

## Cognitive Changes after Deep Brain Stimulation in Parkinson's Disease: A Critical Review

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### Abstract

Concern about cognitive worsening, especially after subthalamic nucleus (STN) deep brain stimulation (DBS) has been reported in Parkinson's disease (PD) patients, although it has not been deemed severe enough to discredit DBS as a powerful tool in the armamentarium against PD. We here provide an in-depth and critical review of the current literature on this topic, summarizing the available data on the impact of STN and globus pallidus interna (GPI) DBS on each of the following cognitive domains: language, executive function, attention and concentration, memory, visual function, psychomotor and processing speed, and global cognition; then looking in more details into controlled studies as well as studies directly comparing GPI and STN DBS. We conclude that worsening of one or more cognitive function is rare and subtle after DBS in PD patients, without negative impact on quality of life, and that there is very little data supporting that STN DBS has a worse cognitive outcome than GPI DBS.

**Keywords:** Deep brain stimulation; Subthalamic nucleus; Globus pallidus interna; Parkinson's disease; Cognitive

### Abbreviations:

DBS: Deep Brain Stimulation; STN: Subthalamic Nucleus; GPI: Globus Pallidus Interna; PD: Parkinson's disease; LID: Levodopa Induced Dyskinesias; DLPFC: Dorsolateral Prefrontal Cortex

### Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the clinical tetrad of tremor at rest, rigidity, akinesia (or bradykinesia) and postural instability (TRAP). It has a prevalence of 1 to 2% above the age of 60 years [1] and typically develops between the ages of 55 and 65 years. Pathologically, PD is classified as a synucleinopathy, associated predominantly with the loss of dopaminergic neurons in the substantia nigra, but other brainstem neurons have been found to degenerate in PD, possibly contributing to not only motor but also non-motor impairment [2]. Indeed, PD is now considered to be a complex syndrome with neurobehavioral, autonomic, dermatological, sensory and special sense disorders [3]. Many studies have also reported cognitive changes, including impairments in language, executive function, vision, memory, and psychomotor speed [4-7].

For the last 50 years, levodopa has been the cornerstone of PD management. However, five years after initiation of therapy, a majority of patients develop medication related motor complications, namely levodopa induced dyskinesias (LID) and motor fluctuations. LID are choreic, stereotypic, and dystonic movements affecting any part of the body [2] and occurring either at peak dose or when the medication is kicking in or wearing off (dyskinesia-improvement-dyskinesia effect). Motor fluctuations occur when the duration of each medication dose is too short and the symptoms of PD recur sooner than initially. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the

globus pallidus pars interna (GPI) grant to patients with PD improved quality of life and decreased motor complications, and has been approved as such by the Food and Drug Administration in the US in 2002 [8]. However, the cognitive impact of DBS in PD patients is unclear, with various studies producing conflicting results. We here endeavor to review the available literature on this subject.

### Methods

Studies were reviewed if they were published in the English language and met our minimum inclusion criteria: 1) at least five subjects followed for a mean of at least 3 months postoperatively, 2) pre- and post-operative cognitive data using at least one standardized measure.

We will first briefly discuss the possible mechanism of action of DBS, then summarize the available data on the impact of STN and GPI DBS on each of the following cognitive domains: language, executive function, attention and concentration, memory, visual function, psychomotor and processing speed, and global cognition. We will then look in more details into controlled studies as well as studies directly comparing GPI and STN DBS.

### Pathophysiology of PD, and Possible Mechanism of Action of DBS

Different motor and non-motor cortical areas project primarily to the striatum which has two major projections: the direct pathway to the GPI and the indirect projection to the GPI via the globus pallidus pars externa and the STN. The GPI serves as the major output nucleus, which connects back to the cortex via the thalamus. Modulated by the substantia nigra pars compacta, the indirect pathway exerts surround inhibition and thus facilitates an excitatory drive to muscles responsible for a given movement and suppresses unwanted motor activity not relevant to the primary movement. Thus, PD is thought to result from overactivation of the indirect pathway leading to an

increased output from the GPi and a decrease in spontaneous movement [8]. This model of the basal ganglia and its connections is, of course, an oversimplification of a complex network that, when disrupted, can result in a range of motor abnormalities [9]. For example, a hyperdirect pathway, projecting directly from the cortex to the STN, and from there to the GPi had recently been added to this model [10]. While it is unclear how the loss of dopaminergic neurons leads to the cardinal symptoms of PD, animal research as well as human recording have provided functional and biochemical evidence that bradykinesia in PD results from excessive activity in the STN and the GPi [11-13], while the rest tremor most likely results from dysfunction of both the striato-pallidal-thalamocortical and the cerebello-dentato-thalamocortical circuits [14], with hyperactivity and hypersynchronization between central oscillators [15].

DBS acts through delivering an electrical current in a specific target area of the brain. This current can be modulated through modification of voltage, frequency and duration of each electrical pulse delivered. The delivered energy creates an electrical field of variable size and shape according to the parameters used for stimulation. Although initially believed to stimulate the target, thus the name of the whole

process, it seems that DBS actually excites the neuronal fibers but inhibits the neural cells [16,17]. Overall, DBS leads to modifications of the firing rate and pattern of neurons [18] in the basal ganglia, as well as local release of neurotransmitters such as glutamate and adenosine [19-21]. In addition, it seems that DBS also increases blood flow and stimulates neurogenesis [22]. However, it is unclear how these changes actually modify the symptoms of Parkinson's disease, and DBS is more of an empirically proven treatment in search of physiological explanation.

### Cognitive Changes after DBS

54 studies totaling 1296 STN DBS patients and 85 GPi DBS patients were reviewed. Among these, only 10 included statistical correction for multiple analyzes [23-32] and 13 had a control arm [23,24,28,33-42].

All these studies were reviewed with post hoc corrections for multiple analyzes when required. Our findings are summarized below (Tables 1 and 2).

#### Studies assessing cognitive change in PD patients after STN DBS

Author, year	N	F/u (mo)	Controlled	Status of stimulation/ medication at cognitive assessment	Cognitive improvement	Cognitive decline	No change
Alberts et al. [25]	8	N/A	No	UL, BL, ON and OFF/ON	None	E	None
Alegret et al. [62]	15	3	No	ON/OFF	None	None	E, PS, E, L, M, V
Ardouin et al. [32]	49	3-6	No	ON/inconstant	E	L	GC, E, PS
Castelli et al. [44]	72	15	No	ON/-	E	L	E, L, M
Castelli et al. [78]	19	17	No	ON/ON	None	L	E,V,M,L,
Castelli et al. [36]	27	12	Yes	ON/ON	None	L	E,A/C, M, L.
Cilia et al. [23]	20	12	Yes	ON/ON	None	L	GC, L, E, A/C
Contarino et al. [79]	11	60	No	ON/ON	None	None	L,V, M,E
Daniele et al. [46]	20	12	No	ON or OFF/ON	None	L	GC, L, E, A/C, M
De Gaspari et al. [28]	12	12	Yes	ON/ON	None	L	
Dujardin et al. [80]	9	3	No	ON/ON	None	None	GC, E, M, PS, L
Erola et al. [81]	19	12	No	ON/ON	None	L	GC, E, PS
Fasano et al. [45]	16	96	No	ON/ON	None	E,L,M	GC,M, E, L
Fraraccio et al. [50]	15	16	No	ON and OFF/ON	None	A/C	E,A/C, M,L,V,CG
Funkiewiez et al. [82]	50	12 a	No	ON/OFF	None	None	GC, E
Funkiewiez et al. [29]	70	36	No	ON/69%OFF	None	L	GC, E, M, PS
Gironell et al. [33]	8	6	Yes	ON/ON	None	None	L E, A/C, M, V, PS
Halbig et al. [47]	12	16	No	ON and OFF/ON	None	None	PS M GC, E, L
Heo et al., [83]	46	12	No	ON/ON	None	None	GC,A/C,M,L,E
Hershey et al. [56]	24	7 b	No	ON and OFF/OFF	None	E	None

Hilker et al. [34]	8	4	Yes	ON/-	M	None	GC, E, L, A/C, M, V
Jahanshahi et al. [51]	7	12	No	ON and OFF/OFF	E, A/C, PS	M	None
Krack et al. [27]	42	60	No	ON/ON	None	None	GC, E.
Lhommée et al. [84]	63	3	No	ON/ON	None	L	GC,E.
Limousin et al. [59]	24	12	No	ON/OFF	None	None	E, L, V, PS
Moretti et al. [43]	9	12	Yes	ON/ON	L	L,E	E,L,, A/C, M, V
Moro et al., [85]	7	9	No	ON/ON	None	None	GC, E, L, M
Morrison et al. [35]	17	3	Yes	ON and OFF/OFF	None	None	L, A/C, M, E, V
Page et al. [61]	12	N/A	No	ON and OFF/ON	PS,A/C	None	PS, A/C, E.
Perozzo et al. [58]	20	6	No	ON/ON and OFF	None	None	E, A/C, M, PS
Pillon et al., 2000 [6]	63	12	No	ON and OFF/75%OFF	None	L	E, PS L, M
Rothlind et al.[53]	15	21	No	ON/ON	None	L	A/C,E,L, V,M
Sáez-Zea et al. [41]	9	6	Yes	ON/ON	None	L, A/C	A,M,V,E, L
Saint-Cyr et al., 2000 [86]	11	12	No	ON/ON	None	L	E, L, M, A/C,V
Saint-Cyr et al. [77]	99	6	No	ON/ON	QOL	L,E	E, L, A/C, M, PS
Schüpbach et al. [30]	37	60	No	ON/ON	None	CG,E	None
Smeding et al. [40]	99	6	Yes	ON/ON	None	L,A/C	L,M,VS, A/C
Trepanier et al. [76]	9	6	No	ON/ON	None	None	A/C,M,V,L,E
Whelan et al. [31]	5	3	No	ON/ON	L	L	None
Williams et al. [37]	19	24	Yes	ON/ON	None	None	GC, M,E, A/C,L, V, PS
Witt et al. [49]	23	12	No	ON and OFF/ON	None	None	L,E,GC
Witt et al. [39]	60	6	Yes	ON/ON	None	A/C	GC, E, L, A/C
Witt et al. [38]	31	6	Yes	ON/ON	None	None	GC, A/C, L
Yágüez et al. [87]	30	9	No	ON/ON	None	L,M	GC,M,L, V,E
York et al. [24]	23	6	Yes	ON/ON	None	M	GC, E, A/C, M, L,V, PS.
Zangaglia et al. [42]	32	96	Yes	ON/ON	None	L	GC, M, E, A/C

**Table 1:** Studies assessing cognitive change in PD patients after STN DBS. PD: Parkinson's disease; STN: subthalamic nucleus; N: number of patients; mo: months; A/C: Attention/Concentration; E: Executive; GC: Global Cognition; L: language; M: Memory; PS: Psychomotor/Processing speed; V: Visual. a: median; b: mean

**Studies assessing cognitive change in PD patients after GPi DBS**

Author, year	N	F/u (mo)	Controlled	Status of stimulation/ medication at cognitive assessment	Cognitive improvement	Cognitive decline	No change
Ardouin et al. [32]	13	3-6	No	ON/inconstant	E	L	GC, E, PS
Jahanshahi et al. [51]	6	12	No	ON and OFF/OFF	None	None	E, A/C, PS,M,

Pillon et al. [6]	13	12	No	ON and OFF/75%OFF	None	None	E, PS L, M
Trepanier et al. [76]	4	6	No	ON/ON	None	None	A/C,M,V,L,E
Rothlind et al. [53]	14	21	No	ON/ON	None	L	A/C, E, L, V, M
Fields et al. [54]	6	5	No	ON/ON	M	None	GC, E, A/C, V, L, M
Tröster et al. [55]	9	3	No	ON/ON	None	V,L	GC,E,A/ C,V,M,L
Vingerhoets et al., [64]	20	3	No	ON/ON	None	None	M,V,E,PS

**Table 2:** Studies assessing cognitive change in PD patients after GPi DBS.

PD: Parkinson's disease; GPi: globus pallidus interna; N: number of patients; mo: months; A/C: Attention/Concentration; E: Executive; GC: Global Cognition; L: language; M: Memory; PS: Psychomotor/Processing speed; V: Visual. a: median; b : mean

## Language

### Subthalamic nucleus

Improvement in at least one measure of language was reported by 2 studies [31,43] while 21 reported statistically significant worsening in one or more language function, most often a decrease in fluency; and 30 reported no statistically significant change in at least one assessed measure of language (Table 1). Among these, 16 studies reported no change in any measure of language. It must be noted that the methodology of one of the studies reporting worsening [44] was not available for full review. It is unclear if a Bonferroni correction for multiple analyzes was applied by its authors, and, if not, whether such a correction would change the conclusions. Another study [45] was not corrected for multiple analyzes and no exact p value was reported. A post hoc correction was not possible either and it is unclear if the reported worsening would have been significant once this correction had been made.

Additionally, 6 Studies compared language ON and OFF stimulation, in the same patients [35,46-50]. Daniele et al. [46] conducted an uncontrolled trial on 20 patients, with cognitive assessment before bilateral STN DBS implant, then at 3, 6, and 12 months afterwards. Postoperative cognitive assessments were carried out with stimulators turned off at three months, and turned on at six and 12 months. After correcting for multiple analyzes, letter verbal fluency was worse compared to the pre-operative assessment only at 3 months, when the stimulation was OFF, but not at 6 or 12 months, when the stimulation was ON. These results might indicate that a decline in verbal fluency was either attenuated by stimulation and/or more pronounced in the early postoperative stages. However, when corrected for multiple analyzes, Pillon et al. [48], reported worsening of fluency with stimulation ON or OFF at 12 months after implant, but not at 3 months. It must be noted that patients were assessed ON medications in the study of Daniele et al., and OFF medication in the study of Pillon et al., which might suggest a synergistic effect of stimulation and medication on fluency. The 4 other studies could not elicit any statistical difference between ON and OFF stimulation states.

In addition, Funkiewiez et al. [29] reported a series of 70 patients assessed OFF medications before surgery, then OFF medication in

94% at 1 year and in 69% at 3 years. They reported worsening of category fluency and total score of fluency at both post-surgical evaluations compared to baseline, without any further worsening between the two post-surgical evaluations. Age was found to be a predictor of decline in executive functions.

It has been suggested that language worsening in some studies was secondary to the parasagittal trajectory taken for electrode implantation [48,51], since functional activation of the paracingulate and cingulate sulci during word generation was demonstrated on fMRI [52]. On the other hand, decreased fluency was associated with perfusion decrements on single photon emission computed tomography (SPECT) in the left dorsolateral prefrontal cortex, anterior cingulate cortex and ventral caudate nucleus [23], suggesting that STN DBS might impact the cognitive circuit involved in language.

### Globus pallidus interna

Three studies totaling 36 patients showed decline in one or more measure of language, most often fluency, up to 21 months after GPi DBS [53-55]. Tröster et al. [55] reported this deterioration in both ablation and DBS of GPi, supporting a consequence of the procedure itself rather than stimulation. However, this study was not corrected for multiple analyzes and p values were not available for a post hoc correction. It is unclear if such a correction would have modified its conclusion. Additionally, 2 of these studies showed no changes in other measures of language. No change in any measure of language was reported in 2 other studies totaling 17 patients followed up to 12 months (Table 2).

## Executive function

### Subthalamic Nucleus

Three studies reported improvement, and 6 showed worsening in at least one measure of executive function. However, one of these [45] was not corrected for multiple analyzes and no exact p value was reported. A post hoc correction was not possible and it is unclear if the reported worsening would have been significant once this correction had been made. Additionally, 34 studies showed no statistical difference in any assessed measures of executive function (Table 1).

Among the 10 studies comparing executive function ON and OFF stimulation [25,35,46-51,56,57], 2 showed worsening of the spatial delayed response under a high but not low memory load condition with stimulation ON [25,56]. Alberts et al. [25] reported a series of 8

patients with bilateral STN DBS, tested OFF medications and in 3 DBS conditions: OFF bilaterally, ON on the most affected side only, and bilaterally ON. The authors found further worsening in executive functions when multitasking in bilateral compared to unilateral stimulation. On the other hand, Jahanshahi et al. [51] reported improvement of frontal executive functions with stimulation ON while the 7 other studies did not yield any statistically significant change.

In addition, Perozzo et al. [58] reported no change in executive function 6 months after surgery with DBS ON, whether ON or OFF medications.

Jahanshahi et al. [51] suggested that post STN DBS improvement in frontal function, including executive and attention/concentration, might be secondary to a decrease in the excessive inhibitory output from the basal ganglia to the frontal cortex. Limousin et al. [59] additionally reported increased activation of the dorsolateral prefrontal cortex (DLPFC) on PET scan after STN DBS.

### **Globus pallidus interna**

Ardouin et al. [32] reported improvement of at least one measure of executive function at 6 months while 7 other studies did not report statistically significant change in any measure of executive function up to 21 months after the surgery (Table 2).

## **Attention and Concentration**

### **Subthalamic Nucleus**

Jahanshahi et al. [51] reported improvement of all reported measures of attention and concentration (A/C) with stimulation ON compared to OFF in 7 patients. Page and Jahanshahi [57] partially replicated these results by reporting similar improvement in some, but not all, the reported measures in 12 patients. It must be noted that there was no comparison to the preoperative functioning in these 2 studies. Conversely, Fraraccio et al. [50] reported worsening of at least one measure of A/C 16 months after implant, with no difference between ON and OFF stimulation. Additionally, 3 studies reported post-operative worsening in at least one measure of A/C, up to 6 months after DBS implant. Finally, 19 other reviewed series, including 2 evaluating patients with stimulators ON and OFF [35,46], reported no statistically significant impact of STN DBS implant and/or stimulation on these cognitive functions. In addition, Perozzo et al. [58] reported no change in attention and concentration 6 months after surgery with DBS ON, whether ON or OFF medications (Table 1).

PET studies have shown that the missing digit task, used by Jahanshahi et al. [51], specifically activates the DLPFC and posterior premotor cortex [60], giving a substratum for the observed improvement since these cortical sites receive input from the STN [61].

### **Globus Pallidus Interna**

No statistically significant change up to 21 months after GPi DBS implant was reported in 5 studies assessing attention and concentration (Table 2). Among these, Jahanshahi et al. [51] could not detect any changes associated with the stimulation status (ON v/s OFF).

## **Memory**

### **Subthalamic Nucleus**

Hilker et al. [34] reported improvement of memory after STN DBS in their series of 8 patients followed for 4 months [34]. The study was not corrected for multiple analyzes and no exact p value was reported. A post hoc correction was not possible and it is unclear if the improvement would have been significant once this correction had been made. On the other hand, 3 studies reported worsening in at least one, but not all, measures of memory, up to 16 months after surgery (Table 1). However, one of these [45] was not corrected for multiple analyzes and no exact p value was reported. A post hoc correction was not possible and it is unclear if this worsening would have been significant once this correction had been made. In addition, Jahanshahi et al. [51] also reported worsening of memory with stimulation ON compared to OFF. Hälbig et al. [47] reported a series of 12 patients assessed post operatively ON and OFF stimulation and reported an improvement in non-declarative memory but a worsening in declarative memory with stimulation turned ON. However, when corrected for multiple analyzes these results were not statistically significant.

Finally, 25 other series did not report any statistically significant impact of the surgery and/or stimulation on memory (Table 1). Among these, Perozzo et al. [58] reported no changes 6 months after surgery with DBS ON, whether ON or OFF medications.

### **Globus pallidus interna**

Fields et al. [54] reported worsening of one, but not all, measures of memory in 6 bilateral GPi DBS patients, followed for 5 months. However, this study was not corrected for multiple analyzes and no exact p value was reported. A post hoc correction was not possible and it is unclear if this worsening would have been significant once this correction had been made. Conversely, 6 other studies, totaling 66 patients followed for up to 21 months, could not detect a statistically significant change in any measure of memory (Table 2). These included 2 studies comparing OFF and ON stimulation states [48,51].

## **Visual Function**

### **Subthalamic Nucleus**

Visual function was not significantly impacted in 17 studies, including 2 assessing patients ON and OFF stimulation [35,50] (Table 1). It has to be noted that Alegret et al. [62] were the first to report a detrimental effects of STN-DBS on visuospatial function. However, this was not statistically significant after correction for multiple analyzes.

### **Globus pallidus interna**

Tröster et al. [55] reported worsening of one but not all measures of visual function in 9 patients followed for 3 months after bilateral GPi DBS. However, this study was not corrected for multiple analyzes and no exact p value was reported. A post hoc correction was not possible and it is unclear if this worsening would have been significant once this correction had been made. Conversely, 4 studies totaling 44 patients followed up to 21 months did not detect a statistically significant change in any used measure of visual function (Table 2).

Visual function is the less frequently investigated cognitive function after DBS. With U<sub>C</sub> et al. [63] reporting significant deficits on visual attention, visual sensory function, spatial perception, and visuo-constructional abilities in PD patients, visual function might need to be included in future cognitive studies in PD.

## Psychomotor and Processing Speed

### Subthalamic Nucleus

Jahanshahi et al. [51] and Page et al. [57] reported improvement in psychomotor and processing speed with STN stimulation ON compared to OFF. No statistically significant change could be detected in 13 other studies, including in 2 evaluating patients with stimulation ON and OFF [47,48] and one evaluating patients ON and OFF medications with stimulation ON [58] (Table 1).

### Globus pallidus interna

No significant change in psychomotor and processing speed from GPi implant with or without stimulation could be detected in 4 studies totaling 52 patients [32,48,51,64] (Table 2).

## Global Cognition

### Subthalamic Nucleus

Global cognition was showed to significantly worsen 5 years after surgery in one series of 37 patients evaluated ON stimulation and ON medications [30]. However, this study had no control arm, and the reported worsening might be secondary to the natural evolution of PD [65]. Furthermore, these results could not be replicated in 21 other studies that showed no significant change up to 5 years after surgery, including 6 controlled studies comparing STN DBS patients to non-surgically treated PD patients [23,24,37-39,42] (Table 1). Aybek et al. [26] calculated the incidence of dementia 3 years after bilateral STN DBS in 50 PD patients, and found it to be 89/1000, comparable to the reported incidence in medically managed PD (42.6 to 112 of 1,000 per year) [66].

### Globus pallidus interna

No statistically significant change in global cognition up to 6 months after surgery could be detected in 3 studies [32,54,55] (Table 2).

## Controlled Studies

Since most of the information available stems from open label uncontrolled series, a major concern is that a detected cognitive worsening might be secondary to the natural history of PD rather than DBS. It is then worthwhile to take a closer look at the few controlled studies available (Table 1).

No difference was detected between DBS and non DBS PD patients in 5 controlled studies. Gironell et al [33] reported 8 PD patients who underwent bilateral STN DBS and compared their evolution 6 months after surgery to 8 age and stage-matched PD patients who refused surgery. Evaluations were done ON medication and ON stimulation, and reported worse semantic verbal fluency in the DBS group. However, when corrected for multiple analyzes, this difference was not statistically significant. In addition, no difference was found in the

other cognitive tasks assessed. A year later, Morrison et al. [35] compared 17 PD patients who underwent bilateral STN DBS with 11 non surgically treated PD patients. There was no statistically significant difference at 3 months between the 2 groups. In addition, within the DBS group, there was no difference with stimulation ON or OFF at 3 months, or between the stimulation ON at 3 months and the pre-operative assessment. York et al. [24] compared 23 STN DBS patients to 27 medically managed PD patients and reported worse verbal memory in the DBS group at 6 months. Visual memory, all measures of fluency and other cognitive measures were non-statistically different between the groups. However, in a follow up to this study, Williams et al. [37] reported on 19 STN patients and 18 medically optimized PD patients 2 years after surgery. While the authors concluded on worsening of some measures of memory, processing and fluency, this was not significant after correction for multiple analyzes. More recently, Sáez-Zea et al. [41] compared the cognitive outcome of 9 bilateral STN DBS patients with 12 non-surgical PD patients 6 months after surgery. While 4 measures of language and attention, out of the 18 cognitive measures assessed, worsened during that interval, there was no difference between the 2 groups. In addition, a non-statistically significant trend to worse phonemic verbal fluency was observed in the STN-DBS patients but was significantly correlated with reductions in the L -dopa-equivalent daily dose, suggesting that worse fluency observed after STN DBS might in fact be secondary to decrease in the anti-parkinsonian medication. Most recently, Witt et al. [38] randomized 62 STN DBS candidates equally to DBS or optimal medical treatment and reported worsening of semantic fluency 6 months after surgery, with no significant change in letter fluency compared to the non-surgical group. However, this difference was not statistically significant after correction for multiple analyzes. Similarly, the other cognitive measures did not differ between the 2 groups.

In contrast, 6 controlled studies suggested worsening of some cognitive measures after DBS, sometimes mitigated by improvement of others. Moretti et al. [43] reported 9 patients with bilateral STN DBS and compared their evolution 12 months after surgery to 9 non-surgically treated PD patients. Assessments were done ON stimulation and ON medications, and reported worsening of some executive function as well as semantic and syllabic fluency, but with an increase in control of linguistic production. The other cognitive measures assessed were not different between the 2 groups. Zangaglia et al. [42] reported worsening of verbal fluency in the STN DBS group (n=32) compared to the medically optimized patient group (n=33) 3 years after surgery. Other cognitive measures were stable over that period of time and did not differ between the 2 groups. Witt et al [39] compared 60 bilateral STN treated PD patients with 63 STN eligible PD patients who declined surgery ON medications and stimulation 6 months after implant. While this study did not compare cognitive functions to the preoperative baseline, it did nevertheless report statistically worse attention on 2 measures in the STN group, but no difference in the other cognitive measures assessed. Smeding et al. [40] compared 99 STN DBS patients to 39 non DBS patients 6 months after implant in the ON stimulation/ON medication state. They reported a significantly worse decline in fluency and attention/concentration in the STN group. Other cognitive measures were stable over that period of time and did not differ between the 2 groups. Cilia et al. [23] reported statistically significant worsening of category fluency in a group of 20 DBS patients compared to 12 non-surgically treated PD patients 12 months after surgery. Phonemic fluency and other cognitive measures did not differ between the 2 groups. Last, Castelli

et al. [36] compared the change in score between pre-operative baseline and 1 year follow up for each assessed cognitive measure, between 27 STN DBS patients and 31 matched non DBS PD patients. Phonemic fluency was worse in the STN group, while semantic fluency and other cognitive measures were not statistically different between the 2 groups.

Hilker et al. [34], however, compared 8 PD patients ON stimulation 4 months after bilateral STN DBS with 10 healthy matched controls and reported significant improvement in verbal and nonverbal long-term memory, suggesting STN DBS might in fact improve memory circuits compared to non-surgically treated PD patients. The study was not corrected for multiple analyzes and no exact p value was reported. A post hoc correction was not possible and it is unclear if the improvement would have been significant once this correction had been made.

Finally, Whelan et al. [31] compared language between 5 PD patients 3 months after bilateral STN DBS and 16 non surgically treated PD patients. Each of these groups was then compared to another group of 16 healthy aged matched and that difference was again compared between these 2 groups. PD patients were all ON medications and DBS patients had their stimulators ON. When compared to the non-surgically treated PD patients, post DBS patients had improvement on the word test-revised but decline in the accuracy of lexical decisions about words with many meanings and a high degree of relatedness between meanings. It is unclear however, how much these detailed differential results would impact the patients' daily life.

In summary, only half the available controlled studies reported statistically significant worsening on some cognitive measures after bilateral STN DBS. Different subtypes of fluency (semantic, phonemic,

category) worsened in some studies but not others. Worsening of attention was also reported in more than one controlled study. On the other hand, 2 controlled studies reported improvement in some cognitive measure after STN DBS. It thus seems that cognitive worsening after STN DBS should not be taken for granted.

### Target Selection

A current tendency is to prefer GPi DBS for patients with mild cognitive impairment for fear that STN DBS is associated with more cognitive side effects. While there is more data reporting cognitive worsening after STN DBS, this data is markedly imbalanced as the studies detailed above have evaluated 1296 STN DBS patients but only 85 GPi patients. Therefore, we took a closer and more critical look at head to head comparison between the 2 targets.

To our knowledge, 5 studies have compared head to head the cognitive impact of STN and GPi DBS [53,67-70] (Table 3). Only one [67] reported correction for multiple analyses. After corrections were applied when needed, only Weaver et al. [69] reported worsening on one memory test 3 years after STN DBS compared to GPi DBS, in 159 patients. The other studies, totaling 514 subjects (251 STN and 263 GPi) followed up to 2 years, could not detect any statistically significant difference between the 2 targets. While this discrepancy might be explained by the longer follow up in the study of Weaver et al., it is interesting to note that it did not report any worse decline in language, fluency, attention or executive function in the STN group, as would have been expected from the open labeled and nonsurgical patient matched series.

### Studies comparing cognitive outcome between GPi and STN DBS in PD patients

Author, year	N STN/GPi	Laterality	F/u (mo)	Status stimulation/ medication cognitive assessment	of at	Cognitive measures assessed	Differences between GPi and STN
Rothlind et al. [53]	19/23	UL	6	ON/ON		A/C,E,L,V,M	None
Rothlind et al. [53]	14/15	BL	21	ON/ON		A/C,E,L,V,M	None
Okun et al. [67]	22/23	UL	7	ON/OFF		L	None
Follett et al., 2010 [68]	147/152	BL	24	ON/OFF		GC, L, V, E, M	None
Weaver et al. [69]	70/89	BL	36	ON/OFF		GC, L, V, E,M	M worse with STN
Odekerken et al. [70]	63/65	BL	12	ON/Integrated ON and OFF		Composite test	None

**Table 3:** Studies comparing cognitive outcome between GPi and STN DBS in PD patients. PD: Parkinson's disease; GPi: globus pallidus interna; STN: subthalamic nucleus; N: number of patients; mo: months; UL: unilateral; BL: bilateral; A/C: Attention/Concentration; E: Executive; GC: Global Cognition; L: language; M: Memory; V: Visual.

### Discussion

As seen above, available studies on the cognitive impact of DBS on PD patients yielded different and sometimes opposite results. However, when cognitive worsening was detected, it was usually not reported by patients, caregiver or health care providers, suggesting that any change revealed by cognitive tests is subtle [32]. In addition,

quality of life was improved after DBS, even when cognitive worsening was detected [46].

Kumar et al. [71] suggested that this could reflect some variability in lead placement inside the target. Comparing postoperative magnetic resonance imaging scans in 8 patients who developed neuropsychological side effects to 30 who did not, Tsai et al. [72] suggested that the neuropsychological effects of chronic STN-DBS were related to an anteriorly located active contact within the ventral

STN. York et al. [73] reported that the surgical trajectory through the frontal lobe, in addition to the precise location of the active electrode inside the STN, might also influence the cognitive outcome. Indeed, Witt et al. [38] reported that a trajectory intersecting the caudate nucleus was associated with a higher risk of decline in global cognition and working memory performance. These results have yet to be duplicated in larger series.

In addition, the stimulation parameters might also influence the outcome. Wojtecki et al. [74] reported improvement of verbal fluency in 12 PD patients with low frequency (10 Hz) STN DBS compared to no stimulation. Stimulation at 130 Hz had a non-significant trend towards worsening of fluency compared to no stimulation, suggesting a frequency-dependent modulation of cognitive circuits involving the STN. In another study on 20 PD patients treated with bilateral STN DBS, Schoenberg et al., [75] reported that increased amplitude and pulse width of the stimulation were associated with improved cognitive test scores.

Trepanier et al. [76] also suspected variations in the characteristics of the patients selected for surgery between different centers (age, preoperative cognitive status, comorbidity with other conditions such as psychiatric disorders). While advanced age might be considered a risk factor for cognitive worsening, studies showing executive worsening [25,30,43,45,56,77-80] did not have an older population than studies reporting improvement [32,44,51] (mean age of 56.8 vs. 58 years).

Several methodological issues can be raised when reviewing studies assessing neuropsychological outcome after DBS for PD. First and foremost, observed cognitive decline might be secondary to the natural evolution of the disease. Indeed most of the available studies lack a control arm of non-surgically treated PD patients. Second, observed cognitive improvement can result from practice effect in the case of serial neuropsychological assessment [46]. The use of parallel forms of cognitive tasks or the comparison of results with a non-surgically treated group of patients might mitigate this practice effect, although this could be logistically difficult. An alternative would be to use relatively long intervals between cognitive assessments [46]. Third, the pharmacological condition of the patients at the time of neuropsychological test is not uniform across all studies. Patients were assessed ON anti-parkinsonian drug treatment in most studies, but OFF anti-parkinsonian drug treatment in others [35,51,56,62,67-69,80-87], or even in a non-homogenous way in some [32]. Finally, it is possible that a postoperative reduction in anti-parkinsonian drugs, seen more after STN DBS than in GPi DBS [8] could to some extent negatively influence performance on cognitive tasks. This could be minimized by a uniform assessment of all patients ON stimulation and OFF medication. However, this could render pre-operative assessment impossible in some patients, because of the severity of their motor symptoms when OFF medications

## Conclusion

We reviewed the available literature on cognitive changes after STN and GPi DBS in PD patients and arrive at the following suggestions. (1) Worsening of one or more cognitive function is rare after DBS in PD patients. Available literature is conflicting, with controlled studies reporting opposite results. (2) When cognitive worsening is detected; it is usually not reported by patients, caregiver or health care providers, suggesting that any change revealed by cognitive tests is subtle. In addition, quality of life is improved after DBS, even when

cognitive worsening is detected. (3) Only one in 5 randomized trial comparing cognitive outcome in and STN and GPi DBS reported worse cognitive outcome in the STN group, namely on one measure of memory. While the choice of the target should be individualized and adapted to the patient's situation, fear of cognitive worsening after STN might not have to weight a lot on this decision. (4) Future studies addressing this topic should ideally have a control arm of non-surgically treated PD patients matched for all clinical and demographic variables to control for the natural evolution of the disease. In addition, assessing the DBS group ON and OFF stimulation would provide direct comparisons of the stimulatory effects while controlling for surgical effects, and yield greater power since patients serve as their own controls. (5) More reports on anatomo-clinical correlation of cognitive worsening after DBS would help improve surgical planning to avoid sensitive structures.

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