

Deep brain stimulation of the globus pallidus internus and Gilles de la Tourette syndrome: Toward multiple networks modulation

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Received: 1 March 12

Accepted: 28 March 12

Published: 26 April 12

This article may be cited as:

Saleh C, Gonzalez V, Cif L, Coubes P. Deep brain stimulation of the globus pallidus internus and Gilles de la Tourette syndrome: Toward multiple networks modulation. *Surg Neurol Int* 2012;3:S127-42.

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Abstract

Background: Gilles de la Tourette's syndrome (GTS) is a complex neuropsychiatric disorder characterized by disabling motor and vocal tics. The pathophysiology of GTS remains poorly understood. Conventional treatment consists in pharmacological and behavioral treatment. For patients suffering severe adverse effects or not responding to pharmacological treatment, deep brain stimulation (DBS) presents an alternative treatment. However, the optimal target choice in DBS for GTS remains a divisive issue.

Methods: A PubMed search from 1999 to 2012 was conducted. Thirty-three research articles reporting on DBS in patients with GTS were selected and analyzed.

Results: Eighty-eight patients with Tourette's syndrome were treated since 1999 with DBS. The majority of patients received thalamic stimulation. Significantly fewer patients were treated with globus pallidus internus stimulation. Occasionally, the anterior limb of the internal capsule and the nucleus accumbens were implanted. The subthalamic nucleus was selected once. All targets were reported with positive results, but of variable extent. Only 14 patients exhibited level 1 evidence.

Conclusion: In light of the wide spectrum of associated behavioral co-morbidities in GTS, multiple networks modulation may result in the most efficacious treatment strategy. The optimal locations for DBS within the cortico-basal ganglia-thalamocortical circuits remain to be established. However, at the current stage, comparison between targets should be done with great caution. Significant disparity between number of patients treated per target, methodological variability, and quality of reporting renders a meaningful comparison between targets difficult. Randomized controlled trials with larger cohorts and standardization of procedures are urgently needed.

Key Words: Deep brain stimulation, globus pallidus, nucleus accumbens, targeting, thalamus, Tourette's syndrome

Access this article
online

Website:

www.surgicalneurologyint.com

DOI:

10.4103/2152-7806.95424

Quick Response Code:



INTRODUCTION

Gilles de la Tourette's syndrome (GTS) is an inheritable childhood-onset neuropsychiatric disorder characterized by multiple disabling motor and vocal tics lasting for more than 1 year.^[4] Community-based studies report prevalence rates of 0.3–0.8%.^[41,48,91] In 50–90% of cases, GTS is aggravated by a plethora of associated behavioral co-morbidities.^[47,75] While disease severity usually diminishes around the second decade of life,^[9,50] some patients may continue to experience severe disabling symptoms and require lifelong medical and behavioral treatment.^[24,62,72] Conservative management consists of α 2-adrenergic agonists (first-line treatment), antipsychotic agents (second-line treatment), anticonvulsant drugs, benzodiazepines, and botulinum toxin infiltration.^[24,62] However, pharmacological management is associated with multiple serious adverse effects such as sedation, akathisia, dystonia, parkinsonism, weight gain, hyperprolactinemia, hypotension, and sedation.^[24,62] For patients experiencing severe adverse effects or becoming refractory to pharmacological treatment, surgery presents an alternative treatment. One of the first reports on surgery for GTS appeared in the early 1960s in the *Canadian Medical Association Journal* describing bimedial frontal leucotomy.^[6] Ten years later, Nadvornik and co-workers from the Czech Republic performed cerebellar surgery for GTS lesioning the cerebellar dentate nuclei.^[65] Around the same time, Hassler and Dieckmann applied stereotactic coagulation of the rostral intralaminar and medial thalamic nuclei.^[38] The same thalamic areas were targeted two decades later by Vandewalle and co-workers,^[95] who performed the first stereotactic bilateral deep brain stimulation (DBS) for refractory GTS. The thalamus was considered a suitable surgical target to treat GTS, as an abnormality in the cortico-striato-thalamocortical circuits leading to an overactive thalamocortical system was thought responsible for GTS.^[7,29,40,88,89] However, the exact location within these pathways remains unknown.^[88] During the last decade, five main target areas were proposed for DBS in GTS patients: The medial thalamus, the posteroventral and anteromedial pallidal territories, the anterior limb of the internal capsule (ALIC), and the nucleus accumbens (NA). Accumulating data suggest a fundamental role of the globus pallidus in the pathophysiology of GTS. Imaging studies demonstrated bilateral lesions in the globus pallidus in patients with GTS.^[18] Successful pallidotomy for dystonia was reported by Lozano and co-workers,^[57] while Coubes and co-workers pioneered DBS of the globus pallidus internus (GPi) for dystono-dyskinetic syndrome.^[15,16] McCairn and co-workers demonstrated recently^[61] in a non-human primate model of Tourette's syndrome that stimulation of the globus pallidus blocks tic-related phasic changes in the firing pattern of pallidal cells and reduces the peak

amplitude of tic events in the electromyography record. Promising results were obtained by Coubes and co-workers^[14] with double bilateral simultaneous stimulation to pallidal motor and limbic territories in Lesch-Nyhan Disease (LND), a devastating genetic disorder of the purine metabolism that shares many features with GTS. Equally, LND presents with severe dystonia, dyskinesia, and a wide spectrum of neurological and behavioral phenotypes.^[55,70] As in GTS, an increasing body of evidence points to basal ganglia implication as a cause of the complex neurobehavioral spectrum in LND,^[25,36,70,100,104] this may explain the promising application of DBS to the basal ganglia network in both conditions. The rationale for using DBS ALIC for GTS was derived from the strong clinical overlap between GTS and obsessive-compulsive disorder (OCD) and was based on previous pioneering work of Leksell and co-workers^[8] and Nuttin and co-workers,^[69] who performed, respectively, anterior capsulotomy and subsequently DBS to the ALIC in OCD patients. The results of each of the DBS targets applied during the last decade in GTS patients will be presented in detail and discussed in this review.

MATERIALS AND METHODS

A PubMed search from 1999 to 2012 was conducted. The key words were “Tourette Syndrome and deep brain stimulation” used in combined search with “GPi/GPe, thalamus, nucleus accumbens, anterior limb of internal capsule and subthalamic nucleus.” The search yielded 102 articles. Thirty-three research articles were selected. Articles other than in English language, editorials, and reviews were excluded. All selected studies were analyzed for multiple variables and tabulated. The level of evidence of each study was determined based on the guidelines provided by the United States Department of Health and Human Services. Yale Global Tic Severity Score (YGTSS) and Yale Brown Obsessive Compulsive Score (YBOCS) were expressed uniformly in percentage change to facilitate comparison of clinical outcome. As primary and secondary outcomes were not reported rigorously, our summary data specify results in relation to the number of patients for whom data were available. For a prompt, clear, and yet detailed account of findings, the text was supported by numerous tables [Tables 1–11]. Tables were organized in function of target and divided in demographics, surgical procedure, and post-surgical period. Studies were listed in decreasing number of subjects. The result section was divided into two parts. The first part provides a summary of main findings across all studies, while the second part provides specifics as to each target and is structured, mirroring the tabulated data, in the three main sections of demographics, surgical procedure, and post-surgical period. Studies are presented regrouped per target in the section “DBS for GTS from 1999 to 2012: Presentation of studies.”

RESULTS

General findings

Target choice

The first DBS application for GTS was reported in 1999 and targeted the thalamus at the ventro-oralis internus–centromedian nucleus–substantia perventricularis crosspoint.^[95] Stimulation of this area aimed at reducing the overactivity of the thalamocortical system that resulted from an apparent deficient inhibitory gamma-aminobutyric acid (GABA)-mediated basal ganglia

influence.^[88] Several target areas within the thalamus have been reported since 1999: The nucleus ventro-oralis internus–centromedian nucleus–parafascicular complex,^[5,43,44,58,83] the centromedian–parafascicular nuclei,^[42,51,80,103] and the dorsomedial thalamus.^[98] The first pallidal DBS study for GTS^[94] reported on posteroventral (motor) GPi implantation (with concomitant thalamic implantation). Further, seven studies^[17,20,22,28,59,99] reported on exclusive pallidal DBS for GTS. Three territories within the GP were implanted: The motor GPi,^[17,20,22,59,86] the limbic GPi,^[59] and the external pallidus.^[99] The limbic anteromedial pallidum was further implanted concomitantly with the medial thalamus.^[42,103] The posteroventral motor GPi was targeted once with the medial thalamus^[3] and once with the ALIC/NA.^[84] Few authors reported on only ALIC/NA implantations.^[11,26,46,68] Only NA was implanted once.^[105] One group treated GTS with subthalamic nucleus (STN) DBS,^[60] implanting the sensorimotor STN.

Primary (YGTSS) and secondary outcomes (YBOCS)

The YGTSS^[49] was used predominantly to rate tic

Table 1: General findings

Mean age in years (SD)/No. of patients	Disease duration in months (SD)/No. of patients	Follow-up in months (SD)/No. of patients	YGTSS in percentage change/No. of patients	YBOCS in percentage change/No. of patients
28 (11)/9	23 (13)/9	15 (7)/11	55 (35)/10	47 (38)/8

No.: Number of patients, SD: Standard deviation

Table 2: Demographics

Authors (year)	Study design	Level of evidence	Sample size	Gender	Age (in years)	Disease duration (in years)	Follow-up (max., in months)
Martinez-Fernandez (2011)	Case series	4	5	M (4), F (1)	38	31	24
Vilela Filho (2006)	Prospective controlled study	2	2	NM	NM	NM	23
Dehning (2008)	Case report	4	1	F	44	39	12
Diederich (2005)	Case report	4	1	M	27	19	14
Dueck (2009)	Case report	4	1	M	16	13	12
Shahed (2007)	Case report	4	1	M	16	13	6
Gallagher (2006)	Case report	4	1	M	26	NM	NM

M: Male, F: Female, NM: Not mentioned, age/disease duration: Mean value for more than three patients

Table 3: Surgical procedure

Author (year)	Target	Target coordinates (x, y, z)	Pre-op	Lead	Mapping	Post-op	Complications
Martinez-Fernandez (2011)	a/m GPi (3 patients) pv GPi (2 patients)	NM	MRI	3389	No	MRI	NM
Vilela Filho (2006)	Dorsal/central Gpe	20, 3, +3	MRI	NM	MS	MRI	NM
Dehning (2008)	pvGPi	20, 3, -4	MRI	3389	1. MER 2. MS	MRI	No
Diederich (2005)	pv Gpi	17, 4, -5	MRI/CT/VG	3389	MER	MRI	ICH
Dueck (2009)	pv Gpi	19, 2, -3	MRI	3389	MER	MRI	No
Shahed (2007)	pv Gpi	NM	NM	NM	NM	NM	NM
Gallagher (2006)	(?) Gpi*	NM	NM	NM	NM	NM	HWI

All procedures bilateral, GPi: Globus pallidus internus, GPe: Globus pallidus externus, a/m: antero-medial, MRI: Magnetic resonance imaging, CT: Computed tomography, VG: Ventriculography, pv: posteroventral, MER: Microelectrode recording, HWI: Hardware infection, MS: Macrostimulation, ICH: Intracranial hemorrhage, NM: Not mentioned, x y z coordinates: in millimeters, z coordinates: positive z: Above anterior–posterior commissures/negative z: Inferior to anterior–posterior commissures, *Pallidal territory of implantation not specified

Table 4: Globus pallidus postoperative variables

Author (year)	Stimulation	YGSS (in % change)	YBOCS (in % change)	Adverse events
Martinez-Fernandez (2011)	2.5–4 V, 20–170 Hz, 60–210 μ s	31	28	1. Anxiety 2. Depression 3. Capsular effects 4. Tiredness 5. Weight gain
Vilela Filho (2006)	Monopolar: 2.5 V, 160 Hz, 90 μ s	81	84	NM
Dehning (2008)	Monopolar: 1. At discharge: 3.2 V, 130 Hz, 120 μ s 2. At 12 months: 4.2 V, 145 Hz, 210 μ s	88	NM	1. Depressive moods 2. Vertigo 3. Stomach aches
Diederich (2005)	Bipolar 2 V, 185 Hz, 60–150 μ s	47	0*	1. Mild transient fatigue 2. Persistent bradykinesia of left hand
Dueck (2009)	3–4 V, 130–210 Hz, 60–240 μ s	0	NM	At high stimulation: 1. nausea 2. Dizziness 3. Moderate anxiety 4. Visual sensations
Shahed (2007)	Monopolar: 5 V, 145–160 Hz, 90 μ s	84	69	NM
Gallagher (2006)	NM	NM	NM	NM

YGSS: Yale Global Tic Severity Score, YBOCS: Yale Brown Obsessive Compulsive Score, NM: Not mentioned, *Scale not mentioned

Table 5: Thalamus main findings

Mean age in years (SD)/ no. of patients	Disease duration in months (SD)/no. of patients	Follow-up in months (SD)/ no. of patients	YGSS in percentage change/no. of patients	YBOCS in percentage change/no. of patients
31 (9)/42	22 (9)/42	18 (15)/43	58 (15)/41	65 (27)/16

No.: Number of patients, SD: Standard deviation

Table 6: Thalamus demographics

Authors (year)	Study design	Level of evidence	Sample size	Gender	Age (in years)	Disease duration (in years)	Follow-up (max., in months)
Servello (2008)	Prospective cohort study	2	18	M (15), F (3)	28	21	19
Ackermans (2011)	Double-blind clinical trial	1	6	M	40	33	12
Maciunas (2007)	Prospective randomized double-blind trial	1	5	M	28	21	3
Savica (2012)	Case series	4	3	M (2), F	17, 35, 17	12, 25, 9	12
V-Vandewalle (2003)	Case series	4	3*	M	42, 28, 45	37, 20, 38	60
Kaido (2010)	Prospective Pilot Study	4	3	M, F (2)	20, 21, 19	7, 11, 8	12
V-Vandewalle (1999)	Case report	4	1	M	42	NM	12
Bajwa (2007)	Case report	4	1	M	50	37	24
Lee (2011)	Case report	4	1	M	31	24	18
Idris (2010)	Case report	4	1	M	24	19	0
Rzesnitzek (2011)	Case report	4	1	M	31	NM	24
Vernaleken (2009)	Case report	4	1**	M	22	12	6

M: Male, f: Female, age/disease duration: mean value for more than three patients, NM: Not mentioned, *One patient previously reported in Vandewalle *et al.* (1999), **Patient previously implanted in GPi

Table 7: Thalamus surgery

Author (year)	Target	Target coordinates (x, y, z)	Pre-op	Lead	Mapping	Post-op
Servello (2008)	voi, cm, pf	SWA	MRI/CT	3387	1. MER, 2. MS	MRI/SWA
Ackermans (2011)	voi, cm, spv	5, 4, 0	CT/MRI	3387	1. MER, 2. MS	CT
Maciunas (2007)	voi, cm, pf	5, 4, 0	MRI	3387	1. MER, 2. S	MRI
Savica (2012)	cm, pf	5, 8, 0	NM	NM	NM	NM
V-Vandewalle (2003)	voi, cm, pf	5, 4, 0	MRI/CT	3387	S	MRI
Kaido (2010)	voi, cm, pf	6.5, 4, +1.5	MRI/SWA	3387	NM	MRI
Vandewalle (1999)	voi, cm, pf	3–5, 4, 0	NM	3387	NM	NM
Bajwa (2007)	voi, cm, spv	5, 4, 0	MRI	3387	NM	MRI
Lee (2011)	cm, pf	5, 4, 0	NA	3387	MS	MS
Idris (2010)	voi, cm, pf	4, 3, 0	SWA	NM	1. MER, 2. MS	CT
Rzesnitzek (2011)	cm, pf	5, 4, 0	NM	NM	NM	NM
Vernaleken (2009)	pf, DMN, LM	Left: 5.5, 3.7, +1.4 Right: 5.0, 3.9, +1.3	NM	NM	NM	MRI

All procedures bilateral, voi: ventro-oralis internus, cmpf: centromedian-parafascicular complex, spv: substantia periventricularis, DMN: Dorsomedial nucleus, LM: Lamella medialis, SWA: Schaltenbrand–Wahren Atlas, MRI: Magnetic resonance imaging, CT: Computed tomography, MER: Microelectrode recording, MS: Macro-Stimulation, S: Stimulation, x y z coordinates: in millimeters, z-coordinates positive: Above anterior–posterior commissures/z-coordinates negative: Inferior to anterior–posterior commissures

Table 8: Thalamus postoperative variables

Author (year)	Stimulation	YGTSS (in % change)	YBOCS (in % change)	Adverse events
Servello (2008)	Bipolar 2.5–4 V, 120–130 Hz, 90–120 μ s	64%	NM	Amplitude > 4 V: 1. Subjective vertigo (transient) 2. Blurring of vision (transient) 3. Abdominal discomfort 4. Upward ocular deviation 5. Infection rate = 19.3%
Porta (2009): 24 months follow-up study of Servello (2008)	-	52	31	NM
Ackermans (2011)	Monopolar (4 pts) and bipolar (2 pts): 1.0–7.3 V, 70–130 Hz, 60–210 μ s	49* 37**	69	1. Infection of PG 2. Gaze disturbances 3. Reduction of energy levels
Maciunas (2007)	3.5–3.6 V, 130–185 Hz, 90–210 μ s	44	45	1. Acute psychosis 2. Spontaneous recurrence of tics
Savica (2012)	Bipolar: 3.7 V, 117 Hz, 120 μ s Bipolar: 4.1 V, 107 Hz, 120 μ s Monopolar: 2.5 V, 130 Hz, 90 μ s	69, 60, 80	NM	NM
V-Vandewalle (2003)	Bipolar/monopolar: 2.0–3.0 V, 65–130 Hz, 210 μ s	90, 72, 83	No preoperative co-morbidity	1. Decreased energy 2. Increased libido 3. Decreased libido
Kaido (2010)	2.1–3.2 V, 180–210 Hz/210 Hz, 80–130 μ s	39	↓ (in 2 pts) ↑ (in 1 pt)	Blurred vision
Vandewalle (1999)	4 V, 130 Hz, 450 μ s	100	No preoperative co-morbidity	NM
Bajwa (2007)	Bipolar 2 V, 130 Hz, 90 μ s	66	78	Mood deterioration
Lee (2011)	Bipolar: 3.6–5 V, 150–200 Hz, 150–180 μ s	58	No preoperative co-morbidity	No
Idris (2010)	3.5 V, 130 Hz, 120 μ s	+	NM	No
Rzesnitzek (2011)	4.0–5.0 V, 130 Hz, 60 μ s	81	100	Doxepin → Acute dystonic reactions
Vernaleken (2009)	Double monopolar: 4.4 V, 130 Hz, 180 μ s	36	+	NM

NM: Not mentioned, NS: Not specified, YBOCS: Yale Brown Obsessive Compulsive Score, PG: Pulse generator, Pts: Patients, ↓: Decrease, ↑: Increase, *12 months versus baseline, **On versus off, "+" Improvement/scale not specified

Table 9: Multiple targets: Demographics

Authors (year)	Study design	Level of evidence	Sample size	Gender	Age (in years)	Disease duration (in years)	Follow-up (max., in months)
Servello (2010)	Prospective cohort study	2	36 [†]	M (28), F (8)	32 (SD = 10.65)	NM	60
Servello/Okun (2009)	Case series	4	4	M (3), F	35	23	51
Welter (2008)	CDBR cross-over study	1	3*	M (1) F (2)	30, 36, 30	24, 29, 17	20
Shields (2008)	Case report	4	1**	F	40	30	3
Ackermans (2006)	Case reports	4	2	M	45, 47	38, 20	12
Houeto (2005)	Prospective, double blind, sham controlled	1	1	F	36	29	24
Van der Linden (2002)	Case report	4	1	M	27	NA	6
Martinez-Torres (2009)	Case report	4	1	M	38	31	12
Flaherty (2005)	Case report	4	1	F	37	27	18
Neuner (2009)	Case report	4	1	M	38	NM	36
Kuhn (2007)	Case report	4	1	M	26	NM	30
Burdick (2010)	Case report	4	1	M	33	NM	30
Zabek (2008)	Case report	4	1	M	31	24	28

CDBR: Controlled, Double-Blind, Randomized cross-over study, M: Male, F: Female, NM: Not Mentioned, NA: Not Available, *One patient previously reported by Houeto et al. (2005), **Patient previously reported by Flaherty et al. (2005), [†]Eighteen patients previously reported by Servello et al.^[83]

Table 10: Multiple targets: Surgery

Author (Year)	Target (bilateral)	N° of pts per target	Target Coordinates (x, y, z)	Preoperative Imaging	Lead	Mapping	Postop Imaging
Servello (2010) [^]	1. Voi, Cm, Pf	31	NM	MRI / SWA	3387	MRI	MRI
	2. Voi, Cm, Pf (uni)	1					
	3. pvGPi + ALIC/NA	1					
	4. Voi, Cm, Pf + ALIC/NA	3					
Servello/Okun (2009)	1. Voi, Cm, Pf + ALIC/NA	3 [‡]	NM	MRI / CT	NM	MER	MRI
	2. ALIC/NA	1					
Welter (2008)	Cm, Pf + amGPi	3	NM	NM	NM	NM	MRI
Shields (2008)	1. Cm	1*	For Cm: 5, 4, 0	CT/MRI	3387	MER	MRI/Atlas
	2. ALIC in 2005						
Ackermans (2006)	1. Voi, Cm, Spv	1**	1. TA: 5, 4, 0	NM	3387	NM	MRI
	2. Voi, Cm, Spv + pv GPi ^{††}	1	2. GPi: 21.5, 4, -3				
Houeto (2005)	Cm, Pf + amGPi	1	NM	MRI	3389	MER	MRI / SWA
van der Linden (2002)	Voi, Cm, Spv + pv GPi	1	NA	NA	NA	NA	NA
Martinez-Torres (2009)	STN	1	NM	MRI	3389	NM	MRI
Flaherty (2005)	ALIC	1	12, y = NM, -7	MRI / CT	3389	MER	MRI
Neuner (2009)	ALIC/NA	1	6.5, 2.5, -4.5	MRI / CT	NM	NM	CT
Kuhn (2007)	ALIC/NA	1	6.5, 2.5, -4.5	MRI/CT	3387	NM	CT
Burdick (2010)	ALIC/NA	1	NM	MRI	3387 [†]	MER	CT/MRI
Zabek (2008)	NA (right)	1	NM	MRI/CT	3389	No	NM

[^]:Three patients excluded from statistical analysis, Schaltenbrand–Wahren Atlas, GPi: Globus Pallidus Internus, voi: ventro-oralis internus, cm-pf: centromedian-parafascicular complex, spv: substantia periventricularis, pv: posteroventral, am: anteromedial, NM: Not Mentioned, NA: Not Available, x y z coordinates: in millimeters, z-coordinates positive: Above anterior–posterior commissures/z-coordinates negative: Inferior to anterior–posterior commissures, y values of ALIC/NA: anterior to MCP, [‡]One patient previously reported in Servello et al. (2008), *Same patient as reported in Flaherty et al. (2005), **Thalamic patient reported previously by V-Vandewalle (2003), [†]4 mm contacts, 3 mm spacing, 25 mm total length for active contact region from dorsal to ventral extent of the four contacts, ^{††}Only pallidal electrodes connected to pulse generator

Table 11: Multiple targets: Post-surgical variables

Author (year)	Stimulation	YGTSS (in % change)	YBOCS (in % change)	Adverse events
Servello (2010)	2–5 V, 60–180 Hz, 90–140 μ s	52	17	1. Lead repositioning 2. Removal of DBS implant 3. Revision of surgical wounds 4. Hardware failure
Servello/Okun (2009)	3 monopolar, 1 bipolar: 4–4.5 V, 130–160 Hz, 150–180 μ s	65	39	NM
Welter (2008)	TA: 1.5–1.7 V GPI: 1.5–3.5 V	TA: 64, 30, 40 GPI: 65, 96, 74 TA + GPI: 60, 43, 76	1. SIB↓ 2. Impulsiveness↓	1. Lethargy 2. Nausea 3. Vertigo 4. Anxiety 5. Libido↓
Shields (2008)	7 V, 180 Hz, 90 μ s	46	No preoperative behavioral disorder	1. Apathy 2. Mood↑ 3. Mood↓
Ackermans (2006)	TA: Double monopolar 6.4 V, 130 Hz, 120 μ s GPI: Triple monopolar 3.1 V, 170 Hz, 210 μ s	TA: 85 GPI: 92	Compulsions disappeared	1. Reduced energy 2. Reduced libido
Houeto (2005)	1. Thalamus: Monopolar 1.5 V 2. GPI: Monopolar 1.5 V 3. TA + GPI: NM	1. TA: 64 2. GPI: 66 3. TA + GPI: 60 4. Sham: +8	1. TA: 55 2. GPI: 25 3. TA + GPI: 49 4. Sham: 21	GPI: 1. Anxiety 2. Nausea 3. Hypotonia
van der Linden (2002)	NA	1. TA: 80 2. GPI: 95	NA	No
Martinez-Torres (2009)	Monopolar 3.0–3.3V, 130 Hz, 60 μ s	UPDRS III: 57 10 min VT: 97	Compulsions↓	NM
Flaherty (2005)	4.1 V, 185 Hz, 210 μ s	25	No preoperative behavioral or mood disorders	1. Mild apathy 2. Depression 3. Hypomania
Neuner (2009)	Double monopolar 6 V, 145 Hz, 90 μ s	44	56	1. Suicide attempt post DBS. Patient with previous suicide attempt prior to DBS
Kuhn (2007)	Tetra monopolar 7 V, 130 Hz, 90 μ s	41	52	NM
Burdick (2010)	Mono-bipolar: 2–6.5 V, 60–135 Hz, 90–210 μ s	+15	0	NM
Zabek (2008)	Bipolar 3 V, 130 Hz, 210 μ s	15 min VT: 82%	Compulsion↓ SIB↓	Hardware malfunction

TA:Thalamus, GPI: globus pallidus, YGTSS: Yale Global Tic Severity Score, positive YGTSS: worsening score, YBOCS: Yale Brown Obsessive Compulsive Score, NM: Not mentioned, SIB: Self-injury behavior; VT: video tape, ↑: Increase, ↓: Decrease

severity, while the YBOCS^[30,31] was prevalently applied to assess for co-morbid OCD symptoms [Tables 4, 8, and 11]. Pallidal studies showed (for 16 patients) a mean YGTSS percentage decrease of 65% (SD = 32) and a mean YBOCS percentage decrease (for 8 patients) of 45% (SD = 38). One study^[22] reported no clinical benefit from DBS. Thalamic studies showed a mean YGTSS percentage decrease (for 46 patients) of 60% (SD = 17) and a mean YBOCS percentage decrease (for 29 patients) of 67% (SD = 20). The combined stimulation of thalamus and globus pallidus resulted (for 3 patients) in a YGTSS percentage decrease of 60% (SD = 17). ALIC/NA application yielded (for 3 patients) a YGTSS

percentage decrease of 37% (SD = 10) and a YBOCS percentage decrease (for 2 patients) of 54% (SD = 3). Unilateral NA stimulation caused a tic reduction of 82%. In one patient, DBS ALIC/NA caused a 17% worsening on the YGTSS and an unchanged YBOCS.^[11]

Lead type: Medtronic 3387 and 3389

The Medtronic leads 3387 and 3389 were applied for all DBS applications. Each lead contains four contacts numbered from the right to the left side from 0 to 3 and from 4 to 7, respectively. Contacts 0 and 4 are the most ventral contacts, and contacts 3 and 7 the most dorsal contacts. While each polymer-coated platinum/iridium electrode has a height of 1.5 mm and a diameter of 1.27

mm resulting in an electrode surface of 5.9 mm², the inter-electrode spacing differs between the 3387 and 3389 leads.^[102] The inter-electrode spacing for the 3387 lead is 1.5 mm, providing a total range of stimulation of 10.5 mm, while the inter-electrode spacing of the 3389 type is 0.5 mm, resulting in a total span of 7.5 mm. Probably due to significant diverse target volumes (GPi = 528 ± 87.4 mm³)^[96], for pallidal implantations the short-spacing lead type 3389 was used [Table 2], while for thalamic implantation the long-spacing 3387 was adopted [Table 5]. For ALIC/NA implantations, no preference for a lead type was observed. The leads 3387^[87] and 3389^[46] were used once each. The lead 3387 (with 4 mm contacts, 3 mm interelectrode spacing) was applied once for ALIC/NA implantation^[11] and the lead 3389 for NA stimulation.^[105] Stimulation settings showed for pallidal implantations a prevalence for monopolar stimulation, while thalamic studies showed prevalence for bipolar stimulation.

Level of evidence

The level of evidence, based on the guidelines provided by the United States Department of Health and Human Services, resulted in the following: The majority of studies ($n = 26$) met only level 4 criteria (observational studies without control), while four studies met level 1 criteria (randomized control studies)^[2,42,58,103] and three studies met level 2 criteria (non-randomized controlled trials).^[83,84,99] This translates into level 1 evidence for 14 GTS patients, level 2 evidence for 38 patients, and level 4 evidence for 36 patients.

Results per target

Globus pallidus

Demographics: Seven out of 33 reviewed studies on DBS for GTS [Table 2] reported exclusively on DBS of the globus pallidus.^[17,20,22,28,59,86,99] In total, 12 patients were operated (8 males, 2 females; one study did not mention the gender). Five studies selected the internal pallidum (GPi),^[17,20,22,59,86] one study the external pallidum (GPe),^[99] and one study did not mention which internal pallidum territory was chosen.^[28] Sample sizes were small, ranging from single case reports ($n = 5$)^[17,20,22,28,86] to case series with five subjects ($n = 1$)^[59]. Mean sample size was 1.7 subjects per study (SD = 1.4). Mean patient age (for 9 patients) was 28 years (SD = 11). Mean disease duration (for 9 patients) was 23 years (SD = 13). Follow-up periods ranged from a minimum of 6 months^[86] to a maximum of 24 months post-surgery.^[59] Mean follow-up duration (for 11 patients) was 15 months (SD = 7). The exclusion criteria were not specified in any of the seven reviewed GP studies.

Surgical procedure: All pallidal procedures [Table 3] were bilateral. Six patients were implanted in the posteroventral GPi,^[17,20,22,59,86] three subjects in the anteromedial GPi,^[59] and two patients in the dorsal/central external pallidus.^[99] One study did not specify the targeted GPi territory.^[28]

Magnetic resonance imaging (MRI) was used in the majority of studies for preoperative targeting. Targeting coordinates for the GPi were reported in five studies as follows: 17–20 mm lateral to the anterior commissure (AC) and posterior commissure (PC) line, 2–4 mm anterior to the mid-commissural point (MCP), and 4–5 mm inferior to the AC–PC.^[17,20,22] The GPe coordinates were reported as 20 mm lateral to the AC–PC, 3 mm posterior and 3 mm superior to the AC. The short-spacing electrode 3389 was used for both internal and external pallidal implantations. Intraoperative physiological mapping was used in three studies,^[17,20,22,99] two studies did not report on this aspect of surgical procedure,^[28,86] while one study specified that physiological mapping was not applied.^[59] The final coordinates of electrode location within the GPi were reported only once as 22 mm lateral to AC–PC, 3 mm anterior to MCP, and 4 mm inferior to AC–PC.^[86] MRI was used in the postoperative setting to ascertain the electrode position. Surgical complications were reported twice in the form of a small hematoma around the electrode tip^[20] and stimulator lead infection that required removal.^[28] Three studies did not mention/report surgical complications,^[59,86,99] while two other studies specified that surgical complications were absent.^[17,22]

Post-surgical period: Stimulation parameters ranged between 2.5 and 5 V, 20 and 210 Hz, and 60 to 240 μs [Table 4]. Varying tic improvement was noted following surgery in four studies,^[17,20,28,59,86] while one study did not observe any tic improvement.^[22] The mean YGTSS percentage decrease (for 10 patients) was 55% (SD = 35%) and the mean YBOCS percentage decrease (for 8 patients) was 47% (SD = 38%). Adverse events ranged from (transient) minor episodes (depressive mood, fatigue, nausea, anxiety)^[17,20,22,59] to one report of persistent bradykinesia of the left hand, caused by a hemorrhage in the right target area.^[20]

Thalamus

Demographics: Twelve out of the 33 reviewed studies [Table 6] on DBS for GTS reported exclusively on thalamic DBS.^[2,5,43,44,51,58,76,80,83,95,98,101] Forty-three patients were operated (37 males, 6 females). Sample sizes varied from case reports ($n = 10$), on 1–6 subjects,^[2,5,43,44,51,58,76,80,95,98,101] to prospective cohort studies with 18 subjects.^[83] Mean sample size was six subjects per study (SD = 5). Two studies were randomized controlled clinical trials.^[2,58] Mean age of thalamic treated DBS patients ($n = 42$) was 31 years (SD = 9). Mean disease duration was 22 years (SD = 9). Follow-up period ranged from minimum 3 months^[58] to a maximum of 60 months.^[101] Mean follow-up duration (for 43 patients) was 18 months (SD = 15). Severe cognitive impairment, major psychiatric disorders, and tic disorders of other medical causes were specified by some authors as exclusion criteria,^[2,44,58] while eight studies did not report on their applied exclusion criteria.^[5,43,51,76,80,83,95,98,101]

Surgical procedure: All procedures were bilateral [Table 7]. The ventrooralis internus–centromedian nucleus–parafascicular thalamic crosspoint was targeted in 37 subjects,^[2,5,43,44,58,83,95,98,101] the centromedian–parafascicular complex was implanted in two patients,^[51,76] while the thalamic dorsomedial nucleus/lamella medialis was implanted in one subject.^[98] Target coordinates for the ventro-oralis internus–centromedian nucleus–parafascicular complex were indicated as 5–8 mm lateral to AC–PC line, 5 mm posterior to MCP, and at AC–PC, while for the dorsomedial nucleus/lamella medialis, the target coordinates were 5.0–5.5 mm lateral to AC–PC, 3.7–3.9 mm posterior to MCP, and 1.3–1.4 mm above AC–PC. Preoperative imaging was done on fused MRI/computed tomography (CT) images ($n = 3$)^[2,83,95,101] or only on MRI ($n = 3$) [5, 44, 58]. Atlas application (Schaltenbrand–Wahren) occurred twice.^[43,44] The long-ranging electrode 3387 was implanted in the majority of studies ($n = 8$).^[2,5,44,51,58,83,95,101] Physiological mapping for supplement intraoperative targeting was reported in six studies,^[2,43,51,58,83,95,101] while six studies did not mention physiological recording.^[5,44,76,80,98] In the postoperative setting, mainly MRI was used ($n = 6$) to ascertain the final electrode location,^[5,44,58,83,95,98,101] CT imaging was applied twice.^[2,43] Final electrode coordinates were largely omitted from papers. Surgical complications were reported in two subjects.^[2,43] Bilateral intracerebral subcortical hematoma^[43] and a hemorrhage ventral to the electrode tip were reported, once each.^[2] The absence of surgical complications was specified in five studies,^[5,44,58,95,98,101] while four studies did not report on this aspect.^[51,76,80,83]

Post-surgical period: The stimulation parameters for amplitude, frequency, and pulse width ranged from 1.0 to 7.0 V, 70 to 200 Hz, and 60 to 210 μ s, respectively. Monopolar and bipolar settings were reported [Table 8]. Mean YGTSS percentage decrease (for 41 patients) was 58% (SD = 15) and mean YBOCS percentage decrease (for 16 patients) was 65% (SD = 27). Decreased energy, reduced libido, blurred vision, and mood deterioration were the reported adverse events.

Multiple targets

Demographics

Thalamus, GPi, NA/ALIC (combined): Seven studies [Table 9] reported the application of multiple targets (thalamus, GPi, ALIC, NA), used in single or combined fashion.^[3,42,84,85,87,94,103] Three studies^[84,85,103] had included previously reported patients,^[42,83] although the precise degree of overlap was not detailed.^[84,85] Sample sizes varied from case reports on 1–4 subjects^[3,42,85,87,94,103] to one trial including 36 subjects.^[84] Mean sample size was nine subjects per study (SD = 13). In total, 48 subjects were operated (35 males and 13 females). Mean age (for 44 patients) was 35 years (SD = 6), and mean disease duration was 28 years (SD = 3). The mean follow-up (for 42 patients) was 22 months (SD = 18).

ALIC/NA: Three studies^[11,46,68] reported on DBS of the ALIC/NA (each implanting one patient), one study targeted the ALIC,^[26] and one other study the NA^[105] [Table 9]. A total of five patients were operated. Four patients were males^[11,46,68,105] and one was a female,^[26] with mean age of 34 years (SD = 5). The disease duration for two patients was 26 years (SD = 2).^[26,105] Follow-up ranged from 18 months^[26] to 36 months,^[68] with a mean follow-up duration (for 5 patients) of 29 months (SD = 7).

Surgical procedure

Thalamus, GPi, ALIC/NA (combined): The thalamus was implanted in 41 patients in single or combined fashion [Table 10]. The ventro-oralis internus–centromedian nucleus–parafascicular crosspoint was targeted in 35 subjects,^[84] the centromedian–parafascicular complex in 3 patients,^[42,103] the ventro-oralis internus–centromedian–substantia periventricularis complex in 2 subjects,^[3,94] and the centromedian nucleus was targeted in 1 subject.^[87] Only thalamus was implanted in 32 subjects.^[84] The thalamic target was combined with the ALIC/NA in five patients^[84,85] and with the globus pallidus (GP) in four patients.^[3,42,103] Three of these latter patients were implanted in the anteromedial globus pallidus^[42,103] and one patient in the posteroventral GP.^[3] The GPi (posteroventral area) was implanted with the ALIC/NA in one patient.^[84] One patient was only targeted at the ALIC.^[85] Target coordinates were not mentioned in three studies^[84,85,103] and documented only once.^[3] MRI was used three times for preoperative target imaging,^[42,84,85] while two studies did not mention the preoperative targeting method.^[3,103] The Medtronic lead 3387 was used in three studies,^[3,84,87] the lead 3389 once,^[42] while two studies did not mention which lead type was applied.^[85,103] Microelectrode recording (MER) was used for intraoperative targeting in four studies,^[42,84,85,87] while two studies did not mention intra-physiological mapping.^[3,103] Postoperative MRI was applied to ascertain the final electrode position in all seven studies. Surgical complications were not mentioned in three studies,^[42,85,103] specified once as absent,^[3] and one other study reported on multiple surgical complications.^[84]

ALIC/NA: Studies reporting only on NA/ALIC DBS used for targeting MRI^[11] or MRI in combination with CT^[26,46,68,105] [Table 10]. Target coordinates for the combined NA/ALIC complex were reported as 6.5 mm lateral to AC–PC, 2.5 mm rostral anterior border of AC, 4.5 mm ventral the AC. The Medtronic lead 3389 was used once^[105] and the lead 3387 twice^[26,46] while one study did not specify the lead application.^[68] The lead 3387 with 4 mm contacts and 3 mm inter-electrode spacing (IES) was applied once.^[11] Intraoperative mapping was applied twice.^[11,26] One study specified that no intraoperative mapping was applied,^[105] while two studies did not report on this aspect of surgical procedure.^[46,68] The position of the contacts was confirmed twice

with CT,^[46,68] once with MRI,^[26] and once on fused CT/MRI scans. No surgical complications occurred twice,^[26,105] while three studies did not mention/report complications.^[11,46,68]

Post-surgical period

Thalamus, GPi, ALIC/NA (combined): Mean stimulation parameters and outcomes of these five studies are difficult to summarize in a coherent way as authors indicated the range of stimulation settings and outcomes for the total of included patients, without differentiating and specifying for each target the (mean) stimulation settings and (mean) YGTSS/YBOCS percentage changes. For a detailed account, please refer to Table 11 and the section “DBS for GTS from 1999 to 2012: Presentation of studies.”

ALIC/NA: Double or tetra monopolar stimulation was applied for the ALIC/NA complex (4–7 V, 60–210 Hz, 90–210 μ s). For ALIC stimulation, the settings were similar as for the combined ALIC/NA stimulation, but differed only by a higher pulse width [Table 11]. Adverse effects were reported once in the form of mild apathy, depression, and hypomania.^[26] One study reported of a suicide attempt following DBS intervention,^[66] but specified that the subject had attempted suicide prior to DBS also. One study reported worsening of YGTSS (+17%) and unchanged YBOCSS following intervention.^[11]

Deep brain stimulation for Gilles de la Tourette's syndrome from 1999 to 2012: Presentation of studies

Deep brain stimulation thalamus

In 1999, Visser-Vandewalle and co-workers^[95] reported the first DBS application for refractory Tourette's syndrome in a 42-year-old man. The thalamic ventrooralis internus–centromedian–parafascicular crosspoint was targeted. This area has projections to the premotor cortex and the limbic–motor striatum. Four months follow-up showed a reduction from 38 tics/minute to 8 tics/minute in “off” settings. In “on” condition, all tics subsided. In 2003, the same authors^[101] reported the follow-up of the above-mentioned patient and presented two cases in addition. Two blinded investigators on 10-min video segments counted tics. A 72–90% tic reduction was noted. Decreased energy and changes in sexual function were observed as adverse effects. In 2010, Ackermans and co-workers^[1] reported of the long-term assessment of two of these patients at 6 and 10 years post-surgery. The benefit of tic control was maintained in one patient at 10 years evaluation compared to the 5 years assessment (92.6% vs. 90.1%) and was slightly reduced in the second patient at 6 years compared to the follow-up at 8 months (78% vs. 82%).

The Cleveland group^[58] reported a prospective randomized double-blind trial with five subjects.

The thalamic ventrooralis internus–centromedian nucleus–parafascicular crosspoint was targeted on MRI. Postoperative MRI scans confirmed correct location of electrodes. Stimulation parameters ranged between 3.5 and 3.6 V, 130 and 185 Hz, and 90 and 210 μ s. Three weeks after surgery, patients were assessed in a randomized, blinded manner in four stimulation combinations. During this 4-week period, no modifications as to the stimulation settings were allowed. During the subsequent open clinical observation phase, stimulation parameters could be changed. Formal assessment of the patients occurred 3 months after the start of the open label period. Three of five patients showed significant improvement with bilaterally active thalamic DBS to all primary and secondary measures. Bilateral stimulation yielded a mean YGTSS improvement of 44%. Unilateral DBS was considered ineffective. Quality of life measures improved in four patients, while it did not in one.

In 2008, Servello and co-workers^[83] from Milan published a series on 18 patients with refractory Tourette's syndrome. The thalamic ventrooralis internus–centromedian nucleus–parafascicular crosspoint was targeted. Postoperative MRI atlas co-registration confirmed electrode position. Stimulation was bipolar through the distal contacts and varied between 2.5 and 4 V, 120 and 130 Hz, 90 and 120 μ s. All 18 patients were evaluated at 3-month intervals and showed improved YGTSS scores. Only in the younger patients (three cases), “waxing and waning” of symptoms was observed after 3–6 months of follow-up. A 64% tic reduction was noted at 12 months follow-up. The first nine patients were evaluated further in a blinded on–off manner. Eight patients were reported to worsen in off-condition. With “sham off,” the patients developed anxiety. Minor adverse effects were noted with intensity values greater than 4 V. Fifteen of the initial 18 patients were followed up by Porta and co-workers^[74] for 24 months. A 52% tic reduction was reported in all 15 patients at 2 years follow-up. Depressive, obsessive–compulsive, and anxiety symptoms improved. Cognitive status was reported stable over the 2-year period.

Ackermans and co-workers^[2] published in 2011 the results of a double-blind clinical trial on six male subjects. Compulsions, history of depression and substance abuse and auto-mutilation were specified as exclusion criteria. Patients were followed up at 3, 6, and 12 months following surgery. The crosspoint of the thalamic centromedian nucleus–substantia periventricularis–nucleus ventro-oralis internus was targeted. Postoperative CT reportedly confirmed lead location. Three patients received monopolar and three others bipolar stimulation. Stimulation parameters varied between 1.0 and 7.3 V, 70 and 130 Hz, and 60 and 210 μ s. The YGTSS showed a 49% reduction at 12 months follow-up. A small hemorrhage ventral to the electrode tip in one patient was reported, which resulted

in vertical gaze palsy. Energy levels were reduced in all patients.

Vernaleken and co-workers^[98] from Germany reported 36% tic improvement in a male patient with thalamic DBS applied to the dorsomedial nucleus. This patient had previous unsuccessful GPi stimulation.

Globus pallidus

Globus pallidus internus: At the University of Vienna, Diederich *et al.*^[20] applied posteroventral GPi for GTS. Bipolar stimulation through the most ventral contacts caused a decrease in mean tic frequency of 73%. No change in the compulsive tendencies could be observed. Depressive and anxiety symptoms improved and cognitive status remained stable at 14 months follow-up. Due to a small hemorrhage noted around the tip of the right electrode on the immediate postoperative MRI, the patient suffered pronation/supination bradykinesia of the left hand. Transient mild fatigue was noted in the postoperative period.

Gallagher *et al.*^[28] from Wisconsin-Madison reported disappearance of vocal tics and improvement of motor tics after bilateral DBS GPi for refractory GTS. After removal of the left infected lead, tics reappeared on the right side, while tics remained absent on the left side, supporting lateralized dysfunctional basal ganglia networks in tic genesis.^[63]

In Houston, Shahed *et al.*^[86] reported bilateral DBS of the posteroventral GPi in a 16-year-old male with several psychiatric co-morbidities. Monopolar stimulation with 5 V, 156 Hz, and 90 μ s resulted in an 84% tic reduction and a 69% decrease in obsessive-compulsive symptoms at 6 months follow-up.

Dehning *et al.*^[17] from Germany reported a 12-month follow-up study of a 44-year-old female. The posteroventral GP was selected. As the most ventral contacts on the right side caused visual symptoms, the more dorsal contact 2 was selected, and on the left side, contact 1 was used for monopolar stimulation with 3.2 V, 130 Hz, and 120 μ s. Stimulation was increased at 12 months follow-up to 4.2 V, 145 Hz, and 210 μ s. The YGTSS showed an improvement of 88%.

Dueck *et al.*^[22] from Germany reported no therapeutic effect of bilateral DBS GPi in a 16-year-old male with mental disability. Postoperative MRI scans showed the most ventral contacts to be in the ventral section of the GPi. No surgical complications were reported. Stimulation parameters at 12 months follow-up were 4.0 V, 130 Hz, and 120 μ s. Antipsychotic medications (Haloperidol, Risperidone) remained unchanged in the postoperative period. At high stimulation settings, nausea, dizziness, moderate anxiety, and visual disturbances were observed.

Martinez-Fernandez and co-workers^[59] from London

reported an open-label trial with a 24-month follow-up on five patients. The limbic anteromedial section of the GPi was implanted in three patients and the sensorimotor posteroventral pallidum in two patients. Stimulation settings varied between 2.5 and 4.2 V, 20 and 170 Hz, and 60 and 210 μ s. As the mean reduction for limbic DBS GPi for motor tics was 75% and for phonic tics was 74%, while the mean reduction following motor DBS GPi was reported as 42% and 60% for motor and vocal tics, respectively, the authors concluded that anteromedial GPi DBS appears superior to posterolateral GPi DBS in GTS. Anxiety with high voltage was observed in two patients and one patient suffered two DBS hardware infections that required hardware removal.

Globus pallidus externus: In 2007, the preliminary results on DBS in the GPe were published by Vilela Filho and co-workers^[99] from Brazil. A tic reduction of 81% and a concomitant 84% improvement in OCD was reported. Previously, in 2004, Francois and co-workers^[27,32] reported of the potential key role of the external globus pallidus in neuronal circuits affected in Tourette's syndrome. The authors observed stereotyped behavior following microinjections of bicuculline, a GABAergic antagonist, into different parts of the GPe in non-human primates.

Multiple targets

TA, GPi, NA/ALIC (combined): In 2002, van der Linden and co-workers^[94] reported the first case on a 27-year-old subject treated with posteroventral GPi DBS for GTS (with concomitant thalamic implantation). Test stimulation resulted for pallidal stimulation in a 95% tic decrease, while thalamic application yielded an 80% tic improvement. Only the GPi leads were connected to the pulse generator.

Welter and co-workers^[103] presented in 2008 a report on three patients enrolled into a controlled, double-blind, randomized cross-over study. The patients were implanted in the centromedian-parafascicular thalamic nuclei and in the anteromedial limbic GP territory. Pallidal stimulation proved to be superior to thalamic stimulation. A 64–82% tic improvement was noted with pallidal stimulation, while thalamic stimulation resulted in a 30–64% tic reduction. A 43–66% reduction was observed with simultaneous thalamic and pallidal stimulation. The Welter *et al.*^[103] study was the extension of the Houeto *et al.*^[42] trial based on one single female patient implanted at the centromedian-parafascicular thalamic complex and limbic pallidum. A 64%, 66%, and 60% tic reduction resulted from thalamic, pallidal, and combined stimulation, respectively. However, thalamic stimulation resulted in a greater YBOCS decrease than pallidal stimulation alone.

Ackermans *et al.*^[3] reported on two patients, one implanted only in the ventro-oralis internus-centromedian nucleus-substantia periventricularis thalamic complex and the other one implanted in the

thalamic centromedian nucleus and posteroventral pallidus. Only the pallidal electrodes were connected to the pulse generator. At 12 months follow-up, thalamic stimulation resulted in a reduction from 20 to 3 tics/minute, while pallidal stimulation resulted in a reduction from 28 to 2 tics/minute. Both patients complained of reduced energy, while one also complained of reduced libido.

The largest prospective study on DBS in GTS patients was published by Servello and co-workers from Milan in 2010^[84] on 36 patients. This cohort included 18 previously reported subjects.^[83] Bilateral thalamic DBS was performed in 31 patients, and unilateral thalamic DBS was performed in 1 patient (for abnormal vasculature in left hemisphere). Three patients with thalamic surgery received subsequently two rescue leads at the ALIC and the NA. All thalamic implantations occurred at the ventro-oralis internus-centromedian nucleus-parafascicular complex. One patient was implanted in the posteroventral GPi and in the ALIC/NA. One patient was implanted only at the ALIC/NA. Rescue DBS surgery was considered only for those patients suffering social impairment due to OCD co-morbidity, who failed to respond to the first DBS procedure. The YGTSS decreased by 55%. Adverse effects were lead repositioning in one patient, removal of DBS-infected implant, and hardware failure.

In 2009, Servello *et al.*^[85] published another study with the DBS team led by Okun from Florida on four GTS subjects; one patient of this cohort was previously reported by Servello and co-workers.^[83] Three subjects were implanted in the ventro-oralis internus-centromedian nucleus-parafascicular thalamic complex, and subsequently had rescue leads at the ALIC/NA for disabling OCD. One patient was implanted only in the ALIC and NA. Only mild improvement of tics and OCD could be observed despite rescue surgery.

A 32% tic improvement was reported by Shields *et al.*^[87] following centromedian thalamic DBS using high stimulation settings (7 V, 185 Hz, and 90 μ s). This patient was previously treated with ALIC DBS that gave poor results.^[26]

The center of the centromedian parafascicular complex was targeted (4 mm posterior to the previously reported target) by Savica *et al.*^[80] The three patients showed a mean YGTSS improvement of 70% at 1-year follow-up.

ALIC/NA: [Figure 1] Flaherty *et al.*^[26] targeted the ALIC in one female. Stimulation with 4.1 V, 185 Hz, and 210 μ s yielded only a 25% YGTSS decrease. The authors noted that stimulation with the ventral contacts caused apathy and depression, while the dorsal most contacts caused hypomania. The effects subsided with turning off the stimulation device.

Kuhn *et al.*^[46] reported ALIC/NA stimulation in a patient

affected with self-injury behavior (SIB). The ALIC/NA was targeted on fused MRI/CT scans, 6.5 mm lateral to ACPC, 2.5 mm rostral anterior border of AC, and 4.5 mm ventral to AC. Stimulation with all four contacts 7 V, 130 Hz, and 90 μ s yielded a 41% improvement on the YGTSS at 30 months follow-up and a 52% YBOCS improvement.

Zabek *et al.*^[105] applied unilateral DBS to the right NA. At 28 months follow-up, a tic reduction of 82% with amelioration of compulsions and SIB was noted. Stimulation settings were reported at 3 V, 130 Hz, and 210 μ s.

Neuner *et al.* reported in 2010^[66] on a suicide attempt in a patient treated with ALIC/NA (Neuner *et al.*, 2009). Subsequent to DBS (tic improvement of 44%), the patient attempted suicide secondary to a major depressive episode. The suicide attempt related to the DBS is unlikely, as the patient had committed a suicide attempt prior to DBS.

Burdick *et al.*^[11] from Florida reported worsening YGTSS and unchanged YBOCS at 30 months follow-up for one patient treated with bilateral ALIC/NA DBS.

Subthalamic nucleus: [Figure 2] Only one group^[60] targeted the dorsolateral (sensorimotor) STN for GTS. Martinez-Torres and co-workers (2009) reported the outcome of DBS STN in a 38-year-old patient with prime diagnosis of PD, who presented as well with a tic disorder. The GTS was not treated medically prior to DBS intervention. Monopolar stimulation parallel to dopaminergic reduction resulted in 97% reduction of tic frequency on a 10-min videotape and a reduction of 57% on the UPDRS III.

DISCUSSION AND CONCLUSION

Each of the five main DBS targets in GTS had



Figure 1: Axial T2-weighted MRI showing the location of the nucleus accumbens (anterior artifacts)

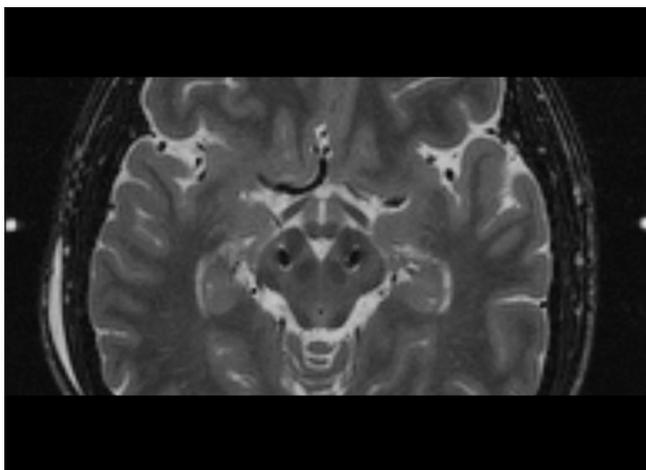


Figure 2: Axial T2-weighted MRI showing the location of the subthalamic nucleus

demonstrated variable tic improvement, with mean YGTSS reduction across targets ranging between 59 and 97%. The greatest mean YGTSS percentage decrease was noted for globus pallidus stimulation (66%), while it was slightly lower for thalamic application (60%). Simultaneous pallidal–thalamic stimulation resulted in a mean YGTSS improvement of 60%. The mean YGTSS for ALIC/NA DBS application decreased by 59% and STN application resulted in a 97% tic reduction.

DBS proved as well beneficial for associated obsessive–compulsive symptoms. The mean YBOCS across targets decreased between 45 and 67%. Thalamic and ALIC/NA stimulation resulted in the largest decrease of associated OC symptoms (67 and 54%, respectively), while pallidal stimulation appeared slightly less beneficial, resulting only in a 45% YBOCS decrease.

However, the comparison of outcome results across studies should be done with greatest caution. One of the prime difficulties summarizing and comparing the reported data on DBS for GTS in a coherent way consists in the basic numeric disparity between (exclusive) pallidal ($n = 7$), thalamic ($n = 12$), ALIC/NA ($n = 5$), and STN ($n = 1$) publications. This disparity introduces a fundamental bias for a meaningful comparison between targets and becomes even more evident, by considering the numeric disproportion of patients treated per target. While 13 patients were treated exclusively with GP DBS,^[3,17,20,22,28,59,86,99] 58 patients had exclusive thalamic stimulation,^[2,5,43,44,51,58,76,80,83,84,87,95,98,101] Eight patients underwent exclusive ALIC/NA implantation,^[11,26,46,68,85,105] while only one patient received STN stimulation.^[60]

Of the 88 GTS patients treated since 1999 with DBS, only for 14 patients evidence-based criterion exists.^[2,42,58,103]

The great variability in target selection has two main reasons: The precise anatomical location(s) and network(s)

involved in GTS remain largely speculative.^[62,88] A further reason is the conceptual divide whether to consider GTS more as an expression of a motor disorder or rather as an expression of a compulsive behavior, i.e. the inability to suppress a tic.^[7,73] Some authors^[42,59,84,103] propose instead a more integrative concept to explain more readily motor and behavioral symptoms of GTS. An increasing body of evidence suggests that both the sensorimotor and the limbic-associative parts of the basal ganglia play a fundamental role in the pathophysiology of GTS.^[34,35,89,90] A simultaneous modulation of motor and associative-limbic targets/networks may prove consequently more efficacious than single target/network stimulation. Simultaneous stimulation of motor and limbic areas of the internal globus pallidus was already successfully applied and reported in 2007 for LND^[14] by the Montpellier group led by Coubes. The authors implanted at each side two leads into the internal globus pallidus (one into the pallidal motor area and the other one into the pallidal limbic section). Pallidal motor stimulation caused a marked reduction in dystonic movements, while limbic stimulation reduced behavioral disorders. Based on physiological data, the pallidal motor and limbic regions were considered two targets each belonging to two functionally independent circuits.^[14] Equally in GTS, an altered interaction between the limbic and motor circuits is thought to be responsible for the clinical manifestations. Simultaneous stimulation of pallidal limbic and motor territories may prove therefore most effective for GTS [Figures 3].

However, the most restrictive factor for an exhaustive evaluation of each target was related to intrinsic methodological limitations of published studies. For thalamic targeting, the majority of authors^[2,5,51,58,76,87] reported the coordinates provided by Vandewalle and co-workers^[95] ($x, y, z = 5$ mm lateral to AC–PC, 4 mm posterior MCP, and at the ACPC plane). Yet, while identical thalamic nomenclature^[37] and coordinates were reported, different thalamic territories were indicated. Some authors referred to the ventrooralis internus–centromedian nucleus–substantia periventricularis complex,^[2,5] others to the ventrooralis internus–centromedian nucleus–parafascicular crosspoint^[43,44,58,83,101] or to the centromedian–parafascicular complex^[76] or to the centromedian nucleus.^[87] However, the ventrooralis internus, centromedian, and parafascicular nuclei are distinct thalamic structures. While the nucleus ventrooralis internus is located more anteriorly, the nucleus parafascicularis is situated medially and more posteriorly with respect to the ventro-oralis internus, while the centromedian nucleus is positioned laterally to the parafascicularis nucleus and posteriorly to the ventro-oralis internus.^[81] Visualization of thalamic sub-regions remains difficult.^[19,54,93] It is critical that applied targeting methodology is detailed. It is of crucial importance to,

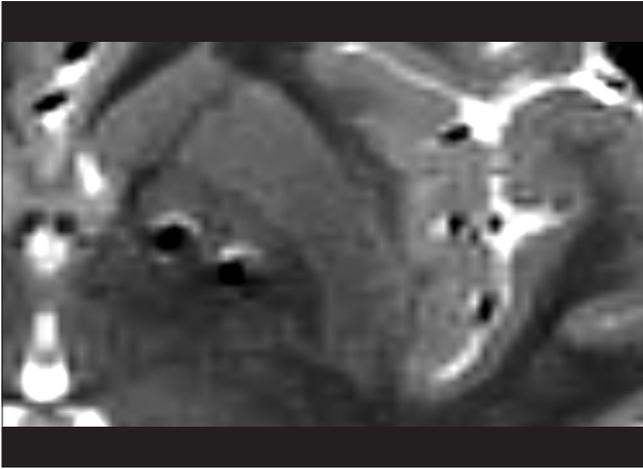


Figure 3: Axial T2-weighted MRI image showing two leads implanted in the anterior (limbic) and posterior (motor) sections of the GPi, according to the implemented protocol in Montpellier, France

first, precisely target this area and second, monitor with post-op MR the actual localization of each electrode.

Defining the location of a target in sole reference to standard (atlas) coordinates neglects further the large inter-/intra-topographic variability of sub-cortical structures^[39,45,53,77,78,92,93,97] and the variability of the AC-PC length between individuals.^[52,71,97] The degree of spatial variability of a basal ganglia structure appears to be proportional to its distance with respect to the landmarks of the third ventricle.^[39] Between those structures targeted in GTS, the posteroventral pallidum is the structure that is furthest away from the landmarks of the third ventricle, and therefore the target with the potentially greatest topographic variability.^[39] Hence, targeting in sole reference to standard (atlas) coordinates harbors the risk of significant targeting error.^[39,92]

From the reviewed data, it is difficult to individuate the source of differences between studies and even the source of differences within the same cohort. Great methodological variability and quality of reporting makes recommendations as to target or stimulating settings difficult. The comparison of clinical results of investigations that differ for selected target should be done further with caution as targets differ considerably for anatomy and morphology, while the size of the applied DBS Medtronic lead is usually similar.^[10,12,96] The wide phenotypic variation of GTS^[33] and its numerous associated co-morbid disorders hamper further the attempt to evaluate which circuitries are precisely affected in GTS and modulated by DBS.

The possibility that predominately positive results were published at the expense of negative outcome introducing therefore significant publication bias has to be considered.^[21,23,82] From the reviewed 33 studies, only two reported no beneficial effect of DBS in two GTS patients.^[11,22] While Vernaleken and co-workers^[98]

published the positive results of thalamic DBS, they did not publish the negative outcome following pallidal intervention for the very same patient.

Randomized controlled trials with larger cohorts are urgently needed. The mean sample size of DBS studies for GTS was six patients. Given the motor and neuropsychiatric components of GTS, systematic pre- and postoperative motor, cognitive, and mood assessments are recommended. In light of the fluctuating course of GTS,^[56] clinical assessments at multiple points in time are necessary. Stimulation parameters should be indicated for each patient instead of being reported as mean values for the entire cohort. Inclusion criteria, targeting methodology, medications at the time of assessment and adverse events need rigorous reporting. Similarly, the absence of adverse effects and negative outcome needs reporting. Standardization of procedures is imperative.^[13,64,79] This pool of data will allow for a more exhaustive evaluation of the efficacy of each target, in order to define the optimal target localization(s) for DBS in GTS.

REFERENCES

- Ackermans L, Duits A, Temel Y, Winogrodzka A, Peeters F, Beuls EA, et al. Long-term outcome of thalamic deep brain stimulation in two patients with Tourette syndrome. *J Neurol Neurosurg Psychiatry* 2010;81:1068-72.
- Ackermans L, Duits A, van der Linden C, Tijssen M, Schruers K, Temel Y, et al. Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. *Brain* 2011;134:832-44.
- Ackermans L, Temel Y, Cath D, van der Linden C, Bruggeman R, Kleijer M, et al. Deep brain stimulation in Tourette's syndrome: Two targets? *Mov Disord* 2006;21:709-13.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed., text revision. Washington, DC: Author; 2000.
- Bajwa RJ, de Lotbiniere AJ, King RA, Jabbari B, Quatrano S, Kunze K, et al. Deep brain stimulation in Tourette's syndrome. *Mov Disord* 2007;22:1346-50.
- Baker EF. Gilles de la Tourette syndrome treated by bimedial frontal leucotomy. *Can Med Assoc J* 1962;86:746-7.
- Berardelli A, Curra A, Fabbrini G, Gilio F, Manfredi M. Pathophysiology of tics and Tourette syndrome. *J Neurol* 2003;250:781-7.
- Bingley T, Leksell L, Meyerson BA, Rylander G. Long term results of stereotactic capsulotomy in chronic obsessive-compulsive neurosis, in *Neurosurgical Treatment in Psychiatry, Pain, and Epilepsy*. Edited by Sweet WH, Obrador S, Martín-Rodríguez JG. Baltimore, University Park Press, 1977, pp 287-9.
- Bloch MH, Leckman JF. Clinical course of Tourette syndrome. *J Psychosom Res* 2009;67:497-501.
- Buhlmann J, Hofmann L, Tass PA, Hauptmann C. Modeling of a segmented electrode for desynchronizing deep brain stimulation. *Front Neuroeng* 2011;4:15.
- Burdick A, Foote KD, Goodman W, Ward HE, Ricciuti N, Murphy T, et al. Lack of benefit of accumbens/capsular deep brain stimulation in a patient with both tics and obsessive-compulsive disorder. *Neurocase* 2010;16:321-30.
- Butson CR, McIntyre CC. Role of electrode design on the volume of tissue activated during deep brain stimulation. *J Neural Eng* 2006;3:1-8.
- Cath DC, Hedderly T, Ludolph AG, Stern JS, Murphy T, Hartmann A, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part I: Assessment. *Eur Child Adolesc Psychiatry* 2011;20:155-71.
- Cif L, Biolsi B, Gavarini S, Saux A, Robles SG, Tancu C, et al. Antero-ventral internal pallidum stimulation improves behavioral disorders in Lesch-Nyhan disease. *Mov Disord* 2007;22:2126-9.
- Coubes P, Echenne B, Roubertie A, Vayssiere N, Tuffery S, Humbertclaude V, et al. [Treatment of early-onset generalized dystonia by chronic bilateral

- stimulation of the internal globus pallidus. Apropos of a case]. *Neurochirurgie* 1999;45:139-44.
16. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B. Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. *Lancet* 2000;355:2220-1.
 17. Dehning S, Mehrkens JH, Muller N, Botzel K. Therapy-refractory Tourette syndrome: Beneficial outcome with globus pallidus internus deep brain stimulation. *Mov Disord* 2008;23:1300-2.
 18. Demirkol A, Erdem H, Inan L, Yigit A, Guney M. Bilateral globus pallidus lesions in a patient with Tourette syndrome and related disorders. *Biol Psychiatry* 1999;46:863-7.
 19. Deoni SC, Josseau MJ, Rutt BK, Peters TM. Visualization of thalamic nuclei on high resolution, multi-averaged T1 and T2 maps acquired at 1.5 T. *Hum Brain Mapp* 2005;25:353-9.
 20. Diederich NJ, Kalteis K, Stamenkovic M, Pieri V, Alesch F. Efficient internal pallidal stimulation in Gilles de la Tourette syndrome: A case report. *Mov Disord* 2005;20:1496-9.
 21. Dirnagl U, Lauritzen M. Fighting publication bias: Introducing the Negative Results section. *J Cereb Blood Flow Metab* 2010;30:1263-4.
 22. Dueck A, Wolters A, Wunsch K, Bohne-Suraj S, Mueller JU, Haessler F, et al. Deep brain stimulation of globus pallidus internus in a 16-year-old boy with severe tourette syndrome and mental retardation. *Neuropediatrics* 2009;40:239-42.
 23. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PloS One* 2008;3:e3081.
 24. Eddy CM, Rickards HE, Cavanna AE. Treatment strategies for tics in Tourette syndrome. *Ther Adv Neurol Disord* 2011;4:25-45.
 25. Ernst M, Zametkin AJ, Matochik JA, Pascualvaca D, Jons PH, Hardy K, et al. Presynaptic dopaminergic deficits in Lesch-Nyhan disease. *N Engl J Med* 1996;334:1568-72.
 26. Flaherty AW, Williams ZM, Amirnovin R, Kasper E, Rauch SL, Cosgrove GR, et al. Deep brain stimulation of the anterior internal capsule for the treatment of Tourette syndrome: Technical case report. *Neurosurgery* 2005;57 Suppl 4:E403; discussion E403.
 27. Francois C, Grabli D, McCairn K, Jan C, Karachi C, Hirsch EC, et al. Behavioural disorders induced by external globus pallidus dysfunction in primates II. Anatomical study. *Brain* 2004;127:2055-70.
 28. Gallagher CL, Garell PC, Montgomery EB Jr. Hemi tics and deep brain stimulation. *Neurology* 2006;66:E12.
 29. Gilbert DL, Bansal AS, Sethuraman G, Sallee FR, Zhang J, Lipps T, et al. Association of cortical disinhibition with tic, ADHD, and OCD severity in Tourette syndrome. *Mov Disord* 2004;19:416-25.
 30. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, et al. The Yale-brown obsessive compulsive scale. II. Validity. *Arch General Psychiatry* 1989;46:1012-6.
 31. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-brown obsessive compulsive scale. I. Development, use, and reliability. *Arch General Psychiatry* 1989;46:1006-11.
 32. Grabli D, McCairn K, Hirsch EC, Agid Y, Feger J, Francois C, et al. Behavioural disorders induced by external globus pallidus dysfunction in primates: I. Behavioural study. *Brain* 2004;127:2039-54.
 33. Grados MA, Mathews CA. Clinical phenomenology and phenotype variability in Tourette syndrome. *J Psychosom Res* 2009;67:491-6.
 34. Graybiel AM. The basal ganglia. *Curr Biol* 2000;10:R509-11.
 35. Groenewegen HJ, van den Heuvel OA, Cath DC, Voorn P, Velthuis DJ. Does an imbalance between the dorsal and ventral striatopallidal systems play a role in Tourette's syndrome? A neuronal circuit approach. *Brain Dev* 2003;25 Suppl 1:S3-14.
 36. Harris JC, Lee RR, Jinnah HA, Wong DF, Yaster M, Bryan RN. Craniocerebral magnetic resonance imaging measurement and findings in Lesch-Nyhan syndrome. *Arch Neurol* 1998;55:547-53.
 37. Hassler R. Anatomy of the thalamus. In: Schaltenbrand G, Bailey P, editors. *Introduction to stereotaxis with an atlas of the human brain*. Stuttgart: Thieme; 1959. p. 230-90.
 38. Hassler R, Dieckmann G. [Stereotaxic treatment of tics and inarticulate cries or coprolalia considered as motor obsessional phenomena in Gilles de la Tourette's disease]. *Rev Neurol* 1970;123:89-100.
 39. Hirabayashi H, Tengvar M, Hariz MI. Stereotactic imaging of the pallidal target. *Mov Disord* 2002;17 Suppl 3:S130-4.
 40. Hoekstra PJ, Anderson GM, Limburg PC, Korff J, Kallenberg CG, Minderaa RB. Neurobiology and neuroimmunology of Tourette's syndrome: An update. *Cell Mol Life Sci* 2004;61:886-98.
 41. Hornsey H, Banerjee S, Zeitlin H, Robertson M. The prevalence of Tourette syndrome in 13-14-year-olds in mainstream schools. *J Child Psychol Psychiatry* 2001;42:1035-9.
 42. Houeto JL, Karachi C, Mallet L, Pillon B, Yelnik J, Mesnage V, et al. Tourette's syndrome and deep brain stimulation. *J Neurol Neurosurg Psychiatry* 2005;76:992-5.
 43. Idris Z, Ghani AR, Mar W, Bhaskar S, Wan Hassan WN, Tharakan J, et al. Intracerebral haematomas after deep brain stimulation surgery in a patient with Tourette syndrome and low factor XIIIa activity. *J Clin Neurosci* 2010;17:1343-4.
 44. Kaido T, Otsuki T, Kaneko Y, Takahashi A, Omori M, Okamoto T. Deep brain stimulation for Tourette syndrome: A prospective pilot study in Japan. *Neuromodulation* 2011;14:123-8; discussion 129.
 45. Kelly PJ, Derome P, Guiot G. Thalamic spatial variability and the surgical results of lesions placed with neurophysiologic control. *Surg Neurol* 1978;9:307-15.
 46. Kuhn J, Lenartz D, Mai JK, Huff W, Lee SH, Koulousakis A, et al. Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome. *J Neurol* 2007;254:963-5.
 47. Kurlan R, Como PG, Miller B, Palumbo D, Deeley C, Andresen EM, et al. The behavioral spectrum of tic disorders: A community-based study. *Neurology* 2002;59:414-20.
 48. Kurlan R, McDermott MP, Deeley C, Como PG, Brower C, Eapen S, et al. Prevalence of tics in schoolchildren and association with placement in special education. *Neurology* 2001;57:1383-8.
 49. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tic Severity Scale: Initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry* 1989;28:566-73.
 50. Leckman JF, Zhang H, Vitale A, Lahnin F, Lynch K, Bondi C, et al. Course of tic severity in Tourette syndrome: The first two decades. *Pediatrics* 1998;102:14-9.
 51. Lee MW, Au-Yeung MM, Hung KN, Wong CK. Deep brain stimulation in a Chinese Tourette's syndrome patient. *Hong Kong Med J* 2011;17:147-50.
 52. Lee TO, Hwang HS, De Salles A, Mattoso C, Pedrosa AG, Behnke E. Inter-racial, gender and aging influences in the length of anterior commissure-posterior commissure line. *J Korean Neurosurg Soc* 2008;43:79-84.
 53. Lemaire JJ, Coste J, Ouchchane L, Caire F, Nuti C, Derost P, et al. Brain mapping in stereotactic surgery: A brief overview from the probabilistic targeting to the patient-based anatomic mapping. *Neuroimage* 2007;37 Suppl 1:S109-15.
 54. Lemaire JJ, Sakka L, Ouchchane L, Caire F, Gabrillargues J, Bonny JM. Anatomy of the human thalamus based on spontaneous contrast and microscopic voxels in high-field magnetic resonance imaging. *Neurosurgery* 2010;66 Suppl Operative 3:161-72.
 55. Lesch M, Nyhan WL. A familial disorder of uric acid metabolism and central nervous system function. *Am J Med* 1964;36:561-70.
 56. Lin H, Yeh CB, Peterson BS, Scahill L, Grantz H, Findley DB, et al. Assessment of symptom exacerbations in a longitudinal study of children with Tourette's syndrome or obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 2002;41:1070-7.
 57. Lozano AM, Kumar R, Gross RE, Giladi N, Hutchison WD, Dostrovsky JO, et al. Globus pallidus internus pallidotomy for generalized dystonia. *Mov Disord* 1997;12:865-70.
 58. Maciunas RJ, Maddux BN, Riley DE, Whitney CM, Schoenberg MR, Ogrocki PJ, et al. Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. *J Neurosurg* 2007;107:1004-14.
 59. Martinez-Fernandez R, Zrinzo L, Aviles-Olmos I, Hariz M, Martinez-Torres I, Joyce E, et al. Deep brain stimulation for Gilles de la Tourette syndrome: A case series targeting subregions of the globus pallidus internus. *Mov Disord* 2011;26:1922-30.
 60. Martinez-Torres I, Hariz MI, Zrinzo L, Foltynie T, Limousin P. Improvement of tics after subthalamic nucleus deep brain stimulation. *Neurology* 2009;72:1787-9.
 61. McCairn KW, Iriki A, Isoda M. High-frequency pallidal stimulation eliminates tic-related neuronal activity in a nonhuman primate model of Tourette syndrome. *Neuroreport* 2012;23:206-10.
 62. McNaught KS, Mink JW. Advances in understanding and treatment of Tourette syndrome. *Nat Rev Neurol* 2011;7:667-76.

63. Mink JW. Basal ganglia dysfunction in Tourette's syndrome: A new hypothesis. *Pediatr Neurol* 2001;25:190-8.
64. Mink JW, Walkup J, Frey KA, Como P, Cath D, DeLong MR, et al. Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome. *Mov Disord* 2006;21:1831-8.
65. Nadvornik P, Sramka M, Lisy L, Svicka I. Experiences with dentatotomy. *Confin Neurol* 1972;34:320-4.
66. Neuner I, Halfter S, Wollenweber F, Podoll K, Schneider F. Nucleus accumbens deep brain stimulation did not prevent suicide attempt in Tourette syndrome. *Biol Psychiatry* 2010;68:e19-20.
67. Neuner I, Kellermann T, Stocker T, Kircher T, Habel U, Shah JN, et al. Amygdala hypersensitivity in response to emotional faces in Tourette's patients. *World J Biol Psychiatry* 2010;11:858-72.
68. Neuner I, Podoll K, Lenartz D, Sturm V, Schneider F. Deep brain stimulation in the nucleus accumbens for intractable Tourette's syndrome: Follow-up report of 36 months. *Biol Psychiatry* 2009;65:e5-6.
69. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet* 1999;354:1526.
70. Nyhan WL. Dopamine function in Lesch-Nyhan disease. *Environ Health Perspect* 2000;108 Suppl 3:S409-11.
71. Pallavaram S, Yu H, Spooner J, D'Haese PF, Bodenheimer B, Konrad PE, et al. Intersurgeon variability in the selection of anterior and posterior commissures and its potential effects on target localization. *Stereotact Funct Neurosurg* 2008;86:113-9.
72. Pappert EJ, Goetz CG, Louis ED, Blasucci L, Leurgans S. Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. *Neurology* 2003;61:936-40.
73. Peterson BS, Skudlarski P, Anderson AW, Zhang H, Gatenby JC, Lacadie CM, et al. A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. *Arch General Psychiatry* 1998;55:326-33.
74. Porta M, Brambilla A, Cavanna AE, Servello D, Sassi M, Rickards H, et al. Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: Two-year outcome. *Neurology* 2009;73:1375-80.
75. Robertson MM. Gilles de la Tourette syndrome: The complexities of phenotype and treatment. *Br J Hosp Med* 2011;72:100-7.
76. Rzesnietzek L, Wachter T, Kruger R, Gharabaghi A, Plewnia C. Suppression of extrapyramidal side effects of doxepin by thalamic deep brain stimulation for Tourette syndrome. *Neurology* 2011;77:1708-9.
77. Saleh C. Is the Schaltenbrand-Wahren atlas a neurosurgical relic of the 20th century? *Stereotact Funct Neurosurg* 2009;87:399.
78. Saleh C. Knowing the limitations of applied deep brain stimulation technology for a clearer understanding of clinical outcomes. *J Neurol Sci* 2010;292:119; author reply 120.
79. Saleh C, Gale JT, Eskandar E. The need for a multifactorial approach to raise the standard in deep brain stimulation reporting. *Neuromodulation* 2011;14:183-4.
80. Savica R, Stead M, Mack KJ, Lee KH, Klassen BT. Deep brain stimulation in tourette syndrome: A description of 3 patients with excellent outcome. *Mayo Clin Proc* 2012;87:59-62.
81. Schaltenbrand G, Bailey P. Introduction to stereotaxis with an atlas of the human brain. Stuttgart, Germany: Georg Thieme Verlag; 1959.
82. Schlaepfer TE, Fins JJ. Deep brain stimulation and the neuroethics of responsible publishing: When one is not enough. *JAMA* 2010;303:775-6.
83. Servello D, Porta M, Sassi M, Brambilla A, Robertson MM. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: The surgery and stimulation. *J Neurol Neurosurg Psychiatry* 2008;79:136-42.
84. Servello D, Sassi M, Brambilla A, Defendi S, Porta M. Long-term, post-deep brain stimulation management of a series of 36 patients affected with refractory gilles de la tourette syndrome. *Neuromodulation* 2010;13:187-94.
85. Servello D, Sassi M, Brambilla A, Porta M, Haq I, Foote KD, et al. De novo and rescue DBS leads for refractory Tourette syndrome patients with severe comorbid OCD: A multiple case report. *J Neurol* 2009;256:1533-9.
86. Shahed J, Poysky J, Kenney C, Simpson R, Jankovic J. GPI deep brain stimulation for Tourette syndrome improves tics and psychiatric comorbidities. *Neurology* 2007;68:159-60.
87. Shields DC, Cheng ML, Flaherty AW, Gale JT, Eskandar EN. Microelectrode-guided deep brain stimulation for Tourette syndrome: Within-subject comparison of different stimulation sites. *Stereotact Funct Neurosurg* 2008;86:87-91.
88. Singer HS, Minzer K. Neurobiology of Tourette's syndrome: Concepts of neuroanatomic localization and neurochemical abnormalities. *Brain Dev* 2003;25 Suppl 1:S70-84.
89. Singer HS, Reiss AL, Brown JE, Aylward EH, Shih B, Chee E, et al. Volumetric MRI changes in basal ganglia of children with Tourette's syndrome. *Neurology* 1993;43:950-6.
90. Stern E, Silbersweig DA, Chee KY, Holmes A, Robertson MM, Trimble M, et al. A functional neuroanatomy of tics in Tourette syndrome. *Arch General Psychiatry* 2000;57:741-8.
91. Tabori Kraft J, Dalsgaard S, Obel C, Thomsen PH, Henriksen TB, Scahill L. Prevalence and clinical correlates of tic disorders in a community sample of school-age children. *Eur Child Adolesc Psychiatry* 2012;21:5-13.
92. Traynor C, Heckemann RA, Hammers A, O'Muircheartaigh J, Crum WR, Barker GJ, et al. Reproducibility of thalamic segmentation based on probabilistic tractography. *Neuroimage* 2010;52:69-85.
93. Traynor CR, Barker GJ, Crum WR, Williams SC, Richardson MP. Segmentation of the thalamus in MRI based on T1 and T2. *Neuroimage* 2011;56:939-50.
94. Van der Linden C, Colle H, Vandewalle V, Alessi G, Rijkckaert D, De Waele L. Successful treatment of tics with bilateral internal pallidum stimulation in a 27-year old male patient with Gilles de la Tourette syndrome. *Mov Disord* 2002;17:341.
95. Vandewalle V, van der Linden C, Groenewegen HJ, Caemaert J. Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. *Lancet* 1999;353:724.
96. Vasques X, Cif L, Mennessier G, Coubes P. A target-specific electrode and lead design for internal globus pallidus deep brain stimulation. *Stereotact Funct Neurosurg* 2010;88:129-37.
97. Vayssiere N, Hemm S, Cif L, Picot MC, Diakonova N, El Fertit H, et al. Comparison of atlas- and magnetic resonance imaging-based stereotactic targeting of the globus pallidus internus in the performance of deep brain stimulation for treatment of dystonia. *J Neurosurg* 2002;96:673-9.
98. Vernaleken I, Kuhn J, Lenartz D, Raptis M, Huff W, Janouschek H, et al. Bilateral deep brain stimulation in Tourette syndrome is associated with reduction in dopaminergic transmission. *Biol Psychiatry* 2009;66:e15-7.
99. Vilela Filho O, Ragazzo PC, Silva DJ, Souza JT, Oliveira PM, Ribeiro TM. Bilateral globus pallidus externus deep brain stimulation (Gpe-DBS) for the treatment of Tourette syndrome: An ongoing prospective controlled study (Abstr.). *Stereotact Funct Neurosurg* 2006;85:42-3.
100. Visser JE, Bar PR, Jinnah HA. Lesch-Nyhan disease and the basal ganglia. *Brain Res Brain Res Rev* 2000;32:449-75.
101. Visser-Vandewalle V, Temel Y, Boon P, Vreeling F, Colle H, Hoogland G, et al. Chronic bilateral thalamic stimulation: A new therapeutic approach in intractable Tourette syndrome. Report of three cases. *J Neurosurg* 2003;99:1094-100.
102. Volkmann J, Herzog J, Kopper F, Deuschl G. Introduction to the programming of deep brain stimulators. *Mov Disord* 2002;17 Suppl 3:S181-7.
103. Welter ML, Mallet L, Houeto JL, Karachi C, Czernecki V, Cornu P, et al. Internal pallidal and thalamic stimulation in patients with Tourette syndrome. *Arch Neurol* 2008;65:952-7.
104. Wong DF, Harris JC, Naidu S, Yokoi F, Marengo S, Dannals RF, et al. Dopamine transporters are markedly reduced in Lesch-Nyhan disease *in vivo*. *Proc Natl Acad Sci U S A* 1996;93:5539-43.
105. Zabek M, Sobstyl M, Koziara H, Dzierzecki S. Deep brain stimulation of the right nucleus accumbens in a patient with Tourette syndrome. Case report. *Neurol Neurochir Pol* 2008;42:554-9.

Disclaimer: The authors of this paper have received no outside funding, and have nothing to disclose.