

# High-Frequency Unilateral Thalamic Stimulation in the Treatment of Essential and Parkinsonian Tremor

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and C. Warren Olanow, MD‡‡

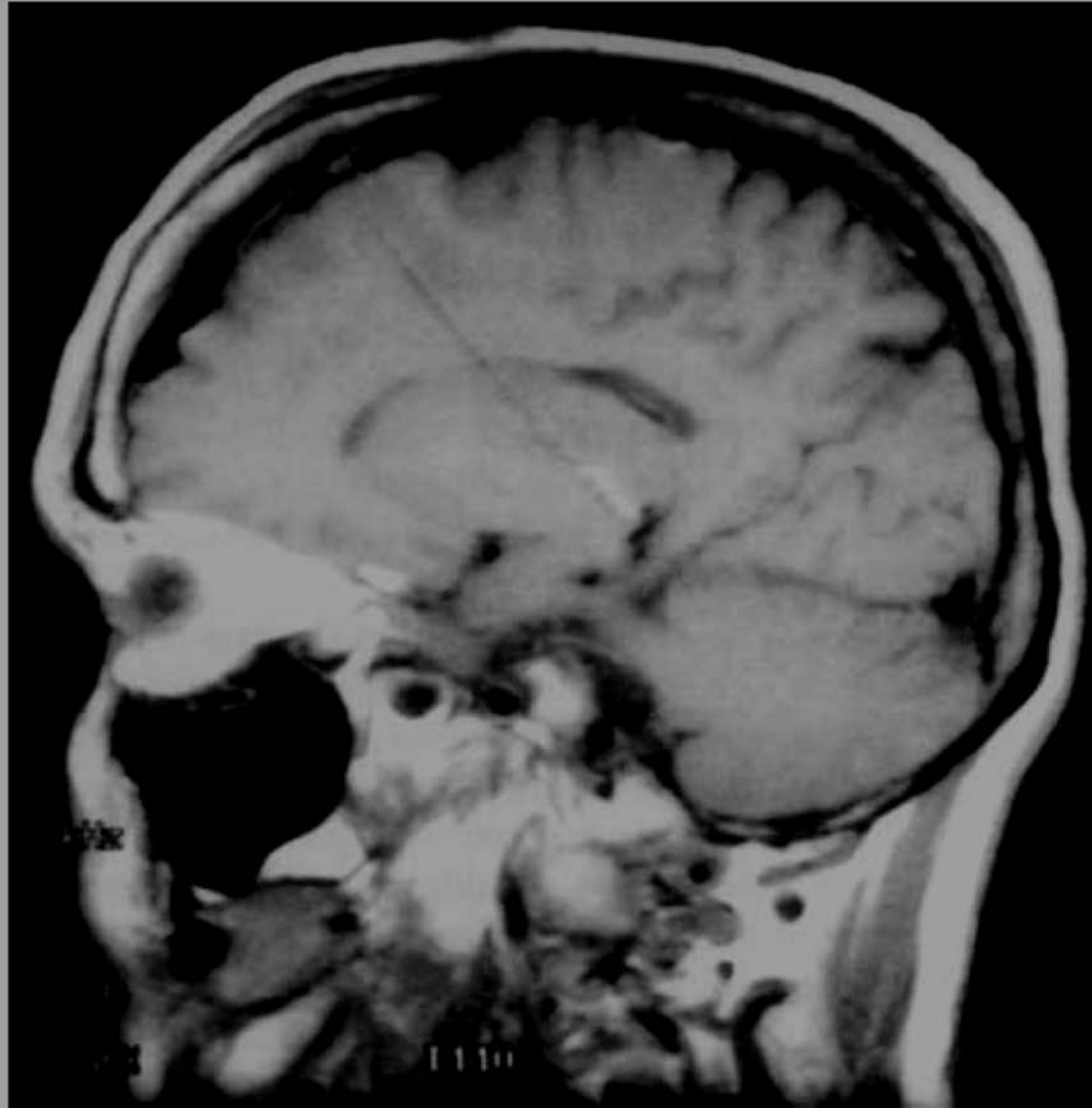
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Pharmacologic treatment for essential tremor and the tremor of Parkinson's disease is often inadequate. Stereotaxic surgery, such as thalamotomy, can effectively reduce tremors. We performed a multicenter trial of unilateral high-frequency stimulation of the ventral intermedius nucleus of the thalamus in 29 patients with essential tremor and 24 patients with Parkinson's disease, using a blinded assessment at 3 months after surgery to compare clinical rating of tremor with stimulation ON with stimulation OFF and baseline and a 1-year follow-up. Six patients were not implanted because of lack of intraoperative tremor suppression (2 patients), hemorrhage (2 patients), withdrawal of consent (1 patient), and persistent microthalamotomy effect (1 patient). A significant reduction in both essential and parkinsonian tremor occurred contralaterally with stimulation. Patients reported a significant reduction in disability. Measures of function were significantly improved in patients with essential tremor. Complications related to surgery in implanted patients were few. Stimulation was commonly associated with transient paresthesias. Other adverse effects were mild and well tolerated. Efficacy was not reduced at 1 year. Chronic high-frequency stimulation is safe and highly effective in ameliorating essential and parkinsonian tremor.

Koller W, Pahwa R, Busenbark K, Hubble J, Wilkinson S, Lang A, Tuite P, Sime E, Lazano A, Hauser R, Malapira T, Smith D, Tarsy D, Miyawaki E, Norregaard T, Kormos T, Olanow CW. High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. *Ann Neurol* 1997;42:292-299

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*Fig 1. Magnetic resonance imaging scan of the brain demonstrating deep brain stimulation lead with four contacts in the ventral intermediate nucleus of the thalamus.*



(3387 lead)

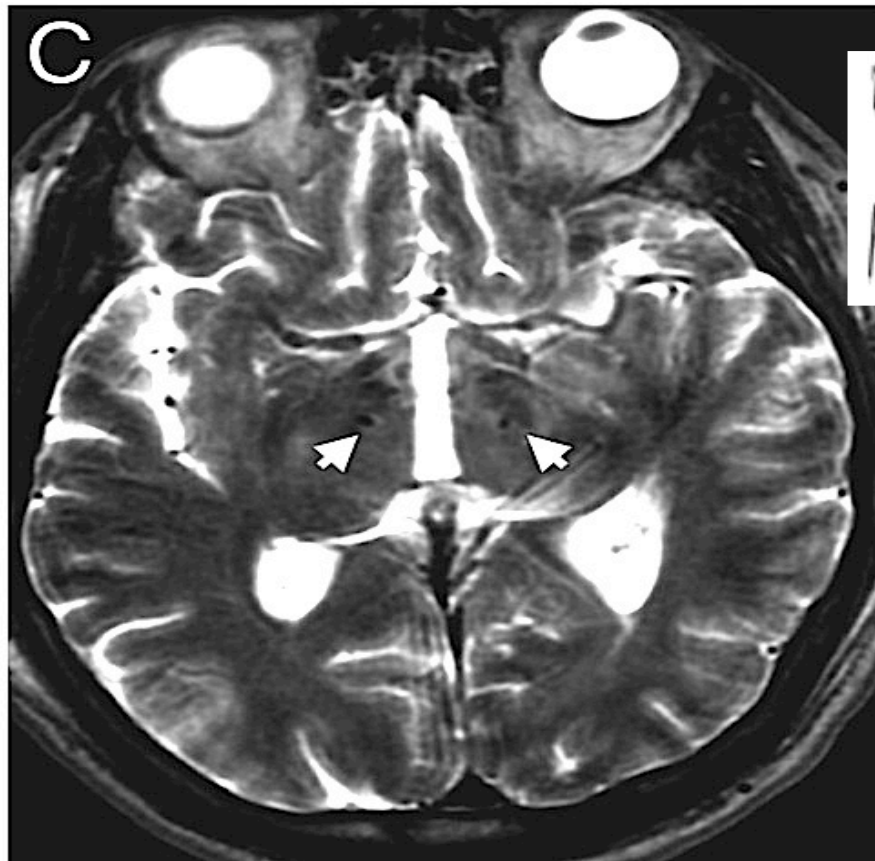
Ann Neurol  
1997



# Three-Dimensional Brain MRI for DBS Patients Within Ultra-Low Radiofrequency Power Limits

*Movement Disorders*, Vol. 29, No. 4, 2014

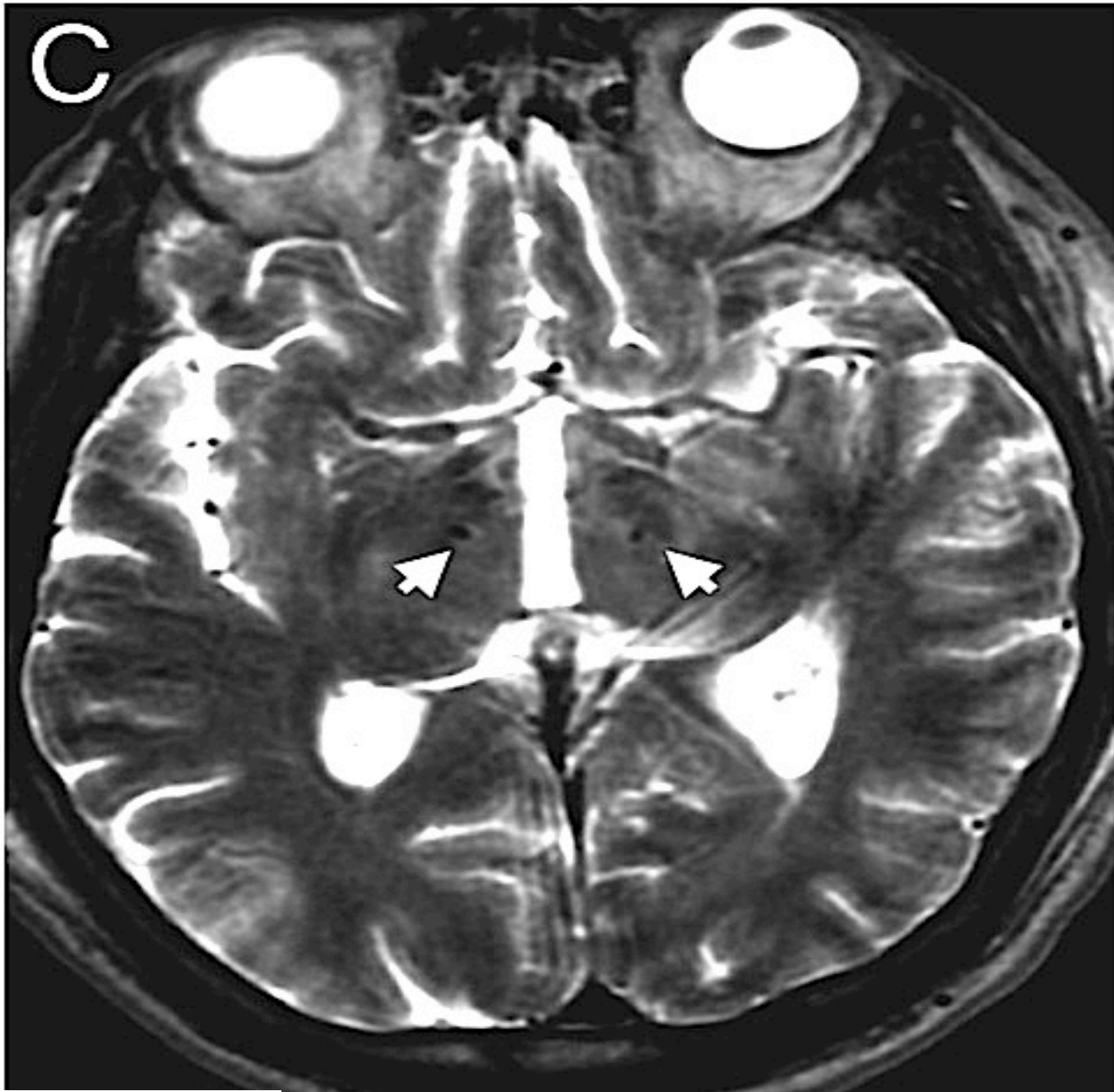
Subhendra N. Sarkar, PhD,<sup>1\*</sup> Efstathios Papavassiliou, MD,<sup>2</sup>  
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(C) a DBS patient (arrows indicate bilateral substantia nigra pars compacta leads;





*There is no  
Nigra  
compacta  
at the  
Level of the  
Third ventricle  
(except at  
Harvard)*

(C) a DBS patient (arrows indicate bilateral sub-  
stantia nigra pars compacta leads;

**DEEP-BRAIN STIMULATION OF THE SUBTHALAMIC NUCLEUS OR THE PARS  
INTERNA OF THE GLOBUS PALLIDUS IN PARKINSON'S DISEASE**

THE DEEP-BRAIN STIMULATION FOR PARKINSON'S DISEASE STUDY GROUP\*

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## DEEP-BRAIN STIMULATION OF THE SUBTHALAMIC NUCLEUS OR THE PARS INTERNA OF THE GLOBUS PALLIDUS IN PARKINSON'S DISEASE

THE DEEP-BRAIN STIMULATION FOR PARKINSON'S DISEASE STUDY GROUP\*

## ABSTRACT

**Background** Increased neuronal activity in the subthalamic nucleus and the pars interna of the globus pallidus is thought to account for motor dysfunction in patients with Parkinson's disease. Although creating lesions in these structures improves motor function in monkeys with induced parkinsonism and patients with Parkinson's disease, such lesions are associated with neurologic deficits, particularly when they are created bilaterally. Deep-brain stimulation simulates the effects of a lesion without destroying brain tissue.

**Methods** We performed a prospective, double-blind, crossover study in patients with advanced Parkinson's disease, in whom electrodes were implanted in the subthalamic nucleus or pars interna of the globus pallidus and who then underwent bilateral high-frequency deep-brain stimulation. We compared scores on the motor portion of the Unified Parkinson's Disease Rating Scale when the stimulation was randomly assigned to be turned on or off. We performed unblinded evaluations of motor function preoperatively and one, three, and six months postoperatively.

**Results** Electrodes were implanted bilaterally in 96 patients in the subthalamic-nucleus group and 38 patients in the globus-pallidus group. Three months after the procedures were performed, double-blind, crossover evaluations demonstrated that stimulation of the subthalamic nucleus was associated with a median improvement in the motor score (as compared with no stimulation) of 49 percent, and stimulation of the pars interna of the globus pallidus with a median improvement of 37 percent ( $P < 0.001$  for both comparisons). Between the preoperative and six-month visits, the percentage of time during the day that patients had good mobility without involuntary movements increased from 27 percent to 74 percent ( $P < 0.001$ ) with subthalamic stimulation and from 28 percent to 64 percent ( $P < 0.001$ ) with pallidal stimulation. Adverse events included intracranial hemorrhage in seven patients and infection necessitating removal of the leads in two.

**Conclusions** Bilateral stimulation of the subthalamic nucleus or pars interna of the globus pallidus is associated with significant improvement in motor function in patients with Parkinson's disease whose condition cannot be further improved with medical therapy. (N Engl J Med 2001;345:956-63.)

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**L**EVODOPA is the mainstay of treatment for Parkinson's disease.<sup>1</sup> However, long-term levodopa treatment is complicated by involuntary movements known as dyskinesia and motor fluctuations in which patients cycle between periods of good mobility ("on" periods) and impaired mobility ("off" periods).<sup>2</sup> These complications result in disability that cannot be satisfactorily controlled by medical therapy in the majority of patients. Advances in understanding of the pathophysiology of the basal ganglia have provided opportunities for new therapeutic strategies to manage these problems.<sup>3-5</sup> In animal models of Parkinson's disease, neuronal activity is increased in the subthalamic nucleus and pars interna of the globus pallidus,<sup>6</sup> and lesions of these structures result in marked improvement in motor function.<sup>6-8</sup> These findings have led to the development of surgical procedures for Parkinson's disease that target the subthalamic nucleus and pars interna of the globus pallidus.<sup>9,10</sup>

In patients with Parkinson's disease, the creation of lesions in the pars interna of the globus pallidus (pallidotomy) improves contralateral dyskinesia and provides moderate antiparkinsonian benefits.<sup>11,12</sup> However, pallidotomy necessitates making a destructive brain lesion and entails the risk of inducing neurologic deficits, particularly with bilateral procedures.<sup>13</sup> The creation of lesions in the subthalamic nucleus also provides benefits to patients,<sup>14</sup> but is associated with the risk of hemiballismus.<sup>15</sup> Accordingly, physicians have been reluctant to perform bilateral pallidotomy or subthalamotomy.<sup>10</sup> High-frequency deep-brain stimulation of specific brain targets simulates the effect of a lesion without deliberately damaging the brain.<sup>16</sup> Deep-brain stimulation of the thalamus has been shown to control tremor<sup>17</sup> but not other, more disabling, features of Parkinson's disease. Studies in small numbers of patients with Parkinson's disease suggest that stimulation of the subthalamic nucleus and pars interna of the globus pallidus can improve the full constellation of parkinsonian motor features.<sup>18-22</sup> We evaluated the results

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The preparation of this article was overseen by the writing committee (J.A. Obeso, M.D., C.W. Olanow, M.D., M.C. Rodríguez-Oroz, M.D., P. Krack, M.D., R. Kumar, M.D., and A.E. Lang, M.D.), who assume responsibility for the overall content and integrity of the manuscript.

\*The members of the Deep-Brain Stimulation for Parkinson's Disease Study Group are listed in the Appendix.

NEJM, 2001

102 bilat. STN DBS  
41 bilat. GPI DBS

**TABLE 5. ADVERSE EVENTS ASSOCIATED WITH  
SUBTHALAMIC AND PALLIDAL STIMULATION.\***

TYPE OF ADVERSE EVENT	SUBTHALAMIC NUCLEUS (N= 102)	PARS INTERNA OF THE GLOBUS PALLIDUS (N= 41)
	number	
Related to procedure		
Intracranial hemorrhage	3	4
Hemiparesis secondary to hemorrhage	3	3
Seizures	3	1
Infection	4	0
Improper lead placement	2	0
Brachial plexus injury	1	0
Confusion	1	0
Dysarthria	0	1
Paralysis (nonhemorrhagic)	1	0
Pulmonary embolus	1	0
Related to device		
Migration	3	2
Infection	3	1
Lead break	1	1
Seroma	1	1
Erosion	1	0
Abnormal healing	1	0
Intermittent function	1	0
Related to stimulation		
Dyskinesia	2	3
Diplopia	2	0
Dystonia	0	2
Abdominal pain	0	1
Accidental injury	1	0
Dysarthria	1	0
Headache	1	0
Paresthesia	1	0

102 bilat. STN DBS  
41 bilat. GPI DBS



NEJM  
Sept 2001

102 bilat. STN DBS  
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**TABLE 5. ADVERSE EVENTS ASSOCIATED WITH SUBTHALAMIC AND PALLIDAL STIMULATION.\***

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Brachial plexus injury	1	0
Confusion	1	0
Dysarthria	0	1
Paralysis (nonhemorrhagic)	1	0
Pulmonary embolus	1	0
Related to device		
Migration	3	2
Infection	3	1
Lead break	1	1
Seroma	1	1
Erosion	1	0
Abnormal healing	1	0
Intermittent function	1	0
Related to stimulation		
Dyskinesia	2	3
Diplopia	2	0
Dystonia	0	2
Abdominal pain	0	1
Accidental injury	1	0
Dysarthria	1	0
Headache	1	0
Paresthesia	1	0



Table 27

= stimulation-related

Summary of therapy-related adverse events reported by  $\geq 2$  patients by implant target and laterality of implant

Therapy-Related Adverse Event <sup>a</sup>	STN (n=105) <sup>b</sup>		GP (n=54) <sup>b</sup>	
	Bilateral (n=96)	Unilateral (n=5)	Bilateral (n=38)	Unilateral (n=15)
Number and Percentage (%) of Patients				
<u>Therapy-related</u>				
Number of patients who experienced any therapy-related event	42 (43.8%)	3 (60.0%)	14 (36.8%)	10 (66.7%)
Dysarthria	16 (16.7%)	0	3 (7.9%)	0
Dyskinesia	10 (10.4%)	0	4 (10.5%)	4 (26.7%)
Dystonia	8 (8.3%)	0	5 (13.2%)	2 (13.3%)
Paresthesia	6 (6.3%)	1 (20.0%)	3 (7.9%)	3 (20.0%)
Diplopia	5 (5.2%)	0	1 (2.6%)	1 (6.7%)
Incoordination	3 (3.1%)	0	2 (5.3%)	2 (13.3%)
Abnormal gait	5 (5.2%)	0	1 (2.6%)	0
Sensory disturbance	5 (5.2%)	0	0	1 (6.7%)
Thinking abnormal	3 (3.1%)	0	1 (2.6%)	1 (6.7%)
Abnormal vision	1 (1.0%)	0	2 (5.3%)	1 (6.7%)
Asthenia	2 (2.1%)	0	0	1 (6.7%)
Pain	1 (1.0%)	0	0	2 (13.3%)
Somnolence	3 (3.1%)	0	0	0
Akinesia	2 (2.1%)	0	0	0
Choreoathetosis	0	0	1 (2.6%)	1 (6.7%)
Confusion	1 (1.0%)	0	0	1 (6.7%)
Hypertonia	1 (1.0%)	0	1 (2.6%)	0
Hypophonia	1 (1.0%)	0	1 (2.6%)	0
Increased Parkinson's symptoms	1 (1.0%)	1 (20.0%)	0	0
Manic reaction	2 (2.1%)	0	0	0
Movement disorder	1 (1.0%)	0	0	1 (6.7%)
Tremor	2 (2.1%)	0	0	0
Worse motor fluctuations	0	0	1 (2.6%)	1 (6.7%)

<sup>a</sup> A patient who reported more than one occurrence of an adverse event was counted only once for that adverse event.



Table 27

= stimulation-related

Summary of therapy-related adverse events reported by  $\geq 2$  patients by implant target and laterality of implant

Therapy-Related Adverse Event <sup>a</sup>	STN (n=105) <sup>b</sup>		GP (n=54) <sup>b</sup>	
	Bilateral (n=96)	Unilateral (n=5)	Bilateral (n=38)	Unilateral (n=15)
Number and Percentage (%) of Patients				
<u>Therapy-related</u>				
Number of patients who experienced any therapy-related event	42 (43.8%)	3 (60.0%)	14 (36.8%)	10 (66.7%)
→ Dysarthria	16 (16.7%)	0	3 (7.9%)	0
→ Dyskinesia	10 (10.4%)	0	4 (10.5%)	4 (26.7%)
→ Dystonia	8 (8.3%)	0	5 (13.2%)	2 (13.3%)
→ Paresthesia	6 (6.3%)	1 (20.0%)	3 (7.9%)	3 (20.0%)
→ Diplopia	5 (5.2%)	0	1 (2.6%)	1 (6.7%)
Incoordination	3 (3.1%)	0	2 (5.3%)	2 (13.3%)
Abnormal gait	5 (5.2%)	0	1 (2.6%)	0
→ Sensory disturbance	5 (5.2%)	0	0	1 (6.7%)
Thinking abnormal	3 (3.1%)	0	1 (2.6%)	1 (6.7%)
Abnormal vision	1 (1.0%)	0	2 (5.3%)	1 (6.7%)
Asthenia	2 (2.1%)	0	0	1 (6.7%)
Pain	1 (1.0%)	0	0	2 (13.3%)
Somnolence	3 (3.1%)	0	0	0
Akinesia	2 (2.1%)	0	0	0
Choreoathetosis	0	0	1 (2.6%)	1 (6.7%)
Confusion	1 (1.0%)	0	0	1 (6.7%)
Hypertonia	1 (1.0%)	0	1 (2.6%)	0
Hypophonia	1 (1.0%)	0	1 (2.6%)	0
Increased Parkinson's symptoms	1 (1.0%)	1 (20.0%)	0	0
Manic reaction	2 (2.1%)	0	0	0
Movement disorder	1 (1.0%)	0	0	1 (6.7%)
Tremor	2 (2.1%)	0	0	0
Worse motor fluctuations	0	0	1 (2.6%)	1 (6.7%)

<sup>a</sup> A patient who reported more than one occurrence of an adverse event was counted only once for that adverse event.

<sup>b</sup> The totals include non-implanted patients, however these patients were not included in this table, since non-implanted patients did not experience therapy-related events.

Extracted from Appendix F: C.19 and C.20.



Table 25 lists the frequencies of adverse events by attempted laterality of implant for each target site.

**Table 25** Summary of procedure-related adverse events reported by  $\geq 2$  patients by implant target and laterality of attempted procedure

Procedure-Related Adverse Event <sup>a</sup>	STN (n=105)		GP (n=54)	
	<u>Bilateral</u> (n=99)	<u>Unilateral</u> (n=6)	<u>Bilateral</u> (n=40)	<u>Unilateral</u> (n=14)
<u>Number and Percentage (%) of Patients</u>				
<u>Procedure-related</u>				
Number of patients who experienced any procedure-related event	44 (44.4%)	3 (50.0%)	14 (35.0%)	7 (50.0%)
→ Confusion	10 (10.1%)	1 (16.7%)	2 (5.0%)	0
→ Intracranial hemorrhage	4 (4.0%)	0	5 (12.5%)	1 (7.1%)
→ Infection	7 (7.1%)	0	0	2 (14.3%)
→ Dysarthria	3 (3.0%)	0	3 (7.5%)	2 (14.3%)
Thinking abnormal	6 (6.1%)	0	2 (5.0%)	0
Headache	3 (3.0%)	0	1 (2.5%)	1 (7.1%)
ok Convulsion	3 (3.0%)	0	1 (2.5%)	1 (7.1%)
Amnesia	4 (4.0%)	0	0	0
Asthenia	3 (3.0%)	0	1 (2.5%)	0
→ Positioning difficulties	4 (4.0%)	0	0	0
Hypophonia	3 (3.0%)	0	0	0
Other	1 (1.0%)	0	2 (5.0%)	0
Abnormal gait	1 (1.0%)	0	1 (2.5%)	0
Depression	1 (1.0%)	0	0	1 (7.1%)
Diplopia	1 (1.0%)	0	1 (2.5%)	0
Incoordination	1 (1.0%)	0	1 (2.5%)	0
Increased Parkinson's symptoms	2 (2.0%)	0	0	0
Nausea and vomiting	1 (1.0%)	0	1 (2.5%)	0
Pain	1 (1.0%)	0	1 (2.5%)	0
Pneumonia	1 (1.0%)	0	0	1 (7.1%)
Seroma	2 (2.0%)	0	0	0
Somnolence	2 (2.0%)	0	0	0

<sup>a</sup> A patient who reported more than one occurrence of an adverse event was counted only once for that adverse event.

Extracted from Appendix F: C.14 and C.15.



Table 23

Summary of device-related adverse events reported by  $\geq 2$  patients by implant target and laterality

Device-Related Adverse Event <sup>a</sup>	STN (n=105)			GP (n=54)		
	Bilateral (n=96)	Unilateral (n=5)	No Implant (n=4)	Bilateral (n=38)	Unilateral (n=15)	No Implant (n=1)
Number and Percentage (%) of Patients						
<u>Device-related</u>						
Number of patients who experienced any device-related event	30 (31.3%)	1 (20.0%)	-	11 (29.0%)	5 (33.3%)	-
→ Continuity, intermittent	10 (10.4%)	0	-	3 (7.9%)	2 (13.3%)	-
→ Migration <sup>b</sup>	4 (4.2%)	0	-	2 (5.3%)	2 (13.3%)	-
→ Infection	4 (4.2%)	0	-	2 (5.3%)	0	-
→ Increased Parkinson's symptoms	3 (3.1%)	0	-	1 (2.6%)	2 (13.3%)	-
→ Lead(s), breakage of	2 (2.1%)	0	-	2 (5.3%)	0	-
EMI (electromagnetic interference)	2 (2.1%)	0	-	2 (5.3%)	0	-
Difficult to program	3 (3.1%)	0	-	0	0	-
Other	1 (1.0%)	0	-	1 (2.6%)	1 (6.7%)	-
→ Healing abnormal	2 (2.1%)	0	-	0	0	-
OK Seroma	1 (1.0%)	0	-	1 (2.6%)	0	-
Pain	1 (1.0%)	0	-	1 (2.6%)	0	-
Printer problem	2 (2.1%)	0	-	0	0	-

<sup>a</sup> A patient who reported more than one occurrence of an adverse event was counted only once for that adverse event.

<sup>b</sup> Includes the following device components: neurostimulator (4), extension (1), and leads (3).

Extracted from Appendix F: C.9 and C.10.



**TABLE 5. ADVERSE EVENTS ASSOCIATED WITH SUBTHALAMIC AND PALLIDAL STIMULATION.\***

N Engl J Med, Vol. 345, No. 13 · September 27, 2001

102 bilat. STN DBS  
41 bilat. GPI DBS

5, No. 13 · September 27, 2001

BS

	SUBTHALAMIC NUCLEUS (N= 102)	PARS INTERNA OF THE GLOBUS PALLIDUS (N= 41)
TYPE OF ADVERSE EVENT		
	number	
Related to procedure		
→ Intracranial hemorrhage	3	4
→ Hemiparesis secondary to hemorrhage	3	3
→ Seizures	3	1
→ Infection	4	0
→ Improper lead placement	2	0
→ Brachial plexus injury	1	0
→ Confusion	1	0
→ Dysarthria	0	1
→ Paralysis (nonhemorrhagic)	1	0
→ Pulmonary embolus	1	0
Related to device		
→ Migration	3	2
→ Infection	3	1
→ Lead break	1	1
→ Seroma	1	1
→ Erosion	1	0
→ Abnormal healing	1	0
→ Intermittent function	1	0
Related to stimulation		
→ Dyskinesia	2	3
→ Diplopia	2	0
→ Dystonia	0	2
→ Abdominal pain	0	1
→ Accidental injury	1	0
→ Dysarthria	1	0
→ Headache	1	0
→ Paresthesia	1	0

***There were many more Adverse events in the database than in the NEJM Paper (authored by prominent neurologist!!)***

MAX PLANCK INSTITUTE

# SCIENTIFIC REPORTS

OPEN

## Changing pattern in the basal ganglia: motor switching under reduced dopaminergic drive

Vincenzo G. Fiore<sup>1,6</sup>, Francesco Rigoli<sup>1</sup>, Max-Philipp Stenner<sup>1,2</sup>, Tino Zaehle<sup>2</sup>, Frank Hirth<sup>3</sup>, Hans-Jochen Heinze<sup>2,4</sup> & Raymond J. Dolan<sup>1,5</sup>

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Published: 23 March 2016

The standard model predicts that a normal balance between competing BG pathways can be restored by decreasing indirect and hyperdirect pathway activity, for example via lesions of the globus pallidus pars externa (GPe) or the STN.

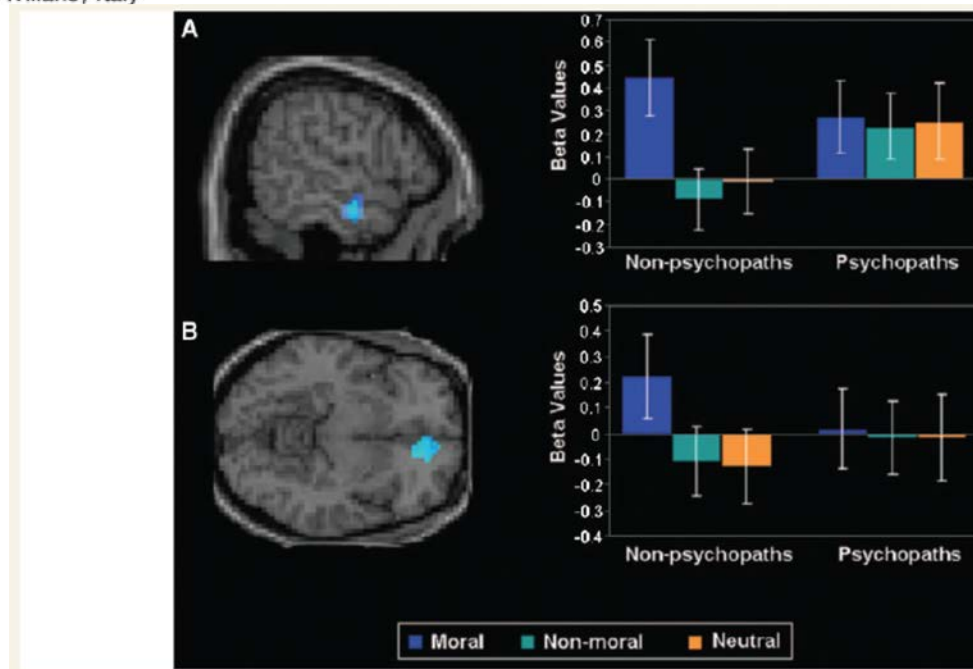
***GPe!!!??? These Max Planck authors Don't know what they are talking about***

## REVIEW ARTICLE

# Functional and clinical neuroanatomy of morality

Manuela Fumagalli and Alberto Priori

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Brain activation during “moral” vs. “non-moral” picture viewing in “psychopaths” and “non-psychopaths”

**Figure 1** Analyses of brain activity during moral picture viewing showed a significant interaction between psychopaths/non-psychopaths and moral versus non-moral and neutral picture viewing in the anterior temporal cortex (A) and in ventromedial prefrontal cortex (B). This finding indicates that non-psychopaths showed a significantly greater moral than non-moral and neutral picture distinction in these regions, whereas psychopaths did not. Error bars are standard errors. (Copyright © 2010 by the American Psychological Association. Reproduced with permission from Harenski *et al.*, 2010. The use of APA information does not imply endorsement by the APA).

February 2012

doi:10.1093/brain/awr334

Brain 2012; Page 1 of 16 | 1

**BRAIN**  
A JOURNAL OF NEUROLOGY

## REVIEW ARTICLE

# Functional and clinical neuroanatomy of morality

Manuela Fumagalli and Alberto Priori

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20122 Milano, Italy

**Suggest the potential use of DBS to treat  
“antisocial behaviour” and “abnormal morality” !!!**

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# The Contemporary Practice of Psychiatric Surgery: Results from a Survey of North American Functional Neurosurgeons

DBS for *Enhancement*

=> 51.4% of North-American neurosurgeon think it is “ethical”



# *Moving Along*



VOLUME 13, ISSUE 2 • 2009 • EDITORS, DR. CARLO COLOSIMO, DR. MARK STACY

**An interview with Prof. Oleh Hornykiewicz**  
held in Catania, Italy on 3-4 April, 2009.



***Which single medical advance would benefit most people?***

The discovery of a pill that would stop people talking nonsense, without necessarily killing them.