Neuropsychological effects of subthalamic nucleus stimulation in Parkinson's disease

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Behavioral changes and executive dysfunction after bilateral STN stimulation

Submitted
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Chapter 7

Abstract

We describe a patient with Parkinson disease, who suffered from behavioral changes and executive dysfunction after bilateral subthalamic nucleus (STN) stimulation. Switching of the stimulators led to dramatic improvement of behavior and cognition, but with loss of improvement in motor functioning. Behavioral changes and executive dysfunction can be due to stimulation effects.
Introduction

Cognitive decline and mood changes have been reported after bilateral stimulation of the subthalamic nucleus (STN) in Parkinson disease (PD).\textsuperscript{1-4} Depressive mood or manic behavior may disappear after switching off the stimulation or changing the parameters.\textsuperscript{5} We describe a patient with advanced PD who showed behavioral changes and executive dysfunction after bilateral STN stimulation.

Patient

A 61-year-old former engineer was diagnosed with PD in 1985. In 1997, a left pallidotomy was performed to abolish disabling dyskinesias. Postoperatively, the patient experienced some right-sided facial paresis, and slight difficulties with word finding and mental arithmetic. Neuropsychological testing showed decline in verbal memory and fluency. In 2004 he had bilateral STN stimulation for the disabling motor fluctuations. At that time he used 550/137.5 mg levodopa/carbidopa, 300 mg amantadine and 8 mg pergolide a day. Neuropsychological testing showed improvement in verbal memory compared to post-pallidotomy results (Table 1). Mental speed was slightly reduced, but other cognitive functions were in the normal range.

Surgery and postoperative management

Surgery was performed using 5-tract microrecordings and macrostimulation for target localization (12 mm lateral, 2 mm posterior and 4 mm inferior to the midcommissural point (MCP)). The electrodes (model 3389, Medtronic) were implanted in the central trajectories, with the deepest contact 8 mm inferior to MCP on the right and 6 mm inferior on the left. At discharge, monopolar stimulation at contact 2 with amplitude 1.7 V, pulse width 60 µsec and frequency 130 Hz was used on both sides. He used 600/150 mg levodopa/carbidopa, 300 mg amantadine and 3mg pergolide a day. Clinically, there was a marked motor improvement without on/off fluctuations or freezing of gait.

Follow up

Four weeks after surgery, the patient was seen because of behavioral changes. According to his wife, he started using aggressive vocabulary a few days after discharge. Over the next days, he became increasingly irritable, distractible and
forgetful. He used to be easy to go on with, but now he was recalcitrant. He drove too fast and violated traffic rules, while he used to be a conscientious driver. His manners were lost, for instance he did not congratulate friends with their birthday anymore and he forgot to greet visitors. He suffered from daytime sleepiness and visual hallucinations. The patient himself had no complaints. Motor functioning, including gait was satisfactory. Reducing the amantadine did not resolve the behavioral problems. Neuropsychological testing showed a significant decline in verbal fluency and attention with normal memory functions (Table 1).

**Figure 1** Fusion of the preoperative T2-MRI and the CT 2 months after surgery, with all CT-signal suppressed except for the electrode artifact. Axial (top) and coronal (bottom) reconstructions. The crosses measure 5 mm, and indicate the targets as determined pre-operatively.
One week after switching off the neurostimulators, his wife stated that all behavioral alterations had resolved. He was able to participate socially in conversation. He did not doze off anymore. His bad manners had disappeared, and interest in his wife had restored. The patient himself did not notice any difference. On neuropsychological testing executive function was in the normal range again improved, although the test results on fluency and divided attention were still reduced compared to the preoperative scores. Motor functioning was severely impaired.

To verify the position of the electrode contacts, a CT-scan co-registered with the preoperative MRI. On the left, contact 0 was 13 mm lateral, 1 mm posterior, 4 mm inferior to MCP (Figure 1), i.e. 2 mm higher than the planned position. On the right, contact 0 was at 11 mm lateral, 2 mm posterior, 8 mm inferior to MCP (Figure 1), i.e. at the planned position.

Various stimulation parameters at all contacts were tried. Eventually, both neurostimulators were reset to monopolar stimulation at contact 1 with amplitude 2 V, pulse width 60 μsec and frequency 130 Hz. Because of frequent freezing, the medication regime was adjusted to levodopa/carbidopa 800 /200 mg and pergolide 4mg daily dose.

Half a year after surgery, the patient complained of freezing of gait. There was no mood disorder, although his affect appeared flattened. His wife described him as self-centered and inflexible. Intimacy between the couple was lost. His wife felt as if “she was out of the picture”. He could not properly plan non-routine activities, e.g. he removed a door because of building activities, which were planned several weeks later.

Frequently, he skipped from one activity to another, leaving a mess behind while he used to be meticulous. He sometimes drove dangerously. The problematic behavior fluctuated in severity depending on the situation. Symptoms did not fit DSMIV criteria for hypomania. Compared to the immediate postoperative period, the behavioral alterations had not worsened, but they were leading to relational difficulties. The patient's wife realized that if the stimulators were switched off, he would return to ‘his own self’ again. However this was no option for him, because of decreased motor functioning. Because of the marital discord, affirmation of the behavioral changes was sought by another family member, who told that when he came for a visit, patient continued with his own activities without greeting him.
## Table 1  Neuropsychological and neurological data at baseline and follow up

<table>
<thead>
<tr>
<th>Test</th>
<th>baseline 1997</th>
<th>6 months post-pallidotomy</th>
<th>2004 FU 7 wks DBS 2</th>
<th>2004 FU 8 wks DBS off</th>
<th>2004 FU 26 wks DBS 1</th>
<th>2004 FU 27 wks DBS off</th>
<th>2004FU 52 wks DBS 2</th>
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<td>37/19</td>
<td>19/</td>
<td>32</td>
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FU= follow-up; DBS 1= deep brain stimulation contact 1; AVLT= Auditory Verbal Learning Test; RBMT: Rivermead Behavioural Memory Test; GIT = Groninger Intelligentie Test; MWCST= Modified Wisconsin Card Sorting Test, DEX = Dysexecutive symptoms; PDQL= Parkinson’s Disease Quality of Life: lower scores implicate higher QOL. T = normally distributed score with mean of 50 and standard deviation of 10, corrected for age and education. Abnormal test scores are printed in bold typeface.
Patient used to have strong opinions, but now he could not reconsider even if he was patently wrong. Neuropsychological testing showed slight impairment in executive functions with excellent memory function (table 1). Compared to the preoperative status there still were significant negative effects on all fluency measures. One week after switching off the neurostimulators, his wife was again surprised by the positive change in his behavior. He showed sincere interest and initiative, such as reminding her of a television program she would like to see. He did not jump anymore from one subject to another in conversation. Motor functioning was evaluated with the stimulator off and on, and also in on and off phase. Several adjustments of the stimulation parameters were tried again. Best motor results were obtained with bilateral monopolar stimulation at contact 2 with amplitude 1.5 V, pulse width 60 ms and frequency 130 Hz. These stimulation parameters were selected to improve motor functioning.

A year after surgery, the patient had deteriorated again. Apart from the above-mentioned behavioral problems, he showed social misconduct. For examples he burped and cleaned his feet in public. In a restaurant he shouted at the waiter for beer without asking his guests what they would like to drink. Marital problems were evident. Compared to the 6 months evaluation there was a decline in memory and attention. Motor functioning was still not optimal. Eventually, he agreed to switch off the neurostimulators and to address the loss of motor functioning by an apomorphine pump.

**Discussion**

STN stimulation improved motor functioning in this patient, but it caused behavioral alterations and executive dysfunction. The remarkable recovery after switching off the stimulators suggests a stimulation induced effect. This is underlined by the fact that adapting the stimulator to a lower contact point, led to less severe executive dysfunction and behavioral changes. Moreover, after returning to the former, higher contact point, the problems reappeared again, although less severe than directly after surgery. The slightly better performance was possibly related to resolving of postoperative edema. Recent studies report that stimulation outside the STN i.e., the zona incerta is superior in improving motor function compared to the STN itself. Others state that the dorsolateral STN border is most effective. However, in our patient the deepest
contact points were in the dorsolateral border of the STN but this did not improve his motor function. Stimulation of higher contact points were more effective but with severe neuropsychological side effects. Those contact points were dorsal to the STN and therefore stimulation probably took place in the fields of forel, in the zone incerta or maybe in the reticular formation. The pallidothalamic projections are passing through these areas and stimulating these structures may in turn negatively influence the orbitofrontal cortex, the anterior cingulate cortex, and the dorsolateral prefrontal cortex. Lesions in these areas may cause personality changes such as apathy, disinhibition, irritability, loss of social behavior, and lack of judgment. They may also cause executive disorders such as poor organizational strategies, poor memory strategies, and impaired set shifting.

Although bilateral STN stimulation after unilateral pallidotomy is usually reported as safe, the previously performed pallidotomy with temporary cognitive decline may have increased the risk of executive dysfunction or behavioral changes after bilateral STN stimulation. Restoration of cognitive function after pallidotomy may have been a result of recruitment of other pathways in the basal ganglia leaving the system more vulnerable. Subsequently, bilateral STN stimulation could lead to the equivalent of bilateral pallidotomy, after which neurobehavioral changes have been observed.

Changes in cognition and behavior were unrelated to the decrease in levodopa dose (LEU) postoperatively, because changes in stimulation parameters induced the behavioral changes, while LEU was unchanged. Changes seemed neither related to the dopamine agonist. Despite a high dose of pergolide preoperatively, behavioral disorders only started after bilateral STN stimulation when the daily dose was reduced. Behavioral disorders disappeared after switching off the stimulators irrespective of the dose.

We conclude that behavioral alterations and executive dysfunction after bilateral STN stimulation can be due to the stimulation per se. Side-effects of this order are rare, but when they occur they can have a serious impact on the personal lives of the patients and their relatives. Professionals involved in deep brain surgery should carefully monitor these possible harmful effects.
Behavioral changes after STN DBS: a case study

References


