

# Neuropsychological evaluation of deep-brain-stimulation in patients with parkinson's disease or essential tremor

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**Abstract** The implantation of a deep brain electrode for functional deactivation of the nucleus ventralis intermedius (VIM) results in a suppression of tremor which is one of the main symptoms of parkinson's disease (PD) or essential tremor (ET).

This elegant method is not completely risk-free. In addition to complications as bleedings and hemiparesis, cognitive impairments have been described.

Since february 1996 implantations of chronic deep brain electrode have been performed in 15 cases in the neurosurgical clinic of the Evangelical hospital in Oldenburg.

A careful neuropsychological evaluation was undertaken: An extensive neuropsychological diagnostic examination was performed pre and post surgery to examine the differential effects of the stimulation on the cognitive capacity respectively to detect undesirable side effects. Special emphasis was placed on mnemonic functions and attention. In this paper we would like to emphasize on the effect of stimulation on the patients cognitive capacity.

**Index terms** Parkinson's disease (PD), essential tremor (ET), stimulation of VIM, cognitive impairments.

## I. INTRODUCTION

Essential tremor is a chronic neurological condition whose sole symptom is trembling of a body part (most often both hands, head or lower jaw). It is the most common movement disorder and frequently runs in families. It is interpreted as an exaggeration of physiological tremor because of a hypersensitivity of betaadrenergic receptors (Poock [1]).

The major effect in PD is loss of the mesostriatal dopamine pathway with less major alterations in the mesocortical dopamine and locus coeruleus noradrenaline pathway. The main symptoms of idiopathic PD are

- *akinesia* which is described as poverty of movements, as bradykinesia which means a motor slowing and the inability to change started movements or to finish them,

- *rigidity* which refers to a resistance to passive movements and is due to an increase of muscular tonus and resting, static *tremor*. It is a low frequent, rhythmic tremor which occurs most often in one or both hands. Willed movements temporarily suppresses it and stress increases it.

Further symptoms are

- *autonomic disturbances* and
- *psychological disturbances* such as depression, dementia, psychotic symptoms and cognitive impairments.

## II. RESULTS OF NEUROPSYCHOLOGICAL RESEARCH IN PARKINSON'S DISEASE PATIENTS

Today many studies have established the view that non-demented patients with idiopathic PD even of an early or middle stage of the disease develop various neuropsychological deficits across a range of cognitive functions. We would like to describe in short the main findings:

- Some of these impairments closely resemble those commonly attributed to frontal lobe dysfunction, but are not as severe as in patients with frontal lobe lesions. Set-shifting and set-formation (Downes [2]) often tested with the Wisconsin Card Sorting Test (WCST [3]) is impaired. Set means the state, which enables a person to react in a specific way if there are reaction-alternatives. You can also say it is the ability to attend to a specific stimulus dimension. The patients show more non- and perseveratoric errors and select not as much categories as controls. The performance of the patients is disturbed only when there are no external information for the shift, when they have to generate effective strategies for the shift internally. Their performance in matching-to-sample-tasks is preserved.

Some results show that PD patients have problems in planning simple and complex movements (movement-sequencing, Sullivan [4]). Their premotor reaction times are prolonged in simple, but not in choice-reaction paradigms which means that they can not use cues effectively in order to decrease their reaction times.

PD patients show problems in temporal ordering and time estimation, due to their increased temporal discrimination threshold. The ability to develop a successful approach to problem solving is reduced in treated PD (Morris [5]). Performance on the tasks varies across patients, however: Some patients in early stages of PD show no impairment (Canavan [6]), but others do.

- Some of the visual spatial deficits found in patients suffering from PD are due to specific impairments in motor-programming and performance, but cognitive dysfunction have been found in the domain of visuospatial perception even when no intellectual deficit is present and the tests include no motor component (e.g. Boller [7]).
- PD patients show visuomotor disabilities. Research of eye movements are correlated with the research of motor programming. External triggering of saccadic eye movements plays the major role. There is e.g. an increased dependence of saccadic eye movements on external cues, due to an impaired disinhibition process in PD patients.
- In memory capacity, PD patients show impaired verbal and non-verbal short-term recall (Sullivan and Sagar [8]), deficits in working memory, recognition and associative learning (Sahakian [9]), but relative preserved long-term recognition (Sullivan and Sagar [10]). Long-term recall is mildly impaired and the capacity to date past events is disproportionately disrupted (Sagar [11]). Procedural learning is mildly impaired in non-demented PD-patients (Heindel [12]) and they show slowed scanning on visual recognition tasks (Wilson [13]). The main problems of PD patients in memory and learning seems to be the input of new information and their encoding according to internal schemes, which is a function of the frontal lobe.
- Language processing (e.g. object naming and vocabulary) and comprehension are, in general, preserved; defective performance on language tests may be due to impaired self-generation (Matison [14]) and motor dysfunction. E.g. researchers found decreased language production and semantic fluency, when the criterion for recall was alternating. This is taken as a hint for a deficit of inhibitory attention processes and a deficit of maintaining internal performance-relevant representation. PD patients often show speech problems (dysarthric speech) and in writing they show micrographia (also called: amyostatic syndrome).
- There are findings of a reduced rate of information processing in PD patients. E.g. Zimmermann (1992) found a disproportional increase of only simple reaction times in untreated PD patients in early stages with no cognitive impairments. Patients with slight cognitive impairments were additionally impaired in automatic and controlled processing and motor programming. Slowing on motor response tasks may reflect both bradykinesia and a central defect of motor programming, but the concept of bradyphrenia itself is controversial.
- Results of the research of attention (e.g. selective attention in the visual modality) are inhomogeneous: E.g. some researchers found a deficit of maintenance of attention and

overall prolonged reaction time (Sharpe [16]), but others did not.

- General intelligence as measured by the WAIS-R is relatively intact, particularly in terms of verbal intelligence.

The relationship between motor and cognitive disorders of PD is controversial:

E.g. positive associations have been shown between severity of bradykinesia and visuospatial deficit, in contrast to tremor severity, which paradoxically correlated with good spatial memory (Mortimer [17]). In a large longitudinal study presence of cognitive deficits was associated with hypokinesia and rigidity, rather than tremor (Portin [18]). Other researchers could not confirm these results (Mortimer [19]).

In comparison with patients suffering from other chronic medical disorders a higher proportion of patients with PD shows evidence of depression. Starkstein [20] reports a rate of 21% with major and 20% with minor depression in his prospective study. Some researchers found, that motor disability correlates strongly with the severity of depression but weakly with cognitive impairment, which was not associated with depression (Cooper [21]). Because of these findings depression is often interpreted as a reaction to the physical disability the patient experience. But other results show, that the severity of depression does not bear a strong relationship to the extent of physical disability, but does relate to cognitive dysfunction (Stern [22]). This suggests that depression is an intrinsic part of the disease process. Anyway depression is a common phenomenon in PD and should be taken into consideration when evaluating test performance.

The results of research of the effect of long term medication on cognitive capacity have been conflicting too: Neuropsychological deficits are not likely to improve with medication, which means that cognitive performance seems to be independent of an intact dopaminergic system.

### III. TREATMENT OF THE SYMPTOM: TREMOR

The implantation of a deep brain electrode for functional deactivation of the nucleus ventralis intermedius (VIM) results in a suppression of tremor. The permanent stimulation leads to a deactivation of the neurons due to depolarization (Pollak et al. [23]). This elegant method is not completely risk-free: In addition to complications such as bleedings and hemiparesis, cognitive impairments have been described: Especially in cases of implantation in the left cerebral hemisphere a reduction of linguistic abilities (in first case: loudness and articulation) has been reported (Benabid et al. [24]).

The thalamic stimulation of the VIM has been applied on 17 patients in Oldenburg by now and we performed 9 unilateral and 8 bilateral with five of them in one surgical session. One patient underwent a contralateral thalamotomy 19 years ago.

### IV. METHOD

#### A. Remarks to the surgical procedure

Detailed description of the surgical treatment we performed can be found elsewhere (e.g. Benabid [24]).

Our experience with fixing the stereotactic frame in a short anesthesia (Dormicum) is very good. The patients do report a significant lower stress-level after the surgical treatment and there are no difficulties to get the people awoken and to reproduce the tremor, when the electrode has to be positioned.

### B. Procedure

In general the patients have to stay nearly 24 days in clinic for treatment. The electrode implantation is done in an average of one week and the generator is implanted nearly 4 days later (see figure 1.).

Because of the findings, that PD patients even in early stages of disease show cognitive impairments as described before we perform an extensive neuropsychological examination before treatment to be able to assess the differential effect of stimulation on cognitive capacity. This is also done to exclude patients with dementia. Emphasis was placed on global cognitive functions as well as mnemonic and attention functions. We used the Hamburg-Wechsler Adult Intelligence Test-Revised (Tewes [25]), the Testbatterie zur Aufmerksamkeitsprüfung (Zimmermann et al. [26]) and the California Verbal Learning-Test (CVLT, Hildebrandt [27]).

After surgery neuropsychological tests are additionally done to detect even slight side effects such as visual disorders or speech dysfunction. We found, that the examination situation is very useful for adjusting the parameters of stimulation. In general the voltage amplitude is set between 1 and 5 volts, pulse width between 60 and 200 microseconds and pulse frequency between 130 and 180 HZ.

Quantification of the tremor was achieved by rating with the Clinical Tremor Rating Scale (Fahn et. al. [28]) before and after treatment and by videotaping.

Depression was quantified with the Beck-Depression Inventory (BDI, Hautzinger et al. [29/30]).

We used parameter-free tests (Mann-Whitney-U-Test) for statistical analysis because of our small patient groups. An Anova was also used to be able to take the effect of depression into consideration.

### C. Description of the patients

Nine of our patients suffered from PD, six patients from essential tremor, one patient suffered from Multiple Sclerosis and one patient from tremor after pontomesencephal bleeding. We will report the results for the both main patient groups here only. There was only a significant difference between disease duration of patients with PD and essential tremor. Further information about the patients can be seen in figure 2.

The severity of PD (see figure 3.) is rated according to the Scale of Hoehn and Yahr (Hoehn & Yahr [31]).

## V. RESULTS

We had to replace the electrode in two cases because of the appearance of visual side effects but had no permanent complication.

- The effect of stimulation on *tremor* is seen in figure 4. It was rated according to the Clinical Tremor Rating Scale which includes the rating of performance in activities of daily living (Fahn et al. [29]). The effect of electrode implantation on tremor severity was significant for both groups (significance level for PD:  $p = 0.008$ , significance level for ET:  $p = 0.043$ ).
- *Depression* (figure 5.): We found with using the Beck-Depression Inventory (BDI) no clinically relevant depression in PD or ET groups and no significant difference between the severity of depression between PD and ET patients. There was also no significant effect of surgical treatment on the depression score of the patients.
- *General Intelligence* (figure 6): The level of performance of ET patients was slightly better than the performance of PD patients. But the level of difference between PD and ET patients in the performance part of the WAIS-R failed significance (significance level:  $p = 0.066$ ). If taken into consideration the depression score as a covariant there was a significant difference between the patient groups (kind of disease:  $p = 0.019$ ) and a significant influence of the covariant (depression:  $p = 0.028$ ) which was mainly due to the subtest „picture ordering“ (effect of the covariant depression:  $p = 0.067$ , kind of disease:  $p = 0.085$ ) and „object assembling“ (effect of the covariant depression:  $p = 0.028$ , kind of disease:  $p = 0.051$ ).
- *Mnemonic functions*: The performance in short term recall tested with the subtest „digit span“ of the WAIS-R was significantly impaired in both groups after treatment (PD:  $p = 0.047$ , ET:  $p = 0.003$ , compare to figure 7). But taking depression into consideration there was no significant influence of surgical treatment. Verbal learning (figure 8), recall and recognition was tested with the California Verbal Learning Test [see for a detailed description of the test: Hildebrand et al [27]: There was no significant difference between PD and ET patients before treatment, but we found a significant covariance of depression for errors in free recall (effect of depression on free recall:  $p = 0.001$ ). The ability to recall was significantly reduced for PD patients after implantation (figure 9, free recall in PD:  $p = 0.037$ , cued recall in PD:  $p = 0.05$ , prolonged free recall in PD:  $p = 0.020$ ), but failed significance for ET patients (free recall in ET:  $p = 0.063$ , cued recall in ET:  $p = 0.066$ ). Prolonged recall was not changed significantly for ET patients (free recall in ET:  $p = 0.066$ , cued recall in ET:  $p = 0.066$ ). There was a significant difference between the patients groups and the side of implantation for errors in the interference trial (kind of disease:  $p = 0.023$ , side of implantation:  $p = 0.005$ ). The performance in recognition was significantly dependent on the covariant depression (effect of the covariant depression:  $p = 0.024$ ) for both groups. The error-level in recognition was

significantly increased in ET patients ( $p = 0.042$ , see figure 10) after treatment, but failed significance for PD patients ( $p = 0.058$ ).

- **Attention** was tested with the „Testbatterie zur Aufmerksamkeitsprüfung“ (TAP, Zimmermann and Fimm, 1993): **Simple reaction task** (Alertness): In this test the patients have to answer simple visual stimuli with or without cueing as fast as they can. Before treatment the patients with ET profit more from cueing than PD patients in this task (profit score:  $p = 0.012$ ). The profit from cueing was significantly increased for ET-patients after treatment ( $p = 0.042$ ) as you can see in figure 11. The implantation of the deep brain electrode reduced the speed of PD patients in the cueing condition significantly ( $p = 0.05$ ). The side of implantation had a significant effect on the profit from cueing (profit score: side of implantation:  $p = 0.005$ , kind of disease  $p = 0.087$ , combined main effect:  $p = 0.010$ , figure 12). **Working memory**: The test require active holding and manipulation of verbal information at the same time. The patients were impaired in all tasks of complex attention measures (figure 13). The covariance of depression score and

missing in working memory was significant after surgical treatment ( $p = 0.032$ ). The missing increased significantly after treatment for PD patients ( $p = 0.042$ ) but not for ET patients ( $p = 0.066$ ). **Divided attention**: In this test the patients have to react to visual and acoustic stimuli at the same time. There was a significant effect of the side of implantation on the reaction time in the divided attention task ( $p = 0.005$ ). The main effect of kind of disease failed significance ( $p = 0.080$ ). This was also true for the errors in a task of **mental flexibility** (side of implantation:  $p = 0.043$ , kind of disease:  $p = 0.055$ ).

## VI. DISCUSSION

Every patient was very satisfied after surgery. The patients who received a short global anesthesia during fixation of the stereotactic frame reported not as much stress and pain as those who received only local anesthesia, so it is an integral part of the surgical treatment in our clinic now when implanting a deep brain electrode.

Figure 1. Clinical stay for treatment

Days in clinic	mean	SD
before electrode placement	6,53	2,59
till generator implantation	9,56	4,05
post implantation	7,24	7,24
total	23,71	5,57

Figure 2. Profile of study subjects

groups	f/m	Age (Y,M/SD)	Education (Y,M/SD)	Disease duration (Y,M/SD)
Parkinson´s disease (n = 9)	3/6	63,4/10,1	9,4/1,2	8,1/7,1
Essential tremor (n = 6)	4/2	67,2/7,7	9,67/1,4	18,9/13,2*
other (n= 2)	2/0	61,5/5	10	8,8/11,6
Total (n = 17)	9/8	64,5/8,7	9,6/1,2	12/10,8

Figure 3. Rating of tremor severity

### Severity of Parkinson´s disease Hoen and Yahr motor disability rating

stages	PD (n)
stage 1.	1
stage 2.	4
stage 3	1

To sum up we found a significant effect of the deep brain stimulation on tremor severity, which improved the performance of the patients in activities of daily living significantly.

We found no clinically relevant depression in our both patient groups, but only moderate depression symptoms, which may be the reaction to the fact of being chronically ill. The two groups, PD and ET patients, did not differ in their depression score. That argues against the view, that depression is an intrinsic part of Parkinson's disease.

The patients with ET performed slightly better than the PD patients in the measures of global intelligence tested with the WAIS-R. But only if taken depression into consideration as a covariant, there was a significant difference between PD and ET patients in the performance part of the test.

In memory capacity we found a significant reduction of performance in verbal short-term recall, but this was mainly due to the covariant depression and not due to the surgical treatment. The patient didn't differ in respect to verbal learning, recall and verbal recognition before treatment. The PD patients were impaired after treatment but not under the condition of prolonged cued recall. We found no significant effect of the side of implantation. The only significant influence of the side of implantation was found for the errors under the condition of interference. Depression covaried significantly with the performance in verbal recognition. ET patients produced more objects under the recognition condition, but also significant more false positives after treatment.

ET patients did profit more from cueing than PD patients in a simple reaction task before treatment. Their profit from cueing increased significantly after treatment. The treatment reduced the speed of PD patients in the cueing condition significantly. Implantation of a deep brain electrode in the right cerebral hemisphere resulted in a reduction of profit from cueing. The missings in a task of working memory were significantly influenced by the depression score after treatment. PD patients missed significantly more critical stimuli after treatment. The side of implantation had an effect on the reaction task in a task of divided attention (reduced speed after implantation in the right cerebral hemisphere, increased reaction times after implantation in the left cerebral hemisphere) and an effect on the error rate in a task of mental flexibility (fewer errors after implantation in the right cerebral hemisphere, increased reaction times after implantation in the left cerebral hemisphere).

During their stay in the clinic we questioned our patients about the subjective outcome of the treatment. Although slight impairments of verbal memory and parameters of attention could be found with neuropsychological tests only two of our patients recognized any impairments themselves. Seemingly they don't recognize their cognitive impairments due to the well structured situation they experienced during their stay in our clinic. We do believe that we have to examine our patients a third time after staying home for a longer period.

One problem of the treatment of tremor with the VIM stimulation is that the knowledge of the afferent and efferent connections of the VIM and the biochemical basis of PD does not provide an explanation for the role of the VIM nucleus in the arrest of

tremor during thalamic stimulation (see for a detailed discussion: Benabid [24]).

Our groups are very small and inhomogeneous so it is not easy to make any conclusions. We need more cases to confirm our results.

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Figure 4. The effect of chronical VIM-stimulation on tremor

Figure 5. Results of BDI

