaptive decision-making, involving motor,
214 attention and non-planning aspects (Brunner and Hen, 1997; Evenden, 1999;
215 Winstanley, 2011). Frequently used paradigms to study impulsivity in rodents are those
216 in which individuals need to withhold from making a response (e.g. measurements of

217 reaction time) or have to properly select a response to obtain a reward (e.g. five-choice
218 serial reaction time task) (Winstanley, 2011). Commonly observed inappropriate
219 responses during such tasks include prematurely responding to the stimuli or making
220 errors of perseveration. In some of these paradigms, STN lesions or the focal
221 administration of GABAergic agonists in otherwise naïve rats induce impulsive-like
222 behaviour (Baunez et al., 1995; Baunez and Robbins, 1997, 1999b). In parkinsonian
223 rodents, STN lesions increase perseverative responses (Baunez and Robbins, 1999a).
224 Compared to lesion studies, the effects of STN DBS are far more controversial. In naïve
225 animals, HFS has been shown not to affect impulse-like behaviour (Desbonnet et al.,
226 2004), reduce premature responses (Desbonnet et al., 2004), or even impair
227 performance (e.g. is a visual attention task) (Baunez et al., 2007). Similarly, studies in PD
228 animals have shown reversal (Temel et al., 2005; Temel et al., 2006b), no effect
229 (Darbaky et al., 2003) or a transient worsening of associated deficits (Baunez et al.,
230 2007). Reasons for discrepancy across studies remain unclear but may be related to
231 differences in behavioural paradigms, current intensity or the use of unilateral vs.
232 bilateral stimulation.

233 Along with impulsivity, gambling and punting are aspects commonly described as
234 part of the so-called dopamine dysregulation syndrome (DDS) (Fenu et al., 2009;
235 O'Sullivan et al., 2009). In the clinic, STN DBS has been used to treat these conditions
236 following the reduction in dopaminergic medication intake (Broen et al., 2011).
237 Preclinical paradigms suited to model some aspects of gambling-type behaviour involve
238 the presentation of animals with options associated with variable amounts of reward,
239 from smaller immediate to late but more gratifying compensations (Cocker and
240 Winstanley, 2015). In otherwise naïve rodents, STN-DBS significantly increases the
241 number of premature responses in some of these paradigms (i.e. the selection of

242 immediate disadvantageous rewards) (Aleksandrova et al., 2013). In contrast, animals
243 bearing STN lesions have a decrease in impulsive decision-making and are able to wait
244 for larger delayed rewards (Winstanley et al., 2005; Uslaner and Robinson, 2006).

245 Another commonly reported side effect of STN DBS is depression (Temel et al.,
246 2006a). Similar to the clinical scenario, rodents treated with STN DBS present
247 depressive-like behaviour in different models (Temel et al., 2007; Creed et al., 2013).

248 In recent years, DBS has been used to treat patients with refractory obsessive-
249 compulsive disorder (OCD) (Mallet et al., 2002; Mallet et al., 2008b; Haynes and Mallet,
250 2010). Preclinical models to mimic this condition are usually characterized by repetitive,
251 excessive and inappropriate behaviours, which may occur either naturally or as a
252 consequence of pharmacological and behavioural manipulations (Joel, 2006; Albelda and
253 Joel, 2012; Hamani and Temel, 2012). A limitation of these paradigms, however, is that
254 they only mimic compulsivity but not obsessions (Albelda and Joel, 2012; Hamani and
255 Temel, 2012). In rodents, STN HFS has been shown to improve perseverative and
256 compulsive-like behaviours (Winter et al., 2008; Klavir et al., 2009). Similarly,
257 nonhuman primates treated with HFS in the limbic portion of the STN had an
258 improvement in compulsive-like features induced the injections of GABAergic
259 antagonists into basal ganglia structures (Baup et al., 2008).

260 Another interesting aspect of the STN physiology is its role in mechanisms of
261 reward and addiction. In rodents, bilateral STN lesions increase motivation to obtain
262 food reward (Baunez et al., 2002; Baunez et al., 2005; Rouaud et al., 2010) while
263 reducing the preference and willingness to work for cocaine (Baunez et al., 2005;
264 Rouaud et al., 2010). When alcohol is considered, STN lesions increase motivation for
265 drug intake in animals considered to be “high drinkers”, inducing an opposite effect “low

266 drinker” rats (Lardeux and Baunez, 2008). These results highlight the complexity of
267 physiological mechanisms of the STN on reward.

268

269 **Mechanisms of DBS**

270 Single pulses of cathodic extracellular stimulation depolarize cells, axons and
271 dendrites. Once action potentials are fired, neurons tend to repolarize and the normal
272 ionic/neurotransmitter baseline equilibrium is reestablished. These same physiological
273 responses do not occur when stimulation is delivered at clinical frequencies (i.e. 130-
274 185Hz). For one, only neural appendages fire action potentials in response to high
275 frequency stimulation. In addition, the continuous delivery of HFS overloads
276 mechanisms responsible for the extracellular removal of certain ions and transmitters
277 (Florence et al., 2016). Ultimately, stimulated regions reach a new dynamic state,
278 characterized by altered ionic currents, non-synaptic mechanisms, excessive
279 extracellular levels of neurotransmitters/ions (e.g. potassium), and microenvironmental
280 changes that favor the development of plasticity (Hamani and Temel, 2012; Florence et
281 al., 2016).

282 From a neuronal perspective, a commonly proposed pattern of response following
283 HFS involves the depolarization of axons and functional inhibition of cell bodies (Lozano
284 et al., 2002; Vitek, 2002; Hamani and Temel, 2012; Florence et al., 2016). Though this is
285 well suited to explain some DBS responses, it is rather simplistic. For example, one of the
286 proposed mechanisms for the effects of HFS is the so-called “depolarization block”
287 (Beurrier et al., 2001; Magarinos-Ascone et al., 2002; Kringelbach et al., 2007). This has
288 been largely defined as a state in which cells undergo depolarization with an almost
289 complete abolishment of spontaneous action potentials (Beurrier et al., 2001;

290 Magarinos-Ascone et al., 2002). The rationale suggesting that depolarization block and a
291 functional target inactivation may play a role in a HFS response stems from the fact that
292 clinical outcome in some DBS applications (e.g. tremor, PD) resembles that observed
293 with lesions. To date, stimulation-induced depolarization blocks have been largely
294 demonstrated in brain slices. *In vivo* studies conducted in rodents (Tai et al., 2003), non-
295 human primates (Meissner et al., 2005), and humans (Filali et al., 2004) have shown
296 striking reductions in the firing of STN cells nearby the electrodes. Yet, the mechanisms
297 responsible for this effect may not only involve a depolarization block but also the
298 excitation of pallidal GABAergic terminals to the STN (Filali et al., 2004).

299 An aspect not commonly reported, however, is that depolarization blocks are not
300 sustainable events. Over time, cells restore repolarizing mechanisms and become once
301 again capable of firing action potentials until the development of a new depolarization
302 block (Zheng et al., 2011; Florence et al., 2016). As a result, the same stimulated region
303 may contain cells that are either functionally blocked or firing in tonic or even bursty
304 modes (Kass and Mintz, 2006; Wu and Shuai, 2012). Also not commonly described is the
305 fact that cells held in a depolarization block are theoretically capable of releasing
306 neurotransmitters. As the membrane potential becomes more positive and the
307 amplitude of action potentials decreases, both intracellular calcium influx and
308 neurotransmitter release are decreased. Depolarized membranes, however, may still
309 release neurotransmitters in smaller non-quantal amounts, even when the cell stops
310 firing. This “synaptic noise” has in fact been shown to modulate postsynaptic currents
311 (Ammari et al., 2011). Depending on the released neurotransmitter, postsynaptic
312 neurons may depolarize or hyperpolarize, becoming more or less responsive to inputs
313 from other presynaptic cells (Fellous et al., 2003; Faisal et al., 2008). Highlighting the
314 importance of this mechanism, STN synaptic noise has been shown to interrupt

315 abnormal oscillatory patterns in parkinsonian animals (Ammari et al., 2011). That said,
316 further evidence is required to confirm the relevance of synaptic noise-associated
317 neurotransmitter release as a mechanism of DBS.

318 Another commonly proposed mechanism underlying the effects of HFS is the
319 excitation of fibre pathways (afferent and efferent projections from targeted regions as
320 well as *en passant* fibers) (Kringelbach et al., 2007). This is of importance, as the
321 anterograde and retrograde propagation of action potentials may influence the
322 physiology of brain regions at a distance from the original stimulation site (Windels et
323 al., 2000; Hashimoto et al., 2003; Kringelbach et al., 2007; Temel et al., 2007). Fibers
324 modulated by HFS may be those arriving, departing or passing through (*en passant*) the
325 target zone. Neurotransmitters released may dictate the effects of DBS at a distance. For
326 example, with a predominance of glutamatergic projection cells DBS in the STN has been
327 shown to increase cell firing in structures innervated by the nucleus (Hashimoto et al.,
328 2003). Microdialysis studies corroborate this assertion, showing glutamate release in
329 output basal ganglia structures (Windels et al., 2000). However, with a complex
330 interplay of modulated afferent and efferent projections, the net effects of DBS are not
331 always predictable. As an example, STN DBS has been shown to significantly reduce
332 neuronal firing in the nigra, particularly when applied at lower amplitudes (Maurice et
333 al., 2003; Tai et al., 2003). This may occur due to an increased release of GABA via the
334 modulation of pallidal activity (Windels et al., 2005). Also contributing to a functional
335 inhibition of circuits, cells at a distance from the DBS target may not recognize
336 stimulation-driven high frequency rhythms that replace physiological firing patterns (i.e.
337 “jamming”) (Benabid et al., 2002). Finally, we note that, though the main consequence of
338 DBS at 130-185Hz is to drive axonal projections, frequencies closer to 200Hz may

339 potentially lead to a state of intermittent excitation or even partial blockage of axonal
340 firing (Kilgore and Bhadra, 2004; Florence et al., 2016).

341 Also described following HFS are changes in glial activity, synaptic transmission
342 and the development of various forms of plasticity (Hamani et al., 2012; Cooperrider et
343 al., 2014). In some clinical applications (e.g. dystonia, epilepsy) the effects of DBS are
344 often protracted or build up with time. Though an immediate clinical benefit is often
345 appreciated in PD, when batteries expire patients may not present the same
346 preoperative symptoms or medication requirements, suggesting that plastic events may
347 have reorganized the system.

348 To date, several studies in PD patients and animal models have shown that STN
349 HFS reduces beta oscillations, coherence between motor cortex and STN activity, and
350 phase amplitude coupling (Wingeier et al., 2006; Eusebio et al., 2008; Kuhn et al., 2008;
351 Bronte-Stewart et al., 2009; Giannicola et al., 2010; Tass et al., 2012; de Hemptinne et al.,
352 2015). Some of these signals have been recently proposed to feed closed-loop
353 stimulation systems. Studies in non-human primates (Rosin et al., 2011; Johnson et al.,
354 2016) and PD patients (Little et al., 2013) have shown that, compared to regular or
355 intermittent HFS, stimulation delivered following the detection of beta oscillatory bursts
356 or according to the pattern of neuronal firing induce a similar or slightly more
357 pronounced clinical improvement. In a recent report, however, closed-loop STN
358 stimulation delivered to PD primates did not improve bradykinesia during a reaching
359 task (Johnson et al., 2016). This result has been attributed to the fact that beta amplitude
360 declines during motion and suggests that additional work is still needed before closed-
361 loop stimulation may be implemented in the clinic.

362

363 **Cytoarchitectonic features and elements modulated by DBS**

364 As most human studies addressing cytoarchitectonic features were conducted with
365 classical staining techniques, a few caveats need to be taken into account. First, the STN
366 has an intimate relationship and is partly enwrapped by fibers. Second, its axes are not
367 arranged in parallel to the main axes of the hemispheres. Third, depending on the plane
368 of section, shape and individual orientation, different profiles and grazing artifacts may
369 be observed in Nissl or Golgi-stained sections. Finally, cytoarchitectonic delineations are
370 subject to inter-individual variability. When thick gallocyanin stained slices and dark-
371 field illumination sections are examined (Heinsen et al., 2000), a few aspects not
372 previously reported in classical *post-mortem* human studies can be appreciated. 1)
373 Rather than a homogeneous structure, the STN has a looser cellular core and densely
374 packed peripheral regions (Figure 4). 2) Fiber bundles may be identified near the STN
375 borders as well as in central parts of the nucleus. 3) The medial STN has a fairly
376 irregular outline, with rostromedial strands of cells almost reaching the hypothalamus
377 (Figure 4).

378 Electrode contacts used for chronic DBS in PD are often located near the dorsal
379 border of the nucleus (Herzog et al., 2004; Pollo et al., 2007). In addition to being part of
380 the motor territory, this region is characterized by the presence of high-density cellular
381 clusters in post-mortem studies. The main fiber pathways entering the motor STN are
382 hyperdirect projections from motor cortical areas, which in fact may be a major
383 substrate modulated by STN DBS (Figure 5). In agreement with this statement,
384 optogenetic studies have shown that stimulation of hyperdirect pathways may rescue
385 behavioural deficits in parkinsonian rodents (Gradinaru et al., 2009). To date, the
386 modulation of fibers in the Fields of Forel, particularly pallidothalamic projections, have

387 been proposed as a potential mechanism for the effects of DBS. Though not many studies
388 have reported anatomical details of these systems in humans, data from non-human
389 primates suggest that most of the AL and FL lie slightly anterior to the region where
390 electrodes are often implanted. Other substrates that could be potentially modulated by
391 DBS are axons within the motor STN territory. These may comprise afferents/efferents
392 to and from the motor STN. Stimulation of the former would theoretically excite or
393 inhibit the target zone, depending on the neurotransmitter released (e.g. glutamate from
394 cortical/thalamic afferents, GABA from pallidal afferents,
395 serotonin/dopamine/acetylcholine from brainstem afferents). The excitation of STN
396 glutamatergic efferents would drive activity in structures receiving its projections.

397 DBS electrodes used to treat obsessive-compulsive disorder are placed in
398 anteromedial regions of the STN (Mallet et al., 2008a). Under these circumstances, cell
399 bodies modulated by stimulation would be those innervating limbic/associative STN
400 territories and nearby hypothalamic regions. Hyperdirect components would be fibers
401 from the dorsolateral prefrontal cortex, orbitofrontal cortex and cingulate gyrus.
402 Stimulated afferents/efferents to and from the STN would be those innervating
403 limbic/associative regions of the basal ganglia, thalamus and brainstem. As PD patients
404 who develop DBS-induced psychiatric side effects often have electrodes implanted
405 medially, the same neural elements could be theoretically involved in mechanisms of
406 these adverse events.

407

408 **Neuroimaging**

409 Adequate visualization of the STN greatly depends on MRI protocols. On T2, T2*
410 and susceptibility weighted images, the nucleus appears as a dark structure. At 1.5T and
411 less so at 3T, MRI identification of the STN may be hindered by limited imaging contrast
412 and the poor identification of the STN/SN border (Figure 6). Ultra-high field (7T and
413 higher) MRI has the potential to overcome some of these limitations and promises to
414 facilitate patient-specific direct targeting (Plantinga et al., 2014).

415 As described above, the STN may be subdivided in different subterritories based
416 anatomical connections and physiological characteristics. The use of diffusion weighted
417 imaging based tractography has been proposed as a potential strategy for classifying
418 deep brain structures into subregions (Behrens et al., 2003). The simplest of these
419 models is diffusion tensor, which can be created with relatively short scan times but fails
420 when there are multiple fiber orientations within one voxel. More advanced models
421 seem to be able to cope with crossing fibers when combined with probabilistic tracking
422 algorithms (Behrens et al., 2007; Tournier et al., 2007). On a group level, these models
423 have been used to subdivide the STN into functional regions in 3T scanners (Lambert et
424 al., 2012). At 7T, the motor region could be successfully discriminated based on
425 structural connectivity (Plantinga et al., 2016) (Figure 6). Though this technique is not
426 without limitations (e.g. false positives and negatives), these results highlight the
427 potential future application of neuroimaging strategies to refine surgical targeting.

428

429 **Conclusions**

430 In summary, the mechanisms involved in the effects of DBS seem to be far more
431 complex than previously anticipated. Instead of a simple excitation of fibers and

432 inhibition of cells, neural elements influenced by DBS reach novel dynamic states over
433 time. From an anatomical perspective, human pathological specimens suggest that the
434 STN has dense cellular aggregates near its borders and a less compact central core,
435 which is infiltrated by fibers. Discriminating the nature of these fibers and those
436 crossing the dorsal STN border (i.e. where active contacts are implanted) will be crucial
437 for a better appraisal of mechanisms responsible for this therapy.

438 One of the ultimate goals to be achieved with DBS is to maximize efficacy while
439 minimizing side effects. The former has been attempted by mimicking brain rhythms so
440 that some forms of beta band activity and other pathological rhythms may be reduced.
441 To date, similar strategies have been effective in preclinical models but still need to be
442 perfected for clinical use. With proven efficacy, a key factor to minimize DBS-induced
443 side effects is to avoid stimulating structures and brain regions involved in adverse
444 events. A major advance towards this objective is the use of directional leads, which may
445 deviate and steer current away from these structures. Also important have been recent
446 advancements in neuroimaging modalities. The use of higher magnetic fields and
447 diffusion/connectivity approaches to identify subregions of the nucleus and specific
448 fiber bundles may advance the way we do surgery by improving targeting precision.

449

450 **Figure Legends**

451

452 **Figure 1.** Subthalamic nucleus (STN) and the tripartite model. Intrinsic organization of
453 the STN, basal ganglia structures and cortical regions according to the tripartite
454 functional subdivision. The motor circuit (blue) includes motor cortical areas (primary
455 motor cortex, supplementary motor cortex, pre-motor cortex, and portions of the

456 somatosensory dorsal parietal cortex), the dorsolateral portion of the postcommissural
457 putamen, the lateral two-thirds of the globus pallidus (GPe and GPi) and a small portion
458 of the substantia nigra (SNr). In the STN, motor regions comprise dorsal-lateral aspects
459 of the rostrocaudal third of the nucleus (Hamani et al., 2004). Associative circuits
460 (purple) comprise associative cortical regions, most of the caudate nucleus, the putamen
461 rostral to the anterior commissure, the dorsal aspect of the medial third of the globus
462 pallidus (GPe and GPi) and most of the substantia nigra. Associative STN regions may be
463 found in ventral-lateral-rostral portions of the nucleus (Hamani et al., 2004). Limbic
464 circuits (grey) are comprised of limbic cortical areas (e.g. orbitofrontal and the anterior
465 cingulum), the nucleus accumbens and the most rostral portions of the striatum, the
466 subcommissural ventral pallidum (VP), small limbic regions in the ventral portion of the
467 medial third of the globus pallidus (GPe and GPi), the medial tip of the substantia nigra,
468 and the ventral tegmental area. The limbic STN lies in mediorostral portions of the
469 nucleus (Hamani et al., 2004). Arrows represent some of the most important
470 connections between structures. D- dorsal; L- lateral; M- medial; V- ventral. We note that
471 this schematic diagram largely represents structures in two planes with the
472 anteroposterior depiction often lacking. This is the main reason for the superposition of
473 colors representing motor, associative and limbic regions.

474

475 **Figure 2.** Anatomical aspects of the subthalamic nucleus (STN). Principal brain
476 structures surrounding the STN. AL- ansa lenticularis; FF- Fields of Forel; FL- fasciculus
477 lenticularis; FS- subthalamic fascicle; GPe- globus pallidus externus; GPi- globus pallidus
478 internus; H1- H1 Field of Forel (thalamic fasciculus); H2- H2 Field of Forel; IC- internal
479 capsule; ML- medial lemniscus; PPN- pedunculopontine nucleus; Put-putamen; SN-
480 substantia nigra; STN- subthalamic nucleus; Thal- thalamus; ZI- zona incerta. Modified

481 and reprinted from reference (Hamani et al., 2004) by permission of Oxford University
482 Press.

483

484 **Figure 3.** Subthalamic nucleus and pallidofugal fibers. Axial (A) and coronal (B)
485 schematic representations of the ansa (AL; red) and fasciculus lenticularis (LF; H2; blue)
486 in relationship to the subthalamic nucleus (STN) in non-human primates. Note that both
487 the tracts travel dorsal to the most anterior aspect of the STN. In A, the thalamic
488 fasciculus is represented in green. ant- anterior; lat- lateral; sup- superior. Modified and
489 reprinted from (Parent and Parent, 2004) with permission from Elsevier.

490

491 **Figure 4.** Histological sections of the subthalamic nucleus region in individuals with no
492 neurological disorders stained for gallocyanin. (A) Coronal section (440 μ m thickness)
493 showing the subthalamic nucleus (STN), zona incerta (ZI), H2 Field of Forel and
494 substantia nigra reticulata (SNr). Note the presence of high-density cellular regions near
495 the borders of the nucleus (white arrow) and fibers inside its core (*). The dark arrow
496 points to a vessel branching in the vicinity of the STN. (B) Sagittal section (400 μ m
497 thickness) showing high-density neuronal clusters (white arrow) and a region largely
498 comprised by capsular fibers (arrowhead) near the dorsal border of the STN. Magnified
499 view is presented in the square above. (C) Axial (horizontal) section (440 μ m thickness)
500 showing the anteromedial aspect of the STN in relation to the lateral hypothalamus (LH)
501 and fornix (Fx). Black arrows denote subthalamic cell strands piercing the internal
502 capsule and forming dissipated accessory cell groups (black open triangle) near the
503 lateral hypothalamus. White open triangles represent the irregular boundary between

504 STN cell clusters and capsular fibers. (D) Coronal section (440 μ m thickness) showing
505 the STN region under dark-field illumination (RN; red nucleus).

506

507 **Figure 5.** Neural elements modulated by DBS delivered to the dorsal region of the motor
508 subthalamic nucleus (STN) territory. (A) Schematic representation of the STN showing
509 potential fiber pathways modulated by DBS. Hyperdirect STN projections from motor
510 cortical regions are depicted in blue. Pallidofugal fibers are depicted in red. (B)
511 Schematic representation of an STN neuron modulated by DBS. STN axons driven by
512 stimulation would excite connected structures. Stimulation of STN afferents would
513 potentially excite these projections, inducing complex effects. STN cells would be excited
514 by stimulation of cortical and thalamic-STN projections (blue) and inhibited by
515 stimulation of globus pallidus projections and appendages from local interneurons
516 (red). Stimulation of brainstem-STN projections would modulate STN neuronal activity
517 via different neurotransmitter systems (green). 5HT- serotonin; ACh- acetylcholine; CM-
518 centromedian nucleus of the thalamus; DA- dopamine; GPe- globus pallidus externus;
519 GPi- globus pallidus internus; LC- locus ceruleus; LDTg- laterodorsal tegmental area; NE-
520 norepinephrine; PPN- pedunculopontine nucleus; SNc- substantia nigra pars compacta.

521

522 **Figure 6.** Tractography based subdivision of the STN. (A) Coronal T2*-weighted images
523 obtained at 7.0T, 3.0T, and 1.5T. (B) Coronal images showing STN connectivity with
524 limbic (red), associative (green), motor (blue) and remaining (yellow) cortical areas. (C)
525 Oblique view of the STN with a superposed DBS electrode and an active contact
526 implanted in the motor territory. Reprinted from (Cho et al., 2010) with permission

527 from the JNS publishing group, (Plantinga et al., 2014) published in *Frontiers in Human*
528 *Neuroscience*, and (Plantinga et al., 2016) with permission from Elsevier.

529

530 **References**

- 531 Afsharpour S (1985) Light microscopic analysis of Golgi-impregnated rat subthalamic neurons. *J Comp*
532 *Neurol* 236:1-13.
- 533 Albelda N, Joel D (2012) Animal models of obsessive-compulsive disorder: exploring pharmacology
534 and neural substrates. *Neurosci Biobehav Rev* 36:47-63.
- 535 Aleksandrova LR, Creed MC, Fletcher PJ, Lobo DS, Hamani C, Nobrega JN (2013) Deep brain
536 stimulation of the subthalamic nucleus increases premature responding in a rat gambling
537 task. *Behav Brain Res* 245:76-82.
- 538 Alexander GE, Crutcher MD, DeLong MR (1990) Basal ganglia-thalamocortical circuits: parallel
539 substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res* 85:119-
540 146.
- 541 Ammari R, Bioulac B, Garcia L, Hammond C (2011) The Subthalamic Nucleus becomes a Generator of
542 Bursts in the Dopamine-Depleted State. Its High Frequency Stimulation Dramatically
543 Weakens Transmission to the Globus Pallidus. *Front Syst Neurosci* 5:43.
- 544 Aziz TZ, Peggs D, Agarwal E, Sambrook MA, Crossman AR (1992) Subthalamic nucleotomy alleviates
545 parkinsonism in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-exposed primate.
546 *Br J Neurosurg* 6:575-582.
- 547 Baunez C, Robbins TW (1997) Bilateral lesions of the subthalamic nucleus induce multiple deficits in
548 an attentional task in rats. *Eur J Neurosci* 9:2086-2099.
- 549 Baunez C, Robbins TW (1999a) Effects of dopamine depletion of the dorsal striatum and further
550 interaction with subthalamic nucleus lesions in an attentional task in the rat. *Neuroscience*
551 92:1343-1356.
- 552 Baunez C, Robbins TW (1999b) Effects of transient inactivation of the subthalamic nucleus by local
553 muscimol and APV infusions on performance on the five-choice serial reaction time task in
554 rats. *Psychopharmacology (Berl)* 141:57-65.
- 555 Baunez C, Nieoullon A, Amalric M (1995) In a rat model of parkinsonism, lesions of the subthalamic
556 nucleus reverse increases of reaction time but induce a dramatic premature responding
557 deficit. *J Neurosci* 15:6531-6541.
- 558 Baunez C, Amalric M, Robbins TW (2002) Enhanced food-related motivation after bilateral lesions of
559 the subthalamic nucleus. *J Neurosci* 22:562-568.
- 560 Baunez C, Dias C, Cador M, Amalric M (2005) The subthalamic nucleus exerts opposite control on
561 cocaine and 'natural' rewards. *Nat Neurosci* 8:484-489.
- 562 Baunez C, Christakou A, Chudasama Y, Forni C, Robbins TW (2007) Bilateral high-frequency
563 stimulation of the subthalamic nucleus on attentional performance: transient deleterious
564 effects and enhanced motivation in both intact and parkinsonian rats. *Eur J Neurosci*
565 25:1187-1194.
- 566 Baup N, Grabli D, Karachi C, Mounayar S, Francois C, Yelnik J, Feger J, Tremblay L (2008) High-
567 frequency stimulation of the anterior subthalamic nucleus reduces stereotyped behaviors in
568 primates. *J Neurosci* 28:8785-8788.
- 569 Behrens TE, Berg HJ, Jbabdi S, Rushworth MF, Woolrich MW (2007) Probabilistic diffusion
570 tractography with multiple fibre orientations: What can we gain? *Neuroimage* 34:144-155.
- 571 Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, Barker GJ,
572 Sillery EL, Sheehan K, Ciccarelli O, Thompson AJ, Brady JM, Matthews PM (2003) Non-
573 invasive mapping of connections between human thalamus and cortex using diffusion
574 imaging. *Nat Neurosci* 6:750-757.

- 575 Benabid AL, Benazzous A, Pollak P (2002) Mechanisms of deep brain stimulation. *Mov Disord* 17
576 Suppl 3:S73-74.
- 577 Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, de Rougemont J
578 (1991) Long-term suppression of tremor by chronic stimulation of the ventral intermediate
579 thalamic nucleus. *Lancet* 337:403-406.
- 580 Benazzouz A, Gross C, Feger J, Boraud T, Bioulac B (1993) Reversal of rigidity and improvement in
581 motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys.
582 *Eur J Neurosci* 5:382-389.
- 583 Bergman H, Wichmann T, DeLong MR (1990) Reversal of experimental parkinsonism by lesions of the
584 subthalamic nucleus. *Science* 249:1436-1438.
- 585 Bergman H, Wichmann T, Karmon B, DeLong MR (1994) The primate subthalamic nucleus. II.
586 Neuronal activity in the MPTP model of parkinsonism. *J Neurophysiol* 72:507-520.
- 587 Beurrier C, Bezard E, Bioulac B, Gross C (1997) Subthalamic stimulation elicits hemiballismus in
588 normal monkey. *Neuroreport* 8:1625-1629.
- 589 Beurrier C, Bioulac B, Audin J, Hammond C (2001) High-frequency stimulation produces a transient
590 blockade of voltage-gated currents in subthalamic neurons. *J Neurophysiol* 85:1351-1356.
- 591 Broen M, Duits A, Visser-Vandewalle V, Temel Y, Winogrodzka A (2011) Impulse control and related
592 disorders in Parkinson's disease patients treated with bilateral subthalamic nucleus
593 stimulation: a review. *Parkinsonism Relat Disord* 17:413-417.
- 594 Bronstein JM et al. (2011) Deep brain stimulation for Parkinson disease: an expert consensus and
595 review of key issues. *Arch Neurol* 68:165.
- 596 Bronte-Stewart H, Barberini C, Koop MM, Hill BC, Henderson JM, Wingeier B (2009) The STN beta-
597 band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep
598 brain stimulation. *Exp Neurol* 215:20-28.
- 599 Brown P, Oliviero A, Mazzone P, Insola A, Tonali P, Di Lazzaro V (2001) Dopamine dependency of
600 oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J Neurosci*
601 21:1033-1038.
- 602 Brunner D, Hen R (1997) Insights into the neurobiology of impulsive behavior from serotonin
603 receptor knockout mice. *Ann N Y Acad Sci* 836:81-105.
- 604 Canolty RT, Knight RT (2010) The functional role of cross-frequency coupling. *Trends Cogn Sci* 14:506-
605 515.
- 606 Carpenter MB, Carleton SC, Keller JT, Conte P (1981) Connections of the subthalamic nucleus in the
607 monkey. *Brain Res* 224:1-29.
- 608 Carvalho GA, Nikkhah G (2001) Subthalamic nucleus lesions are neuroprotective against terminal 6-
609 OHDA-induced striatal lesions and restore postural balancing reactions. *Exp Neurol* 171:405-
610 417.
- 611 Chang HT, Kita H, Kitai ST (1983) The fine structure of the rat subthalamic nucleus: an electron
612 microscopic study. *J Comp Neurol* 221:113-123.
- 613 Chen CC, Litvak V, Gilbertson T, Kuhn A, Lu CS, Lee ST, Tsai CH, Tisch S, Limousin P, Hariz M, Brown P
614 (2007) Excessive synchronization of basal ganglia neurons at 20 Hz slows movement in
615 Parkinson's disease. *Exp Neurol* 205:214-221.
- 616 Cho ZH, Min HK, Oh SH, Han JY, Park CW, Chi JG, Kim YB, Paek SH, Lozano AM, Lee KH (2010) Direct
617 visualization of deep brain stimulation targets in Parkinson disease with the use of 7-tesla
618 magnetic resonance imaging. *J Neurosurg* 113:639-647.
- 619 Cocker PJ, Winstanley CA (2015) Irrational beliefs, biases and gambling: exploring the role of animal
620 models in elucidating vulnerabilities for the development of pathological gambling. *Behav*
621 *Brain Res* 279:259-273.
- 622 Cooperrider J, Furmaga H, Plow E, Park HJ, Chen Z, Kidd G, Baker KB, Gale JT, Machado AG (2014)
623 Chronic deep cerebellar stimulation promotes long-term potentiation, microstructural
624 plasticity, and reorganization of perilesional cortical representation in a rodent model. *J*
625 *Neurosci* 34:9040-9050.

- 626 Creed MC, Hamani C, Nobrega JN (2013) Effects of repeated deep brain stimulation on depressive-
627 and anxiety-like behavior in rats: comparing entopeduncular and subthalamic nuclei. *Brain*
628 *Stimul* 6:506-514.
- 629 Crossman AR, Sambrook MA, Jackson A (1980) Experimental hemiballismus in the baboon produced
630 by injection of a gamma-aminobutyric acid antagonist into the basal ganglia. *Neurosci Lett*
631 20:369-372.
- 632 Darbaky Y, Forni C, Amalric M, Baunez C (2003) High frequency stimulation of the subthalamic
633 nucleus has beneficial antiparkinsonian effects on motor functions in rats, but less efficiency
634 in a choice reaction time task. *Eur J Neurosci* 18:951-956.
- 635 de Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB, Starr PA
636 (2015) Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in
637 Parkinson's disease. *Nat Neurosci* 18:779-786.
- 638 Deffains M, Iskhakova L, Katabi S, Haber SN, Israel Z, Bergman H (2016) Subthalamic, not striatal,
639 activity correlates with basal ganglia downstream activity in normal and parkinsonian
640 monkeys. *Elife* 5.
- 641 Desbonnet L, Temel Y, Visser-Vandewalle V, Blokland A, Hornikx V, Steinbusch HW (2004) Premature
642 responding following bilateral stimulation of the rat subthalamic nucleus is amplitude and
643 frequency dependent. *Brain Res* 1008:198-204.
- 644 Deuschl G et al. (2006) A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J*
645 *Med* 355:896-908.
- 646 Dewey RB, Jr., Jankovic J (1989) Hemiballism-hemichorea. Clinical and pharmacologic findings in 21
647 patients. *Arch Neurol* 46:862-867.
- 648 Dybdal D, Gale K (2000) Postural and anticonvulsant effects of inhibition of the rat subthalamic
649 nucleus. *J Neurosci* 20:6728-6733.
- 650 Eusebio A, Chen CC, Lu CS, Lee ST, Tsai CH, Limousin P, Hariz M, Brown P (2008) Effects of low-
651 frequency stimulation of the subthalamic nucleus on movement in Parkinson's disease. *Exp*
652 *Neurol* 209:125-130.
- 653 Evenden J (1999) Impulsivity: a discussion of clinical and experimental findings. *J Psychopharmacol*
654 13:180-192.
- 655 Faisal AA, Selen LP, Wolpert DM (2008) Noise in the nervous system. *Nat Rev Neurosci* 9:292-303.
- 656 Fellous JM, Rudolph M, Destexhe A, Sejnowski TJ (2003) Synaptic background noise controls the
657 input/output characteristics of single cells in an in vitro model of in vivo activity.
658 *Neuroscience* 122:811-829.
- 659 Fenu S, Wardas J, Morelli M (2009) Impulse control disorders and dopamine dysregulation syndrome
660 associated with dopamine agonist therapy in Parkinson's disease. *Behav Pharmacol* 20:363-
661 379.
- 662 Filali M, Hutchison WD, Palter VN, Lozano AM, Dostrovsky JO (2004) Stimulation-induced inhibition
663 of neuronal firing in human subthalamic nucleus. *Exp Brain Res* 156:274-281.
- 664 Florence G, Sameshima K, Fonoff ET, Hamani C (2016) Deep Brain Stimulation: More Complex than
665 the Inhibition of Cells and Excitation of Fibers. *Neuroscientist* 22:332-345.
- 666 Follett KA et al. (2010) Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N*
667 *Engl J Med* 362:2077-2091.
- 668 Francois C, Savy C, Jan C, Tande D, Hirsch EC, Yelnik J (2000) Dopaminergic innervation of the
669 subthalamic nucleus in the normal state, in MPTP-treated monkeys, and in Parkinson's
670 disease patients. *J Comp Neurol* 425:121-129.
- 671 Frank MJ, Samanta J, Moustafa AA, Sherman SJ (2007) Hold your horses: impulsivity, deep brain
672 stimulation, and medication in parkinsonism. *Science* 318:1309-1312.
- 673 Giannicola G, Marceglia S, Rossi L, Mrakic-Sposta S, Rampini P, Tamma F, Cogiamanian F, Barbieri S,
674 Priori A (2010) The effects of levodopa and ongoing deep brain stimulation on subthalamic
675 beta oscillations in Parkinson's disease. *Exp Neurol* 226:120-127.
- 676 Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K (2009) Optical deconstruction of
677 parkinsonian neural circuitry. *Science* 324:354-359.

- 678 Halbig TD, Tse W, Frisina PG, Baker BR, Hollander E, Shapiro H, Tagliati M, Koller WC, Olanow CW
679 (2009) Subthalamic deep brain stimulation and impulse control in Parkinson's disease. *Eur J*
680 *Neurol* 16:493-497.
- 681 Hamada I, DeLong MR (1992) Excitotoxic acid lesions of the primate subthalamic nucleus result in
682 transient dyskinesias of the contralateral limbs. *J Neurophysiol* 68:1850-1858.
- 683 Hamani C, Temel Y (2012) Deep brain stimulation for psychiatric disease: contributions and validity of
684 animal models. *Sci Transl Med* 4:142rv148.
- 685 Hamani C, Saint-Cyr JA, Fraser J, Kaplitt M, Lozano AM (2004) The subthalamic nucleus in the context
686 of movement disorders. *Brain* 127:4-20.
- 687 Hamani C, Machado DC, Hipolide DC, Dubiela FP, Suchecki D, Macedo CE, Tescarollo F, Martins U,
688 Covolan L, Nobrega JN (2012) Deep brain stimulation reverses anhedonic-like behavior in a
689 chronic model of depression: role of serotonin and brain derived neurotrophic factor. *Biol*
690 *Psychiatry* 71:30-35.
- 691 Hammond C, Feger J, Bioulac B, Souteyrand JP (1979) Experimental hemiballism in the monkey
692 produced by unilateral kainic acid lesion in corpus Luysii. *Brain Res* 171:577-580.
- 693 Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL (2003) Stimulation of the subthalamic nucleus
694 changes the firing pattern of pallidal neurons. *J Neurosci* 23:1916-1923.
- 695 Hassani OK, Mouroux M, Feger J (1996) Increased subthalamic neuronal activity after nigral
696 dopaminergic lesion independent of disinhibition via the globus pallidus. *Neuroscience*
697 72:105-115.
- 698 Haynes WI, Mallet L (2010) High-frequency stimulation of deep brain structures in obsessive-
699 compulsive disorder: the search for a valid circuit. *Eur J Neurosci* 32:1118-1127.
- 700 Haynes WI, Haber SN (2013) The organization of prefrontal-subthalamic inputs in primates provides
701 an anatomical substrate for both functional specificity and integration: implications for Basal
702 Ganglia models and deep brain stimulation. *J Neurosci* 33:4804-4814.
- 703 Heinsen H, Arzberger T, Schmitz C (2000) Celloidin mounting (embedding without infiltration) - a
704 new, simple and reliable method for producing serial sections of high thickness through
705 complete human brains and its application to stereological and immunohistochemical
706 investigations. *J Chem Neuroanat* 20:49-59.
- 707 Herzog J, Fietzek U, Hamel W, Morsnowski A, Steigerwald F, Schrader B, Weinert D, Pfister G, Muller
708 D, Mehdorn HM, Deuschl G, Volkmann J (2004) Most effective stimulation site in subthalamic
709 deep brain stimulation for Parkinson's disease. *Mov Disord* 19:1050-1054.
- 710 Hutchison WD, Allan RJ, Opitz H, Levy R, Dostrovsky JO, Lang AE, Lozano AM (1998)
711 Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's
712 disease. *Ann Neurol* 44:622-628.
- 713 Joel D (2006) Current animal models of obsessive compulsive disorder: a critical review. *Prog*
714 *Neuropsychopharmacol Biol Psychiatry* 30:374-388.
- 715 Johnson LA, Nebeck SD, Muralidharan A, Johnson MD, Baker KB, Vitek JL (2016) Closed-Loop Deep
716 Brain Stimulation Effects on Parkinsonian Motor Symptoms in a Non-Human Primate - Is Beta
717 Enough? *Brain Stimul* 9:892-896.
- 718 Kass JL, Mintz IM (2006) Silent plateau potentials, rhythmic bursts, and pacemaker firing: three
719 patterns of activity that coexist in quadristable subthalamic neurons. *Proc Natl Acad Sci U S A*
720 103:183-188.
- 721 Kilgore KL, Bhadra N (2004) Nerve conduction block utilizing high-frequency alternating current. *Med*
722 *Biol Eng Comput* 42:394-406.
- 723 Kim R, Nakano K, Jayaraman A, Carpenter MB (1976) Projections of the globus pallidus and adjacent
724 structures: an autoradiographic study in the monkey. *J Comp Neurol* 169:263-290.
- 725 Klavir O, Flash S, Winter C, Joel D (2009) High frequency stimulation and pharmacological inactivation
726 of the subthalamic nucleus reduces 'compulsive' lever-pressing in rats. *Exp Neurol* 215:101-
727 109.
- 728 Krack P, Hariz MI, Baunez C, Guridi J, Obeso JA (2010) Deep brain stimulation: from neurology to
729 psychiatry? *Trends Neurosci* 33:474-484.

- 730 Kringelbach ML, Jenkinson N, Owen SL, Aziz TZ (2007) Translational principles of deep brain
731 stimulation. *Nat Rev Neurosci* 8:623-635.
- 732 Kuhn AA, Tsui A, Aziz T, Ray N, Brucke C, Kupsch A, Schneider GH, Brown P (2009) Pathological
733 synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to
734 both bradykinesia and rigidity. *Exp Neurol* 215:380-387.
- 735 Kuhn AA, Kempf F, Brucke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, Trottenberg T, Kupsch A,
736 Schneider GH, Hariz MI, Vandenberghe W, Nuttin B, Brown P (2008) High-frequency
737 stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with
738 Parkinson's disease in parallel with improvement in motor performance. *J Neurosci* 28:6165-
739 6173.
- 740 Kuo JS, Carpenter MB (1973) Organization of pallidothalamic projections in the rhesus monkey. *J*
741 *Comp Neurol* 151:201-236.
- 742 Lambert C, Zrinzo L, Nagy Z, Lutti A, Hariz M, Foltynie T, Draganski B, Ashburner J, Frackowiak R
743 (2012) Confirmation of functional zones within the human subthalamic nucleus: patterns of
744 connectivity and sub-parcellation using diffusion weighted imaging. *Neuroimage* 60:83-94.
- 745 Lardeux S, Baunez C (2008) Alcohol preference influences the subthalamic nucleus control on
746 motivation for alcohol in rats. *Neuropsychopharmacology* 33:634-642.
- 747 Lavoie B, Parent A (1994) Pedunculopontine nucleus in the squirrel monkey: projections to the basal
748 ganglia as revealed by anterograde tract-tracing methods. *J Comp Neurol* 344:210-231.
- 749 Lavoie B, Smith Y, Parent A (1989) Dopaminergic innervation of the basal ganglia in the squirrel
750 monkey as revealed by tyrosine hydroxylase immunohistochemistry. *J Comp Neurol* 289:36-
751 52.
- 752 Lee MS, Marsden CD (1994) Movement disorders following lesions of the thalamus or subthalamic
753 region. *Mov Disord* 9:493-507.
- 754 Levesque JC, Parent A (2005) GABAergic interneurons in human subthalamic nucleus. *Mov Disord*
755 20:574-584.
- 756 Levy R, Hutchison WD, Lozano AM, Dostrovsky JO (2000) High-frequency synchronization of neuronal
757 activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *J Neurosci*
758 20:7766-7775.
- 759 Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO (2002) Dependence of
760 subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. *Brain*
761 125:1196-1209.
- 762 Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E, Perret JE, Benabid AL (1995)
763 Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation.
764 *Lancet* 345:91-95.
- 765 Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, Foltynie T, Limousin P, Ashkan K, FitzGerald J,
766 Green AL, Aziz TZ, Brown P (2013) Adaptive deep brain stimulation in advanced Parkinson
767 disease. *Ann Neurol* 74:449-457.
- 768 Lopez-Azcarate J, Tainta M, Rodriguez-Oroz MC, Valencia M, Gonzalez R, Guridi J, Iriarte J, Obeso JA,
769 Artieda J, Alegre M (2010) Coupling between beta and high-frequency activity in the human
770 subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. *J*
771 *Neurosci* 30:6667-6677.
- 772 Lozano AM, Dostrovsky J, Chen R, Ashby P (2002) Deep brain stimulation for Parkinson's disease:
773 disrupting the disruption. *Lancet Neurol* 1:225-231.
- 774 Magarinos-Ascone C, Pazo JH, Macadar O, Buno W (2002) High-frequency stimulation of the
775 subthalamic nucleus silences subthalamic neurons: a possible cellular mechanism in
776 Parkinson's disease. *Neuroscience* 115:1109-1117.
- 777 Magarinos-Ascone CM, Figueiras-Mendez R, Riva-Meana C, Cordoba-Fernandez A (2000) Subthalamic
778 neuron activity related to tremor and movement in Parkinson's disease. *Eur J Neurosci*
779 12:2597-2607.
- 780 Magill PJ, Bolam JP, Bevan MD (2001) Dopamine regulates the impact of the cerebral cortex on the
781 subthalamic nucleus-globus pallidus network. *Neuroscience* 106:313-330.

- 782 Mallet L, Mesnage V, Houeto JL, Pelissolo A, Yelnik J, Behar C, Gargiulo M, Welter ML, Bonnet AM,
783 Pillon B, Cornu P, Dormont D, Pidoux B, Allilaire JF, Agid Y (2002) Compulsions, Parkinson's
784 disease, and stimulation. *Lancet* 360:1302-1304.
- 785 Mallet L et al. (2008a) Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *N*
786 *Engl J Med* 359:2121-2134.
- 787 Mallet L et al. (2008b) Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *N*
788 *Engl J Med* 359:2121-2134.
- 789 Mallet N, Pogossyan A, Sharott A, Csicsvari J, Bolam JP, Brown P, Magill PJ (2008c) Disrupted
790 dopamine transmission and the emergence of exaggerated beta oscillations in subthalamic
791 nucleus and cerebral cortex. *J Neurosci* 28:4795-4806.
- 792 Matsumura M, Kojima J, Gardiner TW, Hikosaka O (1992) Visual and oculomotor functions of monkey
793 subthalamic nucleus. *J Neurophysiol* 67:1615-1632.
- 794 Maurice N, Thierry AM, Glowinski J, Deniau JM (2003) Spontaneous and evoked activity of substantia
795 nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. *J*
796 *Neurosci* 23:9929-9936.
- 797 Meissner W, Leblois A, Hansel D, Bioulac B, Gross CE, Benazzouz A, Boraud T (2005) Subthalamic high
798 frequency stimulation resets subthalamic firing and reduces abnormal oscillations. *Brain*
799 128:2372-2382.
- 800 Mesulam MM, Mash D, Hersh L, Bothwell M, Geula C (1992) Cholinergic innervation of the human
801 striatum, globus pallidus, subthalamic nucleus, substantia nigra, and red nucleus. *J Comp*
802 *Neurol* 323:252-268.
- 803 Nambu A, Takada M, Inase M, Tokuno H (1996) Dual somatotopical representations in the primate
804 subthalamic nucleus: evidence for ordered but reversed body-map transformations from the
805 primary motor cortex and the supplementary motor area. *J Neurosci* 16:2671-2683.
- 806 Nambu A, Tokuno H, Inase M, Takada M (1997) Corticosubthalamic input zones from forelimb
807 representations of the dorsal and ventral divisions of the premotor cortex in the macaque
808 monkey: comparison with the input zones from the primary motor cortex and the
809 supplementary motor area. *Neurosci Lett* 239:13-16.
- 810 Nambu A, Tokuno H, Hamada I, Kita H, Imanishi M, Akazawa T, Ikeuchi Y, Hasegawa N (2000)
811 Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. *J*
812 *Neurophysiol* 84:289-300.
- 813 O'Sullivan SS, Evans AH, Lees AJ (2009) Dopamine dysregulation syndrome: an overview of its
814 epidemiology, mechanisms and management. *CNS Drugs* 23:157-170.
- 815 Okun MS, Fernandez HH, Wu SS, Kirsch-Darrow L, Bowers D, Bova F, Suelter M, Jacobson CEt, Wang
816 X, Gordon CW, Jr., Zeilman P, Romrell J, Martin P, Ward H, Rodriguez RL, Foote KD (2009)
817 Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus
818 interna deep brain stimulation: the COMPARE trial. *Ann Neurol* 65:586-595.
- 819 Parent A, Hazrati LN (1993) Anatomical aspects of information processing in primate basal ganglia.
820 *Trends Neurosci* 16:111-116.
- 821 Parent A, Hazrati LN (1995a) Functional anatomy of the basal ganglia. II. The place of subthalamic
822 nucleus and external pallidum in basal ganglia circuitry. *Brain Res Brain Res Rev* 20:128-154.
- 823 Parent A, Hazrati LN (1995b) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-
824 thalamo-cortical loop. *Brain Res Brain Res Rev* 20:91-127.
- 825 Parent M, Parent A (2004) The pallidofugal motor fiber system in primates. *Parkinsonism Relat Disord*
826 10:203-211.
- 827 Parent M, Wallman MJ, Gagnon D, Parent A (2011) Serotonin innervation of basal ganglia in monkeys
828 and humans. *J Chem Neuroanat* 41:256-265.
- 829 Perier C, Agid Y, Hirsch EC, Feger J (2000) Ipsilateral and contralateral subthalamic activity after
830 unilateral dopaminergic lesion. *Neuroreport* 11:3275-3278.
- 831 Plantinga BR, Temel Y, Roebroek A, Uludag K, Ivanov D, Kuijff ML, Ter Haar Romenij BM (2014) Ultra-
832 high field magnetic resonance imaging of the basal ganglia and related structures. *Front Hum*
833 *Neurosci* 8:876.

- 834 Plantinga BR, Temel Y, Duchin Y, Uludag K, Patriat R, Roebroek A, Kuijf M, Jahanshahi A, Ter Haar
835 Romenij B, Vitek J, Harel N (2016) Individualized parcellation of the subthalamic nucleus in
836 patients with Parkinson's disease with 7T MRI. *Neuroimage*.
- 837 Pollo C, Vingerhoets F, Pralong E, Ghika J, Maeder P, Meuli R, Thiran JP, Villemure JG (2007)
838 Localization of electrodes in the subthalamic nucleus on magnetic resonance imaging. *J*
839 *Neurosurg* 106:36-44.
- 840 Ray NJ, Jenkinson N, Wang S, Holland P, Brittain JS, Joint C, Stein JF, Aziz T (2008) Local field potential
841 beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated
842 with improvements in bradykinesia after dopamine and deep brain stimulation. *Exp Neurol*
843 213:108-113.
- 844 Robledo P, Feger J (1990) Excitatory influence of rat subthalamic nucleus to substantia nigra pars
845 reticulata and the pallidal complex: electrophysiological data. *Brain Res* 518:47-54.
- 846 Rodriguez MC, Obeso JA, Olanow CW (1998) Subthalamic nucleus-mediated excitotoxicity in
847 Parkinson's disease: a target for neuroprotection. *Ann Neurol* 44:S175-188.
- 848 Rodriguez-Oroz MC et al. (2005) Bilateral deep brain stimulation in Parkinson's disease: a multicentre
849 study with 4 years follow-up. *Brain* 128:2240-2249.
- 850 Rosin B, Slovik M, Mitelman R, Rivlin-Etzion M, Haber SN, Israel Z, Vaadia E, Bergman H (2011)
851 Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron* 72:370-
852 384.
- 853 Rothlind JC, York MK, Carlson K, Luo P, Marks WJ, Jr., Weaver FM, Stern M, Follett K, Reda D, Group
854 CSPS (2015) Neuropsychological changes following deep brain stimulation surgery for
855 Parkinson's disease: comparisons of treatment at pallidal and subthalamic targets versus best
856 medical therapy. *J Neurol Neurosurg Psychiatry* 86:622-629.
- 857 Rouaud T, Lardeux S, Panayotis N, Paleressompouille D, Cadot M, Baunez C (2010) Reducing the
858 desire for cocaine with subthalamic nucleus deep brain stimulation. *Proc Natl Acad Sci U S A*
859 107:1196-1200.
- 860 Sadikot AF, Parent A, Francois C (1992) Efferent connections of the centromedian and parafascicular
861 thalamic nuclei in the squirrel monkey: a PHA-L study of subcortical projections. *J Comp*
862 *Neurol* 315:137-159.
- 863 Shimamoto SA, Ryapolova-Webb ES, Ostrem JL, Galifianakis NB, Miller KJ, Starr PA (2013)
864 Subthalamic nucleus neurons are synchronized to primary motor cortex local field potentials
865 in Parkinson's disease. *J Neurosci* 33:7220-7233.
- 866 Shink E, Bevan MD, Bolam JP, Smith Y (1996) The subthalamic nucleus and the external pallidum: two
867 tightly interconnected structures that control the output of the basal ganglia in the monkey.
868 *Neuroscience* 73:335-357.
- 869 Smith Y, Hazrati LN, Parent A (1990) Efferent projections of the subthalamic nucleus in the squirrel
870 monkey as studied by the PHA-L anterograde tracing method. *J Comp Neurol* 294:306-323.
- 871 Syed EC, Benazzouz A, Taillade M, Baufreton J, Champeaux K, Falgairolle M, Bioulac B, Gross CE,
872 Boraud T (2012) Oscillatory entrainment of subthalamic nucleus neurons and behavioural
873 consequences in rodents and primates. *Eur J Neurosci* 36:3246-3257.
- 874 Tai CH, Boraud T, Bezard E, Bioulac B, Gross C, Benazzouz A (2003) Electrophysiological and metabolic
875 evidence that high-frequency stimulation of the subthalamic nucleus bridles neuronal activity
876 in the subthalamic nucleus and the substantia nigra reticulata. *FASEB J* 17:1820-1830.
- 877 Tass PA, Qin L, Hauptmann C, Dovero S, Bezard E, Boraud T, Meissner WG (2012) Coordinated reset
878 has sustained aftereffects in Parkinsonian monkeys. *Ann Neurol* 72:816-820.
- 879 Temel Y, Kessels A, Tan S, Topdag A, Boon P, Visser-Vandewalle V (2006a) Behavioural changes after
880 bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review.
881 *Parkinsonism Relat Disord* 12:265-272.
- 882 Temel Y, Boothman LJ, Blokland A, Magill PJ, Steinbusch HW, Visser-Vandewalle V, Sharp T (2007)
883 Inhibition of 5-HT neuron activity and induction of depressive-like behavior by high-
884 frequency stimulation of the subthalamic nucleus. *Proc Natl Acad Sci U S A* 104:17087-17092.

- 885 Temel Y, Blokland A, Ackermans L, Boon P, van Kranen-Mastenbroek VH, Beuls EA, Spincemaille GH,
886 Visser-Vandewalle V (2006b) Differential effects of subthalamic nucleus stimulation in
887 advanced Parkinson disease on reaction time performance. *Exp Brain Res* 169:389-399.
- 888 Temel Y, Visser-Vandewalle V, Aendekerk B, Rutten B, Tan S, Scholtissen B, Schmitz C, Blokland A,
889 Steinbusch HW (2005) Acute and separate modulation of motor and cognitive performance
890 in parkinsonian rats by bilateral stimulation of the subthalamic nucleus. *Exp Neurol* 193:43-
891 52.
- 892 Tournier JD, Calamante F, Connelly A (2007) Robust determination of the fibre orientation
893 distribution in diffusion MRI: non-negativity constrained super-resolved spherical
894 deconvolution. *Neuroimage* 35:1459-1472.
- 895 Uslaner JM, Robinson TE (2006) Subthalamic nucleus lesions increase impulsive action and decrease
896 impulsive choice - mediation by enhanced incentive motivation? *Eur J Neurosci* 24:2345-
897 2354.
- 898 Vitek JL (2002) Mechanisms of deep brain stimulation: excitation or inhibition. *Mov Disord* 17 Suppl
899 3:S69-72.
- 900 Weaver FM et al. (2009a) Bilateral deep brain stimulation vs best medical therapy for patients with
901 advanced Parkinson disease: a randomized controlled trial. *Jama* 301:63-73.
- 902 Weaver FM et al. (2009b) Bilateral deep brain stimulation vs best medical therapy for patients with
903 advanced Parkinson disease: a randomized controlled trial. *JAMA* 301:63-73.
- 904 Wichmann T, Bergman H, DeLong MR (1994a) The primate subthalamic nucleus. I. Functional
905 properties in intact animals. *J Neurophysiol* 72:494-506.
- 906 Wichmann T, Bergman H, DeLong MR (1994b) The primate subthalamic nucleus. III. Changes in motor
907 behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in
908 the MPTP model of parkinsonism. *J Neurophysiol* 72:521-530.
- 909 Windels F, Carcenac C, Poupard A, Savasta M (2005) Pallidal origin of GABA release within the
910 substantia nigra pars reticulata during high-frequency stimulation of the subthalamic
911 nucleus. *J Neurosci* 25:5079-5086.
- 912 Windels F, Bruet N, Poupard A, Urbain N, Chouvet G, Feuerstein C, Savasta M (2000) Effects of high
913 frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in
914 substantia nigra and globus pallidus in the normal rat. *Eur J Neurosci* 12:4141-4146.
- 915 Wingeier B, Tcheng T, Koop MM, Hill BC, Heit G, Bronte-Stewart HM (2006) Intra-operative STN DBS
916 attenuates the prominent beta rhythm in the STN in Parkinson's disease. *Exp Neurol*
917 197:244-251.
- 918 Winstanley CA (2011) The utility of rat models of impulsivity in developing pharmacotherapies for
919 impulse control disorders. *Br J Pharmacol* 164:1301-1321.
- 920 Winstanley CA, Baunez C, Theobald DE, Robbins TW (2005) Lesions to the subthalamic nucleus
921 decrease impulsive choice but impair autoshaping in rats: the importance of the basal ganglia
922 in Pavlovian conditioning and impulse control. *Eur J Neurosci* 21:3107-3116.
- 923 Winter C, Mundt A, Jalali R, Joel D, Harnack D, Morgenstern R, Juckel G, Kupsch A (2008) High
924 frequency stimulation and temporary inactivation of the subthalamic nucleus reduce
925 quinpirole-induced compulsive checking behavior in rats. *Exp Neurol* 210:217-228.
- 926 Wu XX, Shuai JW (2012) Multistability in a neuron model with extracellular potassium dynamics. *Phys*
927 *Rev E Stat Nonlin Soft Matter Phys* 85:061911.
- 928 Zheng F, Lammert K, Nixdorf-Bergweiler BE, Steigerwald F, Volkmann J, Alzheimer C (2011) Axonal
929 failure during high frequency stimulation of rat subthalamic nucleus. *J Physiol* 589:2781-
930 2793.

931

Figure 1

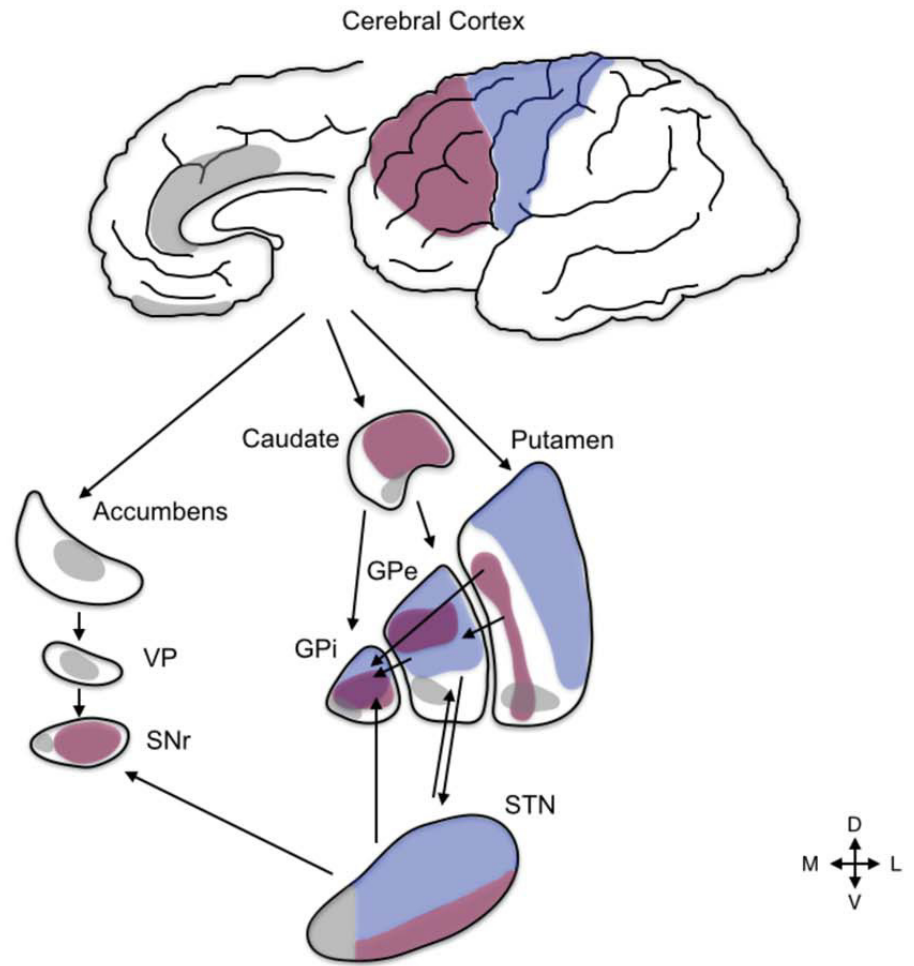


Figure 2

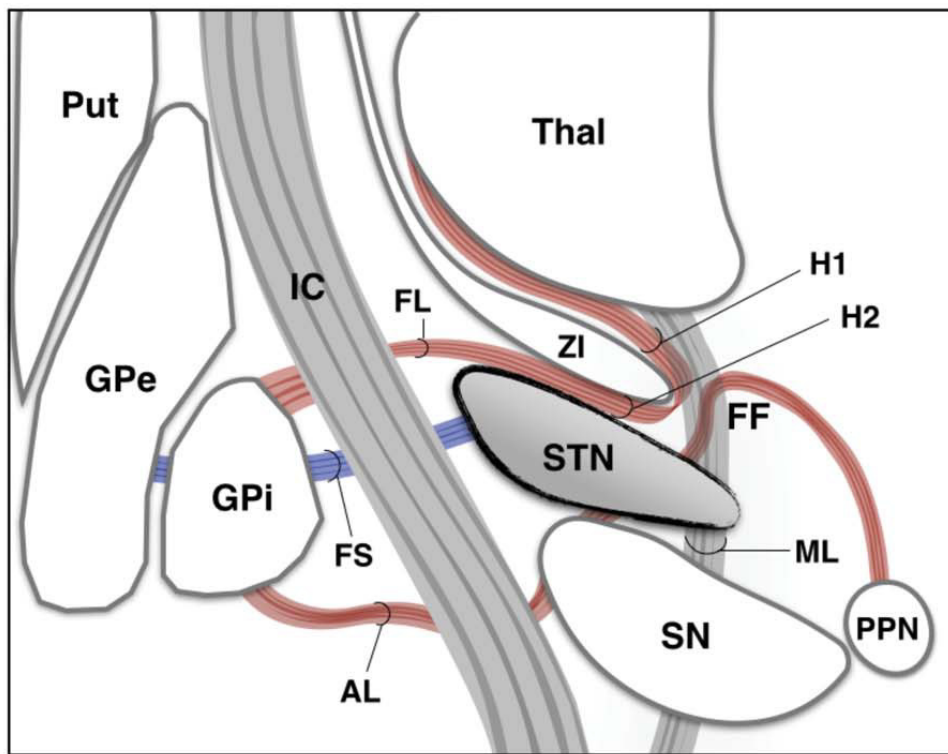
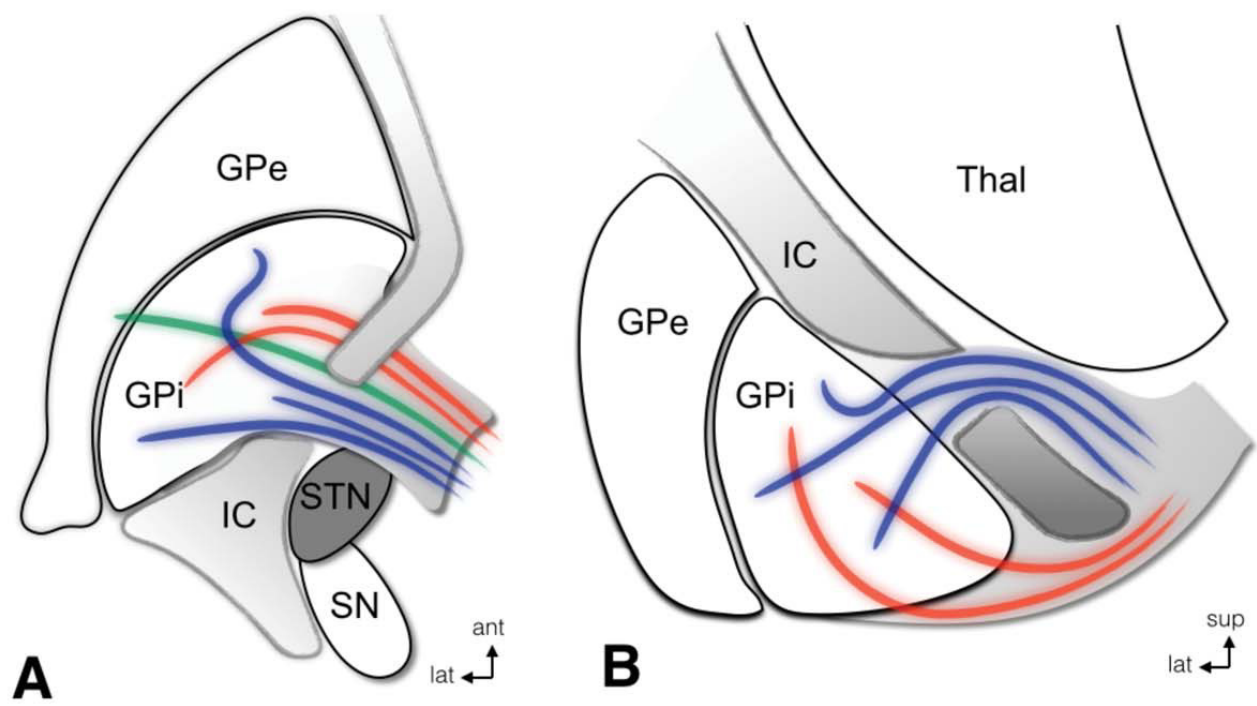


Figure 3



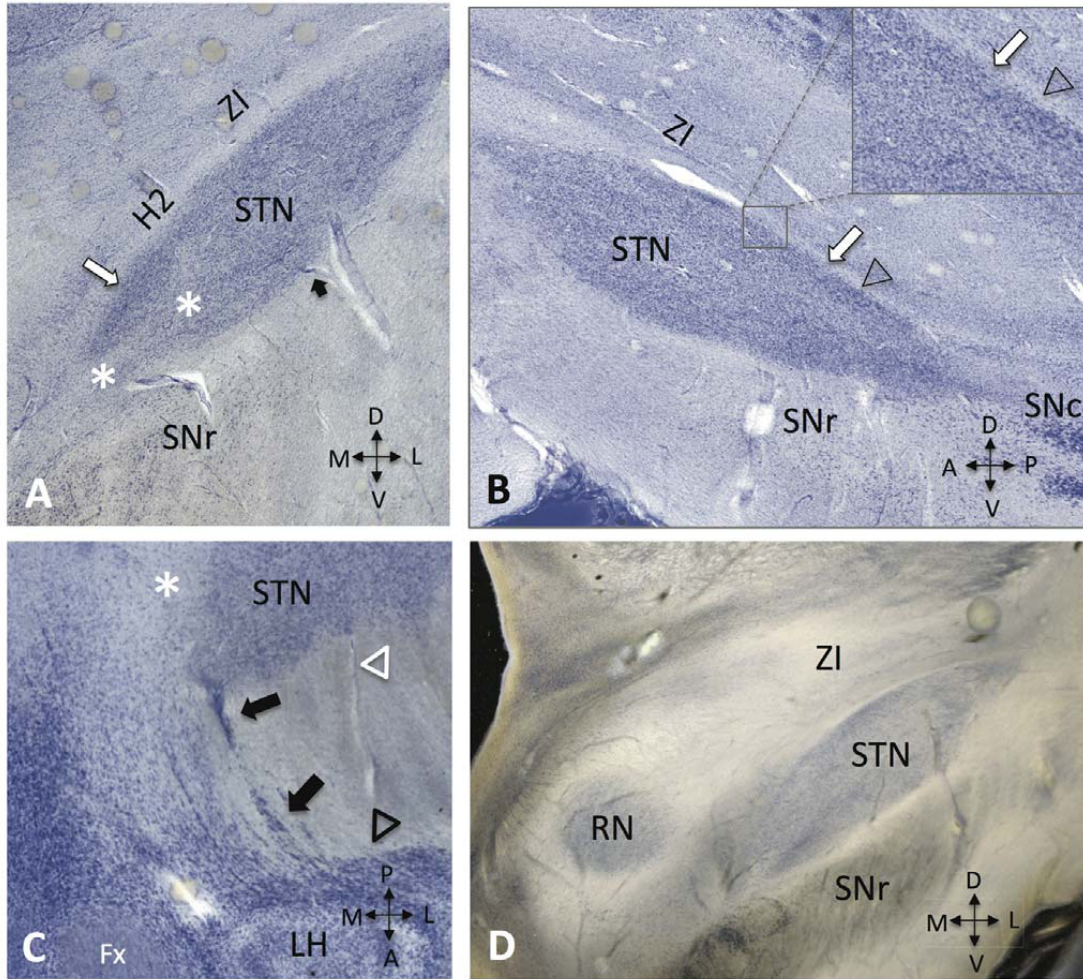


Figure 4

Figure 5

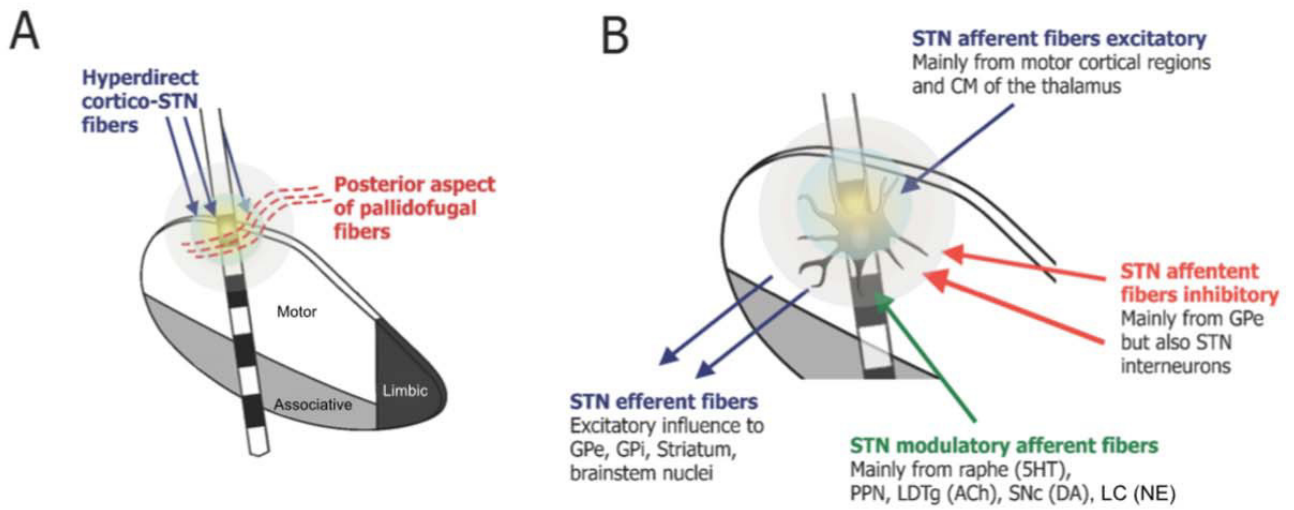


Figure 6

