

Cognitive Functions in a Patient With Parkinson-Dementia Syndrome Undergoing Deep Brain Stimulation

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Background: Dementia represents one of the most challenging health problems. Despite intense research, available therapies have thus far only achieved modest results. Deep brain stimulation (DBS) is an effective treatment option for some movement disorders and is under study for psychiatric applications. Recently, diencephalic DBS revealed selective effects on memory functions, another facet of subcortical DBS.

Objective: To report a new DBS strategy for the modification of cognitive functions in a patient with severe Parkinson-dementia syndrome.

Design: Prospective study with double-blinded sham stimulation period.

Setting: Departments of Stereotaxy and Functional Neurosurgery and Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany.

Patient: A 71-year-old man with slowly progressive Parkinson-dementia syndrome.

Intervention: We inserted 2 electrodes into the nucleus basalis of Meynert in addition to electrodes in the subthalamic nucleus.

Main Outcome Measure: Improvement of cognitive functions.

Results: Turning on the subthalamic nucleus electrodes improved motor symptoms but left cognitive performance almost unchanged. Turning on electrical stimulation of the nucleus basalis of Meynert resulted in markedly improved cognitive functions. The improvement in attention, concentration, alertness, drive, and spontaneity resulted in the patient's renewed enjoyment of former interests and enhanced social communication.

Conclusions: Such a broad effect on cognition is consistent with ample experimental evidence revealing that the nucleus basalis of Meynert provides cholinergic innervation to the cortical mantle, complemented by glutaminergic and γ -aminobutyric acid-transmitting projections from the basal forebrain. These projections provide background tuning facilitating cortical operations. Furthermore, nucleus basalis of Meynert stimulation paired with sensory stimuli can accomplish persistent reorganization of specific processing modules. The improvements in cognitive and behavioral performance in our patient are likely to be related to the effects of stimulating residual cholinergic projections and cell bodies in the nucleus basalis of Meynert.

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REGARDING THE EFFECTS OF deep brain stimulation (DBS) of the subthalamic nucleus (STN) on cognitive functions, a randomized, multicenter study showed that STN-DBS does not reduce overall cognition but is associated with a selective decrease in frontal cognitive functions.¹ Clear improvements in the cognitive state in patients with Parkinson disease dementia (PDD) have so far not been shown. We describe a new DBS strategy for the modification of cognitive functions by stimulating the nucleus basalis of Meynert (NBM) in addition to the STN in a patient with PDD.

REPORT OF A CASE

A 71-year-old man developed slowly progressing PD over a 22-year period. At the time of observation, the clinical picture was characterized by akinetic-rigid PD without prominent tremor. For an extended period, the patient had responded well to dopaminergic medication but had increasingly experienced on-off fluctuations over the last 2-3 years.

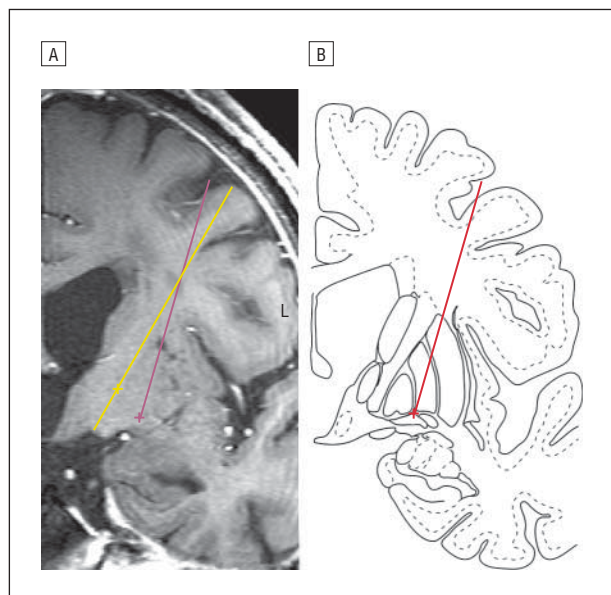


Figure 1. Graphic and anatomical presentation of the electrode trajectory. A, Reconstructed electrode trajectories to the nucleus basalis of Meynert (magenta line) and the subthalamic nucleus (yellow line) superimposed on preoperative T1-weighted magnetic resonance image. B, Structural outline of the coronal section at the level of the electrode tip in the nucleus basalis of Meynert (red line). L indicates left side.

Table 1. Stimulation Parameters

STN Stimulation		NBM Stimulation	
Right Side	Left Side	Right Side	Left Side
-5/+C; 4.2 V; 60 μ s; 130 Hz	-1/+C; 3.5 V; 60 μ s; 130 Hz	-4, -5/+C; 1.0 V; 120 μ s; 20 Hz	-0, -1/+C; 1.0 V; 120 μ s; 20 Hz

Abbreviations: C, case; NBM, nucleus basalis of Meynert; STN, subthalamic nucleus; μ s, microsecond.

In addition, the patient had a history of cognitive decline over the last 2 years that intensified over the last 6 months. Prominent symptoms were apathy, rigid thinking, poor short-term memory, slowing of thought processes, an impaired capacity to use acquired knowledge, and a lack of concentration. Fluctuation in cognitive function and visual hallucinations complemented the core features of PDD according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision)² criteria and as distinguished from Alzheimer disease (AD) and other dementias.³

Because of the severity of the patient's PDD and the progressive nature of the PD-associated dementia, we considered it possible that an individual clinical trial of bilateral DBS of the STN and the NBM could prove beneficial. The patient and his wife were informed of the potential risks and benefits of the surgical procedure 6 months before its performance. Because his dementia precluded informed consent to be obtained from the patient, surrogate consent was obtained from his wife who was the only person entitled to do so according to German law. The risk of morbidity was described as 2% to 3% in his case, because of the use

of 4 electrodes instead of the usual 2 electrodes. It was further emphasized that it was uncertain if the stimulation of the NBM would achieve any improvement in cognitive function.

METHODS

SURGICAL PROCEDURE

Stereotactically guided bilateral DBS electrodes were implanted in the STN and the NBM on January 1, 2008. The tips of the NBM electrodes were directed into the laterodorsal portion of the intermediate sector of the NBM (Ch4 intermedius). The Talairach coordinates of the selected target points were chosen according to the atlas of Mai et al,⁴ transformed to the corresponding position of the patient's brain: y=4 mm posterior to the anterior border of the posterior commissure, x=12.5 mm lateral to the wall of the third ventricle, and z=5 mm ventral to the anterior commissure–posterior commissure line. Since the NBM is a flat, almost horizontal structure, a deep frontolateral approach was chosen to enable placement of the 2 distal poles of the electrode within the NBM (**Figure 1**).

The Ch4 intermedius sector of the NBM was selected for the following reasons: First, the location of the Ch4 intermedius is easily determined by magnetic resonance imaging owing to its proximity to compact fiber bundles. It is located below the lateral medullary lamina that separates the external segment of the globus pallidus from the putamen and neighboring ansa lenticularis. This stretch of cells extends anteroposteriorly at the level at which the posterior limb of the anterior commissure bends medially at the base of the putamen. On horizontal sections, it appears in the area in which the anterior commissure and the optic tract cross. Second, Ch4 intermedius represents the most compact cell cluster of the NBM and is the largest out of all Ch4 groups in the ventrodorsal dimension. The probability of placing the electrode tip within a conglomerate of cholinergic cells was maximized with an additional possibility of targeting this sector with 2 electrode poles. Third, Ch4 intermedius represents a bottleneck for the NBM output that is severely affected in dementia.⁵ The electrode tip had close contact with axons that form the lateral pathway of the NBM and that extend into the external capsule to reach the neocortex⁶ as well as with cholinergic axons that project into the ventral amygdalofugal pathway and the inferior thalamic peduncle and axons that proceed from the Ch4 intermedius via the magnocellular basal forebrain to the brainstem nuclei, the reticular formation, locus ceruleus, and the peripeduncular nucleus. Fourth, Ch4 intermedius is particularly affected in severe cases of dementia as demonstrated by the notable correlation between a variety of cholinergic markers and trophic factors (nerve growth factor–receptor and trk-receptor gene expression)⁷ and dementia severity.

Subthalamic nucleus stimulation parameters were maintained as adjusted before NBM over the observation period (**Table 1**). Medication for the treatment of PD was reduced from the preoperative levodopa-equivalent dose of 850 mg/d to 312.5 mg/d (total daily dose) at the beginning of NBM stimulation.

NEUROPSYCHOLOGICAL/MEMORY EVALUATION

A neuropsychological test battery was conducted 1 week before implantation of the electrodes (t_{-1} ; surgery= t_0) as well as after treatment with DBS in 4 double-blind phases: sole STN stimulation (t_1), combined STN and NBM (on 1) stimulation

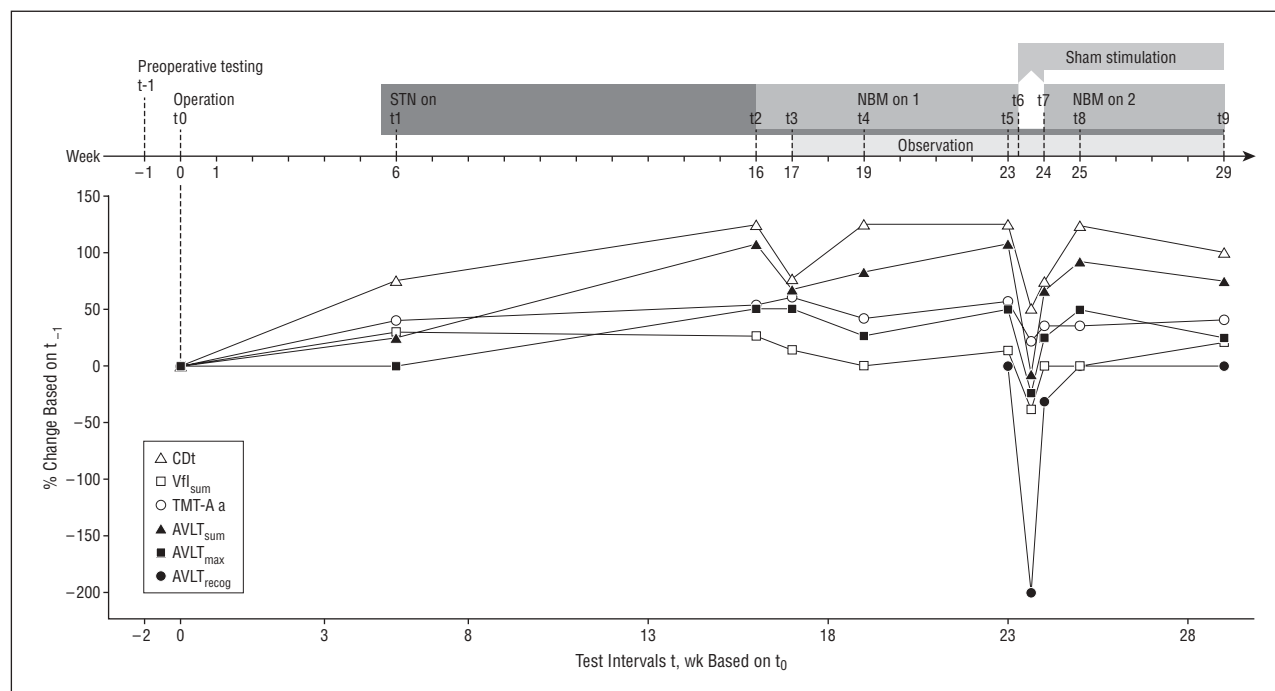


Figure 2. Timetable and graphic illustration of Clock Drawing Task (CDT), Trail Making Test Part A (TMT-A), and Auditory Verbal Learning and Memory Test (AVLT) values during treatment with deep brain stimulation of the subthalamic nucleus (STN) and nucleus basalis of Meynert (NBM). Off indicates patient is receiving no treatment; on, patient is receiving treatment; max, maximum; recog, recognition; sum, summary; t, time; and VFI_{sum}, verbal fluency summary.

(t_{2-5}), sole STN stimulation (NBM off; t_6), and combined STN and NBM (on 2) stimulation (t_{7-9}) (**Figure 2**). The patient's cognitive impairment was so severe that the assessment of the Letter-Number-Span test, Digit Symbol Test, Trail Making Test (TMT) Part B, Rey Auditory Verbal Learning Test (AVLT) interference and long-term condition could not be tested before NBM stimulation, but it was partially possible subsequently, thus illustrating the effectiveness of NBM as contrasted with the previous 10-week STN stimulation. Nevertheless, the following paper and pencil tests could be administered: AVLT,⁸ TMT Part A,⁹ Verbal Fluency Test, and Clock Drawing Task (CDT). Significant depressive symptoms were assessed and excluded using the Beck Depression Inventory-II.¹⁰

RESULTS

PREOPERATIVE TIME (t_{-1} ; 1 WEEK BEFORE SURGERY)

The patient seemed helpless and absent minded. A lack of attention and concentration, impaired judgment, decreased cognitive flexibility, reduced spontaneous speech, and memory dysfunction were apparent. Consequently, we had to abstain from applying the delayed conditions of the AVLT. In the remaining tests (**Table 2**), the patient showed severe deficits in immediate memory and only marginal learning efficiency (AVLT). A marked reduction of visual-motoric speed (TMT-A) and verbal fluency as well as impairment of visual scanning (TMT-A) and visual spatial organization (CDT) was found. According to behavioral observations, the patient had difficulties sustaining the topic of conversation. At t_{-1} the Multiple Choice Vocabulary Test was applied as a measure of premorbid intelligence. The validity of the test has been demonstrated

for healthy adults.¹¹ For our patient, the test revealed an average (97) IQ. In light of the patient's academic level, we assume that the Multiple Choice Vocabulary Test underestimated premorbid intelligence.

BILATERAL STIMULATION OF THE STN (t_1 ; 12 WEEKS AFTER SURGERY)

Under bilateral stimulation of the STN, the patient achieved better results in tests that, among other abilities, measured motor skills and processing speed (CDT, TMT-A, and verbal fluency). Measures of memory performance remained almost unchanged (eg, AVLT maximum) (Table 2 and Figure 2).

COMBINED BILATERAL STIMULATION OF THE STN AND THE NBM (t_{2-5} ; 16-23 WEEKS AFTER SURGERY)

Under additional bilateral stimulation of the NBM, significant and impressive improvement was observed in memory tasks (AVLT). Furthermore, outcomes on the remaining neuropsychological measures (mainly CDT and TMT-A) were enhanced and reached higher levels than had been attained using isolated STN stimulation. These results remained almost stable over a 2-month period (t_{3-5}).

Owing to the patient's generally improved cognitive functioning—compared with t_{-1} —he was also examined for long-term memory functions using the time-delayed conditions (recognition and recall) of the AVLT. Findings from these tests revealed persisting impairment of delayed memory function although the patient was able to recognize 6 words in the recognition condition (3 false-positive recognitions).

Table 2. Beck Depression Inventory (BDI)-II and Neuropsychological Evaluation Results Across Assessment Occasions

Test	Test Intervals									
	t ₋₁	t ₁	t ₂	t ₃	t ₄	t ₅	t ₆	t ₇	t ₈	t ₉
Clock Drawing Task, points	4	7	9	7	9	9	6	7	9	8
Vfl _{sum} , No. of words	23	30	29	26	23	26	14	23	23	28
Vfl _{max} , No. of words	8	11	12	11	10	9	6	9	10	11
TMT-A, time, min:s	5:24	3:02	2:23	2:07	3:05	2:19	4:10	3:30	3:30	3:11
AVLT A1, No. of words	2	2	4	3	3	4	2	3	4	3
AVLT _{sum} , No. of words	12	15	25	20	22	25	11	20	23	21
AVLT _{max} , No. of words	4	4	6	6	5	6	3	5	6	5
AVLT _{learn} , No. of words	2	2	2	3	2	2	1	2	2	2
AVLT _{recall} , No. of words	NA	NA	NA	NA	NA	0	0	0	0	0
AVLT _{recog} , No. of words	NA	NA	NA	NA	NA	6r; 3f	2r; 5f	4r; 2f	6r; 3f	5r; 2f
AVLT _{recog} diff r – f	NA	NA	NA	NA	NA	3	-3	2	3	3
BDI-II, points	26	20	19	22	22	20	24	19	20	20
STN	-	On	On	On	On	On	On	On	On	On
NBM	-	Off	On	On	On	On	Off	On	On	On

Abbreviations: AVLT, Auditory Verbal Learning and Memory Test; f, number of words false-positive; max, maximum; NA, not applicable; NBM, nucleus basalis of Meynert; off, patient not receiving treatment; on, patient receiving treatment; r, number of words right positive; recog, recognition; STN, subthalamic nucleus; sum, summary; TMT-A, Trail Making Test Part A; and Vfl, verbal fluency.

ISOLATED STIMULATION OF THE STN AND “SHAM” STIMULATION OF THE NBM (t₆: WEEK 24)

To examine the beneficial effects of stimulating the NBM, a double-blind off/on period was applied. After 24 hours without stimulation of the NBM (off), major cognitive deterioration was observed. The results of all assessed neuropsychological tests showed worse outcomes compared with t₃₋₅ and almost reached the baseline level. The most impressive impairment was found in the recognition condition of the AVLT (Figure 2). We did not test STN off, because trying to do so rapidly deteriorated his motor state, which he was not willing to tolerate. Furthermore, the patient was on STN on/NBM off stimulation for almost 3 months without noticeable improvement in cognitive functions.

COMBINED BILATERAL STIMULATION OF THE STN AND THE NBM (t₇₋₉: WEEKS 24-29)

Twenty-four hours after restarting stimulation of the NBM, cognitive functioning notably improved. Results of the neuropsychological measures were restored to those levels attained at t₃₋₅. The most impressive improvement was observed for AVLT conditions. Subsequent assessments over a 5-week period revealed test results that were almost unchanged at upper levels.

COMMENT

Parkinson disease with dementia is characterized by subcortical and cortical Lewy body formation. Prevalence of PDD in patients with PD approaches as high as 30%.¹² Coexisting AD pathologic features with amyloid plaques and neurofibrillary tangles is observed in 72% of these patients. A key feature in the course of both AD and PDD is basal forebrain degeneration.^{13,14} Compared with AD, central cholinergic deficits in PDD occur earlier and are

more pronounced and widespread.^{13,15} Downregulation of cholinergic input has been associated with the pathogenesis of protein aggregation.¹⁶ These findings suggest a potential key role of the NBM in both types of dementia. For this reason, a phase 1 clinical study has been initiated to evaluate the safety and efficacy of stereotactic surgical delivery of CERE-110 (Trial registration: clinicaltrials.gov Identifier: NCT00087789)—an adeno-associated virus-based gene delivery vector that encodes for human nerve growth factor—to the human NBM in human patients with AD according to Bishop et al.¹⁷ Neuromodulation of ascending basal forebrain projections of the NBM may represent a new and complementary strategy for enhancing the residual nucleus basalis output. For this purpose, excitatory actions had to be accomplished. This can be achieved by using low-stimulus rates (20 Hz). There is converging evidence from different experimental conditions that low-frequency stimulation has excitatory rather than inhibitory actions.¹⁸⁻²⁰ Furthermore, NBM neuronal discharge rates at approximately 20 Hz are typically observed during active behavior in rats.²¹ Cyclic higher-frequency stimulation (50 Hz) of the NBM failed to improve cognitive functions in a patient with AD²² possibly also because of mere unilateral stimulation.

The effects observed in our patient developed over the first few weeks and were subsequently consolidated. During the 13-week observation period following the initiation of NBM stimulation, there was no continuation of the cognitive decline that had been observed in the 6 months before DBS. Instead, we observed clear improvements in various aspects of cognitive functioning following NBM stimulation. The AVLT results provide the best evidence for improved memory functions. Results of this test revealed no overlap with improvement due to STN stimulation (with sole STN stimulation, AVLT results at t₁ were unchanged). Assessments of other aspects underlying cognitive functioning such as attention, concentration, alertness, drive, and spontaneity, however, also

demonstrated clear improvement following initiation of NBM stimulation and subsequent deterioration in the intermittent NBM-off phase. These changes reflecting general tuning effects may be instrumental for a better use of the remaining mental capacities. Our clinical observation supports such a view since the overall improvement of the personality features and of social communication were more impressive than selective memory enhancement. Memory improved but remained deficient. This global improvement is in accord with the suggested role²¹ of the NBM system as a structural basis for the concept of generalized ascending activation proposed by Moruzzi and Magoun²³ and stands in contrast to the highly selective effects on memory elicited by diencephalic stimulation presumably mediated by current spread to the fornix.²⁴

In conclusion, our observations revealed marked improvements in cognitive functioning by NBM-DBS in a patient with PDD that led to clear improvement of the patient's quality of life. The positive effects of stimulation on a largely degenerated nucleus are surprising and may be transient in such a severely affected patient. Therefore, the study of less severely affected patients and the relationship between the severity of dementia and the duration of positive effects should provide more information about this issue.

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