Acta Neurochir Suppl (2008) 101: 9–12

Printed in Austria

Deep brain stimulation for movement disorders and its neuropsychological implications

H. M. Mehdorn[1], S. Goebel[1], D. Falk[1], J. Volkmann[2], B. Leplow[3], M. O. Pinsker[1]

[1] Department of Neurosurgery, University Clinics of Schleswig-Holstein Kiel, Kiel, Germany
[2] Department of Neurology, University Clinics of Schleswig-Holstein Kiel, Kiel, Germany
[3] Institute of Psychology, University of Halle, Halle, Germany

Summary

Deep brain stimulation (DBS) has gained increasing attention as a therapy for movement disorders. Neuropsychological alterations can accompany the disease evolution and medical therapy of PD. Also, interfering abruptly with the biological balance by means of a surgical intervention into complex circuits with motor but also cognitive and limbic functions, could potentially cause severe problems. Because cognitive or emotional impairments may have an even stronger impact on quality of life, than motor symptoms, care must be taken to perform surgery in the safest possible way to exclude adverse effects in these domains.

Detailed neuropsychological evaluations may become helpful to further understand the mechanisms underlying some aspects of the clinical pictures both pre- and postoperatively and to define risk populations, that should be excluded from this intervention.

Keywords: Deep brain stimulation; movement disorders; neuropsychological alterations; dementia; depression.

Introduction

Deep brain stimulation has gained increasing attention over the last years particularly for treatment of movement disorders, but also other diseases could potentially be treated with DBS, particularly neuropsychiatric disorders.

A well known part of the natural history of PD is mental deterioration. Cognitive deficits are observed very frequently in Parkinson's disease (PD): in some studies, more than 90% of the patients were impaired compared to matched normal controls [25]. The cognitive changes are an important predictor for quality of life [28].

Correspondence: H. Maximilian Mehdorn, M.D., Ph.D., Department of Neurosurgery, University Clinics of Schleswig-Holstein Campus Kiel Schittenhelmstr. 10 D – 24105 Kiel, Germany.
e-mail: mehdorn@nch.uni-kiel.de

Between 15 and 20% of PD patients develop a frank dementia [1]. However, also less severe cognitive impairment is a well recognized feature of the disease. Cognitive deficits may be prominent even in early stages of the disease [22] and were actually found in first-degree relatives without PD [13].

PD patients without dementia predominantly exhibit impairments in executive functions. Executive functions are higher-level cognitive processes involved in cognitive control and are mainly executed by the frontal lobes [15]. Impairments in cognitive functions tend to show up globally, affecting all aspects of cognition and behaviour.

The underlying pathology lies within the disturbances of the frontal-subcortical circuits due to the loss of dopaminergic cells within the substantia nigra [2, 6, 20]. Fronto-striatal circuits connect the frontal lobes with the basal ganglia and mediate not only motor, but also cognitive and behavioural programs.

It is obvious that neuropsychological alterations of potential candidates may have an impact on the outcome of surgical interventions. Although they aim at the basal ganglia with the intention to improve motor functions they may affect these delicate circuits resulting in alterations of neuropsychological or even neuropsychiatric importance. These interferences may become important from a surgical point of view in three regards:

1. patient selection for surgery
2. acute side effects during surgery
3. outcome following surgery

These aspects will be discussed on the basis of our own experience as well as those of others (More extensive review s. 23).

Table 1. *Patients treated with DBS from January 1999 to June 2007 at Kiel*

Underlying disease	Total number of patients	Mean age of patients (years)
PD	234	59.8
Dystonia	52	43.5
Essential tremor	23	67.3
ED-related tremor	27	38.5
Cluster headache	2	43.0
Others	15	58.0

Material and methods

In our centre we have, between January 1999 and June 2007, performed 353 DBS operations on patients with a variety of disorders which are listed in Table 1.

Our centre has initiated and participated in a series of multi-centre studies investigating the benefits and risks of DBS in order to clarify its role for various conditions (e.g., improvement of PD due to DBS compared to best medical treatment or stimulation related improvement in dystonic patients compared to those with sham stimulation).

The indications for DBS in PD were those commonly agreed upon. Surgical techniques may vary slightly from site to site, our techniques have also been described in detail [21]. From a neuropsychological point of view it is important to note that patients with dementia or those thought unable to actively cooperate during the procedure are excluded from surgery since the major part of DBS in PD is performed under local anaesthesia.

Neuropsychological evaluation before and after the operation includes Mini Mental score, Mattis dementia rating and if possible additional tests. The patients are followed as outpatients in a regular fashion and are re-admitted to our centre e.g., for exchange of the pulse generators.

Results

Patient selection for surgery

From all patients admitted to our centre for possible DBS, approx. only 10% are considered candidates for DBS and eventually undergo the procedure. A variety of reasons account for this low number of surgical candidates: a majority is thought to be not sufficiently well treated medically, i.e., medical therapy could be optimized; approx. 20% are thought to have contraindications against surgery because of poor mental status – often presenting with a MRI scan presenting cerebral atrophy to such a degree that placement of DBS electrodes is considered to harbour extensive risk of cortical vessel injury or ventricular passage by the electrodes.

Acute side effects during and after surgery

Depending on the site of microelectrode placement into the subthalamic nucleus resp. its vicinity a variety of unwanted symptoms can be provoked: mania, euphoria and laughter when the posterior dorsal part of the STN is stimulated [18] and hypomania up to depression and anxiety [3] when the substantia nigra is stimulated. Using multi-trajectory microelectrode recordings (MER) and test-stimulation with up to five electrodes, to delineate the borders of the STN, we have observed only in one single patient such a side effect as unexplained happiness and laughter as well as tears.

Our group [32] studied the acute effects of DBS to the STN vs. a single L-Dopa dose upon symptoms of depression and hedonic tone and observed that, while depressive symptoms improved to the same extent under both therapies, hedonic tone improved only with L-dopa.

Outcome following surgery

Few larger studies have been concerned about neuropsychological alterations. Mallet *et al.* [19] stimulated the ventral posterior (limbic) part of the STN and were able to alleviate symptoms of obsessive compulsive disorder (OCD), in addition to symptoms of PD in 2 patients. On the other hand, Dujardin *et al.* [11] studied patients who had undergone DBS to the STN and found reduced emotional facial expression decoding capacities. They postulated that such restrictions might influence later social life.

Schneider *et al.* [27] have shown that DBS of the STN enhances emotional processing in PD patients which is in contrast to the findings of Dujardin *et al.* [11]. Also conflicting data are published with regards to the development of cognitive functions which were found to decline [29] while others had seen no alterations over time [8, 16]. The recently published multicentre study on STN DBS [9] particularly studied the benefit concerning quality of life. Highly significant improvement was noted in the surgical group concerning the parameters which constitutes PDQ-39, i.e., mobility, activities of daily living, emotional well-being and stigma, while significant improvement was noted concerning bodily discomfort. On the other hand it needs to be noted that one patient in the surgical group committed suicide 5 months after DBS while a patient in the medically treated group died from a car accident which he had provoked during a psychotic episode. Also, transient symptoms of depression were noted in two surgical patients and in eight medical patients. Patients who had undergone DBS from our centre within the framework of this study were evaluated closely by Mattis dementia scale, and there was no statistical difference for a follow-up period of 6 months.

Discussion

Patient selection for DBS on the basis of neuropsychological considerations alone is certainly not the standard today; however, these considerations need to be taken into account seriously since, as Perriol *et al.* [24] state, the current implantation procedure does not fully take into account the functional heterogeneity within the target. There are, however differences between various targets: while the STN is closely related to neuropsychologically relevant areas and circuits, the GPi does not seem to be so closely related: Vidailhet *et al.* [31] did not see any change of mood and cognition three years after bilateral pallidal DBS for generalized dystonia while slight improvements were noted in concept formation, reasoning, and executive functions. On the other hand, members of the same group had noted a 30% overall decline of cognitive functions 3 months after DBS surgery [12].

Especially three circuits are held responsible for these conspicuities. The first circuit links basal ganglia and dorsolateral prefrontal cortex and leads to dysexecutive syndromes (e.g., deficits in planning, metacognition, self-monitoring or strategic functions). The second circuit connects basal ganglia and the anterior cingulate cortex and accounts for symptoms of apathy (e.g., slowdown of cognitive speed, deficits in initiation, productivity and spontaneity). The third circuit links basal ganglia and orbitofrontal cortex, resulting in symptoms of disinhibition (e.g., distractibility, stimulus-driven behaviour as well as deficits in feedback utilization, decision making and social functions) [for reviews, see 10, 26, 33]. Other common cognitive deficits (e.g., memory, language or visuospatial functions) are usually thought to be secondary to the named difficulties or reflecting cortical Lewy body pathology as well as changes in other transmitter systems [e.g., 5, 17, 33]. An exception lies within procedural learning which is mainly subserved by the basal ganglia and often impaired in PD [14].

Despite good knowledge about the underlying pathology, predictions about the cognitive sequelae of the individual are difficult to make. The population of Parkinson patients is extremely heterogeneous. Many factors have been proved to influence the cognitive profile, including patients' age, age at onset of the disease, duration and severity of PD, premorbid intelligence, level of education, motor symptoms, medication, on- and off-stages or accompanying psychiatric disorders like depression [4, 7, 22, 30]. Also, from a neurosurgical point of view it remains to be determined whether there may be additional or other targets among the above mentioned areas and circuits to optimize benefit of DBS for the patients. Close cooperation between neurosurgeons, neurologists and neuropsychologists will open up new exciting avenues.

Conclusions

The data regarding neuropsychological evaluation of patients who have undergone DBS to various targets need to be further clarified in order to better select the best target for DBS in a variety of disorders, and the patients, their relatives and their doctors need to be informed about the possible sequelae concerning neuropsychological disturbances in order to better decide on an individual basis how to cope with possible problems and to follow the patients with the goal of major sustained improvement of quality of daily living.

References

1. Aarsland D, Tandberg E, Larsen JP, Cummings JL (1996) Frequency of dementia in Parkinson's disease. Arch Neurol 53: 538–542
2. Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 9: 357–381
3. Bejjani BP, Damier P, Arnulf I, *et al* (1999) Transient acute depression induced by high-frequency deep-brain stimulation. N Engl J Med 340: 1476–1480
4. Braak H, Rub U, Del Tredici K (2006) Cognitive decline correlates with neuropathological stage in Parkinson's disease. J Neurol Sci 248: 255–258
5. Calabresi, P, Picconi B, Parnetti L, Di Filippo M (2006) A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine-acetylcholine synaptic balance. Lancet Neurol 5: 974–983
6. Carbon M, Marie RM (2003) Functional imaging of cognition in Parkinson's disease. Curr Opin Neurol 16: 475–480
7. Cohen OS, Vakil E, Tanne D, *et al* (2007) Educational level as a modulator of cognitive performance and neuropsychiatric features in Parkinson's disease. Cognit Behav Neurol 20: 68–72
8. Contarino MF, Daniele A, Sibilia AH, *et al* (2007) Cognitive outcome 5 years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 78: 248–252
9. Deuschl G, Schade-Brittinger C, Krack P, *et al* (2006) German Parkinson Study Group, Neurostimulation Section A randomized trial for deep brain stimulation in Parkinson's disease. N Engl J Med 355: 896–908
10. Dubois B, Pillon B (1997) Cognitive deficits in Parkinson's disease. J Neurol 244: 2–8
11. Dujardin K, Blairy S, Defebvre L, *et al* (2004) Subthalamic nucleus stimulation induces deficits in decoding emotional facial expressions in Parkinson's disease. J Neurol Neurosurg Psychiatry 75: 202–208
12. Dujardin K, Defebvre L, Krystkowiak P, *et al* (2001) Influence of chronic bilateral stimulation of the subthalamic nucleus on cognitive function in Parkinson's disease. J Neurol 248: 603–611

13. Dujardin K, Degreef JF, Rogelet P, *et al* (1999) Impairment of the supervisory attentional system in early untreated patients with Parkinson's disease. J Neurol 246: 783–788
14. Dujardin K, Laurent B (2003) Dysfunction of the human memory systems: role of the dopaminergic transmission. Current Opin Neurol (16 Suppl) 2: S11–S16
15. Funahashi S (2006) Prefrontal cortex and working memory processes. Neuroscience 139: 251–161
16. Funkiewiez A, Ardouin C, Caputo E, *et al* (2004) Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 75: 834–839
17. Gibb WR, Luthert PJ, Janota I, Jantos PL (1989) Cortical Lewy body dementia: clinical features and classification. J Neurol Neurosurg Neuropsych 52: 185–192
18. Krack P, Kumar R, Ardouin C, *et al* (2001) Mirthful laughter induced by subthalamic nucleus stimulation. Mov Disord 16: 867–875
19. Mallet L, Mesnage V, Houeto JL, *et al* (2002) Compulsions. Parkinson's disease, and stimulation. Lancet 360: 1302–1304
20. Mega MS, Cummings JL (2001) Frontal subcortical circuits: anatomy and function. In: Salloway SP, Malloy PF, Duffy JD (eds) The frontal lobes and neuropsychiatric illness. American Psychiatric Publishing, Washington, pp 15–33
21. Mehdorn HM, Pinsker MO, Volkmann J, *et al* (2005) Deep brain stimulation for idiopathic or secondary movement disorders. Acta Neurochir Suppl 93: 105–111
22. Muslimovic D, Post B, Speelman JD, Schmand B (2005) Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 65: 1239–1245
23. Okun MS, Rodriguez RL, Mikos A, *et al* (2007) Deep brain stimulation and the role of the neuropsychologist. Clin Neuropsychol 21: 162–189
24. Perriol MP, Krystkowiak P, Defebvre L, *et al* (2006) Stimulation of the subthalamic nucleus in Parkinson's disease: cognitive and affective changes are not linked to the motor outcome. Parkinsonism Relat Disord 12: 205–210
25. Pirozollo FJ, Hansch EC, Mortimer JA, *et al* (1982) Dementia in Parkinson's disease. A neuropsychological analysis. Brain Cognit 1: 71–83
26. Saint-Cyr JA (2003) Frontal-striatal circuit functions: context, sequence, and consequence. J Int Neuropsychol Soc 9: 103–127
27. Schneider F, Habel U, Volkmann J, *et al* (2003) Deep brain stimulation of the subthalamic nucleus enhances emotional processing in Parkinson disease. Arch Gen Psychiatry 60: 296–302
28. Schrag A, Jahanshahi M, Quinn NP (2000) What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatr 69: 308–312
29. Schupbach WM, Chastan N, Welter ML, *et al* (2005) Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. J Neurol Neurosurg Psychiatry 76: 1640–1644
30. Ueckermann J, Daum I, Peters S, *et al* (2003) Depressed mood and executive dysfunction in early Parkinson's disease. Acta Neurol Scand 107: 341–348
31. Vidailhet M, Vercueil L, Houeto JL, *et al* (2007) French SPIDY study group. Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. Lancet Neurol 6: 223–229
32. Witt K, Daniels C, Herzog J, *et al* (2006) Differential effects of L-dopa and subthalamic stimulation on depressive symptoms and hedonic tone in Parkinson's disease. J Neuropsychiatry Clin Neurosci 18: 397–401
33. Zgaljardic DC, Borod JC, Foldi NS, *et al* (2003) A review of the cognitive and behavioural sequelae of Parkinson's disease: relationship to frontostriatal circuitry. Cognit Behav Neurol 16: 193–210