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Alterations of non-motor symptoms in Parkinson's disease, after of subthalamic deep brain stimulation

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ABSTRACT

The effect of subthalamic deep brain stimulation (STN DBS) on motor symptoms of Parkinson's disease (PD) has been thoroughly analyzed. The influence of STN DBS on non-motor symptoms (NMS) is still debatable. We analyzed the effect of STN DBS on NMS in PD.

Materials and methods: 17 PD patients were qualified for STN DBS according to CAPSIT-PD criteria. Demographic data and clinical status according to the Hoehn–Yahr (H–Y) were recorded. The efficacy of STN DBS on NMS was measured with the NMS Scale before surgery and twelve months after surgery.

Results: Global NMS Scale score decreased by 1–75 points (mean 25,67) in 12 patients. No improvement or deterioration was reported in 5 patients (29%). The mean age of the improved group was 56 years and 59,8 years in the non-improved group. The mean duration of PD in the improved group was 11 years and 21 years in the non-improved group. In the non-improved group, four patients were rated 4 and one patient~~s~~ 3 according to the H–Y Scale. In the improved group, two patients were rated 4, six patients 3 and four patients 2 according to the H–Y Scale The most significant improvement of the NMS Scale was recorded in the domain IV- Perceptual problems/Hallucinations- (by 77%), domain I- Cardiovascular including falls- (by 68%) and domain III- Mood/Cognition- (by 58%). Deterioration of the NMS Scale was reported in the domain IX- Miscellaneous- (by 10%) and the domain VII- Urinary- (by 6%).

Conclusions: STN DBS has a positive impact on NMS among PD patients. The most important factors that influence improvement are: young age, short disease duration, and good clinical status measured with the H–Y Scale. The NMS Scale domains that tend to respond the best are the domains I, III and IV. The NMS Scale domains that might deteriorate after STN DBS are the domains VII and IX.

Parkinson's disease (PD) is one of the most common movement disorders and the second most common neurodegenerative progressive disease with age-dependent increasing prevalence (1–3% in the population aged over 65 years).[1] PD is a serious medical and socio-economic problem and remains incurable until today. Loss of dopaminergic neurons in substantia nigra-is considered a hallmark of PD.[1] It is believed that reduced dopaminergic input is responsible for the main motor symptoms of PD (bradykinesia, rigidity, resting tremor, and postural instability) and explains a remarkable clinical response to dopamine replacement therapy.[2] Progression of PD symptoms besides initial effective conservative treatment (pharmacological "honeymoon") led to a renaissance of neurosurgical neuromodulation that included deep brain stimulation (DBS). The introduction and popularization of DBS was the next milestone in the understanding and treatment of PD.[1] Until today the treatment of movement disorders ~~have~~ has focused on, and developed treatment algorithms that can extend patients' ~~life~~ lives and positively influence their quality of life by alleviating motor symptoms of PD.[3,4,5,1,2]

The development of the animal, laboratory model of PD in 1976, allowed us to identify alterations of direct and indirect cortical-basal-thalamic-cortical loops that are responsible for the development of PD symptoms. Recently it has become apparent that the neuropathological changes of PD extend beyond the basal ganglia system, affecting also the olfactory, limbic and autonomic systems with morphological changes in

Abbreviations: DBS, deep brain stimulation; LEDD, levodopa equivalent daily dose; NMS, non-motor symptoms; PD, Parkinson's disease; STN, subthalamic nucleus.

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the brain stem and cortex. Even though non-motor symptoms (NMS) of PD like: pain, fatigue, changes ~~of~~ in blood pressure, restless legs, bladder and bowel problems, skin sweating, sleep alterations, swallowing, and saliva control, communication issues and eye control remain essential, until recently were not in the main field of research.[6,7,8,9,10] NMS can be measured in a repeatable manner with the NMS scale provided by the Movement Disorders Society where: cardiovascular symptoms, alertness, mood, cognition, hallucinations, attention, memory, gastrointestinal tract symptoms, urinary and sexual functions, pain, taste and smell, weight changes and excessive sweating are evaluated.[11] The extra basal ganglia pathological changes of the brain are considered to be responsible for the NMS that influences the quality of PD patient's life.

1. Objectives

To evaluate the influence of STN DBS for PD on NMS. To identify a group of PD patients that will benefit the most from STN DBS in the aspect of NMS. To identify the domains of the NMS Scale those tend to respond the best and the worst to STN DBS for PD.

2. Materials and methods

Seventeen eligible PD patients[12] qualified by movement disorders specialists for STN DBS according to the CAPSIT-PD criteria[13] entered the study. Consent forms for the study were obtained before each interview. Ethics committee approval was not required as long as the NMS Scale provided by the Movement Disorders Society belongs to a standard test package of PD evaluation.[4,1,2] Demographic data were collected: initials, age, gender, disease duration, clinical status according to the H–Y Scale and date of birth of eight female and nine male patients were analyzed. The mean age was 57,17 (30–75 years old, standard deviation, SD = 12,084). The mean H–Y Scale score was 3,1 (four patients were rated 2, seven patients were rated 3 and six were rated 4, SD = 0,781). The mean PD duration before STN DBS was 12,76 (7–22 years, SD = 4789). The 30- questions NMS Scale evaluates nine domains of NMS in PD with a total score from 0 (no impairment) to 360. The presurgical interviews for the NMS Scale were carried out at the in-patient clinic before implantation. On the day before surgery, patients underwent MRI and CT. The stereotactic frame was placed under local anesthesia. MRI and CT images were fused with a neuronavigation system and the coordinates of STN were calculated using direct and indirect methods. During surgery the neurophysiological evaluation was conducted by a neurophysiologist and the neurological state of the subjects during macrostimulation ~~were~~ was evaluated by a neurologist at the operating theater. The characteristic pattern of STN was recorded bilaterally in each patient. Macrostimulation was performed later and permanent DBS electrodes were implanted. The internal pulse generators were implanted in the subject's chest. On the day following the surgery, a control brain CT scan was performed. The stimulation was initialized after implantation. The main outcome measure was the NMS Scale score. The interviews for the NMS Scale and adverse effects were carried out at the out-patient clinic six to twelve months after implantation. Two subgroups were identified.

- improved group: a group of patients with decreased global NMS Scale score,
- non-improved group: a group of patients with unchanged or increased global NMS Scale score.

3. Results

Seventeen patients completed evaluation before implantation and after STN DBS. All patients underwent standard battery tests following surgery that included UPDRS part III and psychological evaluation. LEDD (levodopa equivalent daily dose) and its changes were recorded before and after surgery. In the analyzed group of patients, the LEDD did change after surgery. The global NMS Scale score of the analyzed group decreased by 29%. Global NMS Scale score decreased by 1–75 points (mean 25,67, SD = 24,889) in 12 patients (71%) (Table 1, Fig. 1).

The non-improved group included four patients with an increased global NMS Scale score by 1–20 points (mean [14],25) and one patient had an unchanged NMS Scale score. The mean age of the non-improved group (comprising four females and one male) was 59,8 years (SD = 6685). The mean age of the group with reported improvement (which included four female~~s~~ and eight male patients) was 56 years (SD = 13, 846) (Table 1, Fig. 2). In the non-improved group, four patients were rated 4 and one patient 3 according to the H–Y. In the improved group, two patients were rated 4, six patients 3 and four patients 2 according to the H–Y Scale (Table 1). The mean duration of PD in the non-improved group was 17 years (SD = 4). The mean duration of PD in the group that reported improvement was 11 years (SD = 4) (Table 1, Fig. 3). The most significant improvement in the analyzed group was measured in the domain IV (Perceptual problems/hallucinations)- by 77%, in domain I (Cardiovascular including falls)- by 68% and domain III (Mood/Cognition)- by 58%. Deterioration was reported in the domain IX (Miscellaneous)- by 10% and the domain VII (Urinary)- by 6% (Fig. 4). No adverse effects related to the therapy were reported in the analyzed group.

4. Discussion

The progressive degeneration of the dopaminergic system in PD is responsible for the appearance of side effects caused by ~~the~~ long-term dopaminergic therapy, like motor fluctuations and dyskinesias. Those motor symptoms are poorly managed by ~~the~~ oral therapy and more than 10% of PD patients should be qualified for DBS.[13,1] The best candidates are those with severe motor fluctuations (severe off-medication conditions and substantial benefit from the L-dopa therapy). The main exclusion criteria are: suspicion of atypical ~~p~~ Parkinsonian syndrome or presence of psychiatric (depression, hallucinations) or cognitive alterations.[1] During the last three decades, functional neurosurgery has developed rapidly, mainly due to the introduction of DBS. Previously published studies have confirmed the significant improvement of motor symptoms observed in PD after STN DBS.[3,4,5,2] Long-term studies provided evidence that DBS - induced motor improvement was evident at 8 - year follow-up.[15,8] However, it has to be kept in mind that DBS does not modify the speed of PD progression. With time, patients can develop disabling motor and NMS symptoms.[7,16,17,9] NMS significantly impairs the quality of PD patients' life. NMS in PD have been more attentively analyzed in recent years, but the influence of DBS on those symptoms is not thoroughly evaluated and understood.[18,19,20] The ~~W~~ whole group of patients qualified ~~to~~ for the study met CAPSIT-PD criteria and suffered ~~of~~ from motor and non-motor symptoms. None subject of the analyzed group had psychiatric or cognitive alterations.

The DBS effect is mainly based on inhibiting the target structure (STN) that is excessively active and responsible for symptoms observed in PD. The main mechanisms of STN DBS are the depolarization blockade of neurons and axons (the inactivation of sodium ion channels), synaptic depolarization, antidromic release of GABA within the basal ganglia network, and activation of local inhibitory mechanisms within STN. The most significant feature of DBS is the reversible power of inhibition of hyperactive target structure. This explains why it is reasonable to implant DBS in the portion of the STN that is hyperactive. Neuroimaging methods of visualization of the STN use a high-field, 1,5T or 3T MRI. Direct visual STN identification is mainly based on high-resolution T2 axial scans. Indirect identification is based on the position of the anterior and posterior commissure and the walls of the third ventricle. MRI-based determination of the target point in the majority of cases is the same as one identified by intrasurgical neurophysiological evaluation. Selected reports indicate sole MRI to be sufficient for STN identification, although the majority of centers find neurophysiological evaluation during surgery (microrecording and macrostimulation) to be

Table 1
Patient's number, age, sex, duration of the disease (years), clinical status in the Hoehn–Yahr Scale score, clinical status in the Non Motor Symptoms Scale score: before and after surgery.

Subject No	Age (years)	Sex F- female, M– male	Duration of the disease (years)	Hoehn–Yahr Scale score	Non Motor Symptoms Scale score before surgery	Non Motor Symptoms Scale score after surgery
1	62	M	22	4	22	22
2	65	F	12	3	94	51
3	58	M	10	3	81	66
4	30	M	9	3	34	6
5	66	M	16	4	73	46
6	53	M	9	3	54	43
7	41	M	7	2	12	4
8	70	F	20	3	44	56
9	75	M	8	3	18	17
10	53	F	16	4	62	74
11	47	F	8	2	97	22
12	53	M	12	3	116	66
13	75	M	14	4	46	34
14	45	F	7	2	19	9
15	59	F	12	4	54	74
16	55	F	15	2	31	32
17	65	F	20	4	76	48

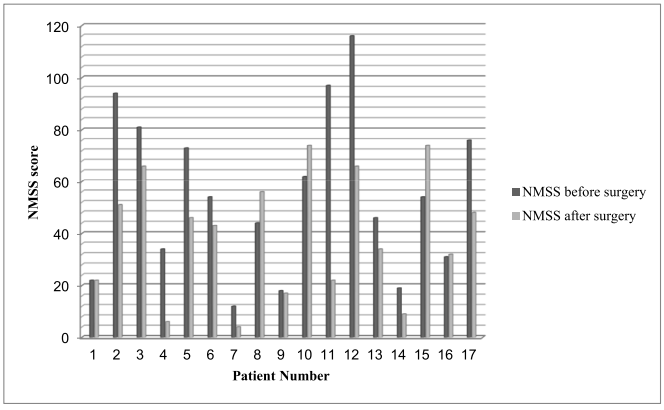

Fig. 1. The Non Motor Symptoms Scale (NMSS) (global) among 17 patients before and after surgery.

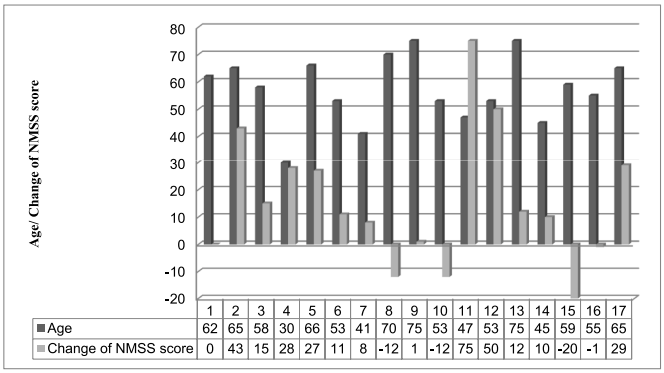

Fig. 2. Correlations between the Non Motor Symptoms Scale (NMSS) score (global) value changes (higher number-more significant improvement) and age of 17 patients. Better results were recorded among younger patients.

necessary to achieve maximal clinical benefit.[1] In the dedicated DBS centers for movement disorders, specific neuroimaging techniques and intraoperative neurophysiological evaluation are used routinely to maximize the therapeutic effect of the treatment and minimize the risk of adverse events. During the surgeries ~~y~~ of ~~patients~~ the ~~from~~ analyzed

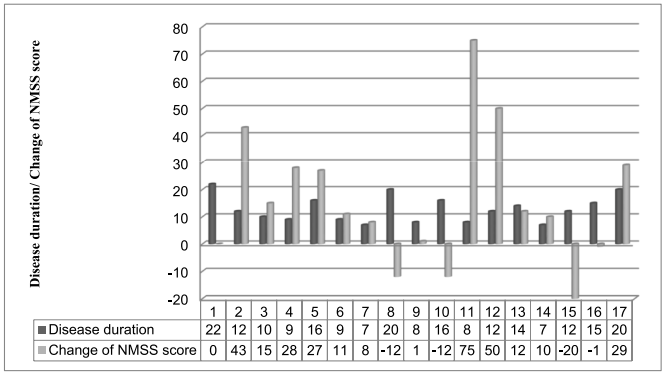

Fig. 3. Correlations between the Non Motor Symptoms Scale (NMSS) score value changes (higher number-more significant improvement) and duration of Parkinson's disease of 17 patients. Better results were recorded among patients with shorter duration of the disease.

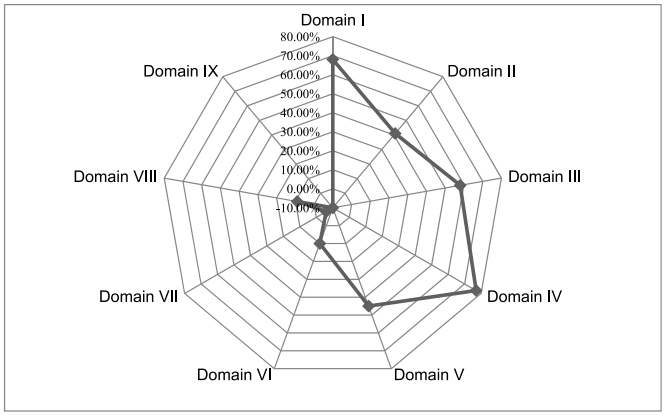

Fig. 4. Mean percentage changes following surgery of nine domains of Non Motor Symptoms Scale (NMSS) score among 17 patients. The highest improvement was recorded at domain IV(Perceptual problems/hallucinations) by 77%. The highest deterioration was recorded at domain IX (Miscellaneous) by 10%.

group all indicated and available techniques were used to maximize potential benefits and minimize the risk of adverse events.

The mechanism of DBS action is not completely understood. By inhibiting STN by DBS, the harmony between basal ganglia, thalamus and brain cortex is ~~being~~ restored (the cortical-basal-thalamic-cortical circuit). The presented mechanism of DBS explains the improvement of motor symptoms in PD.[1] The influence of DBS on NMS seems to be more complex. STN is a small structure of almond shape and size. In this deeply located structure, three portions are defined: the motor portion (target for the DBS treatment), the limbic portion (responsible for mood and its alterations) and the associative portion (responsible for cognitive functions). The size of a DBS electrode is that of a match (1.3 mm in diameter integrating four contacts of 1.5 mm length each, spaced with 0, 5 or 1,5 mm gaps and connected to the internal pulse generator implanted on the chest) and depending on the voltage amplitude might inhibit solely the motor portion of STN or the surrounding structures as well (for instance limbic or associative portion of STN) influencing appearance or disappearance of NMS.[16,1,21] The ~~S~~ standardized anatomical target for the electrode ~~at~~ in the presented study was the dorso-lateral (motor) portion of STN. Microrecording and macro-stimulation performed during surgery allowed to optimize the placement of permanent electrodes in depth (20 mm) and in a radius of 2 mm (anterior, posterior, central, lateral and medial path).

According to the CAPSIT-PD criteria,[13] patients qualified for DBS should be younger than 65 years of age. Recently the age regime has been widened making the biological age more important than the metrical age.[18] In the presented study six patients were 65 years old or older. Undoubtedly more advanced age carries a higher risk of adverse events and gives fewer chances for improvement in the motor and non-motor aspects of PD. In the presented study deterioration following DBS measured with the NMS Scale was reported in the advanced age group of patients (above 65 years of age). Disease duration was also indicated in the CAPSIT-PD criteria as one of the main elements of the qualification protocol. As long as PD is a progressive disorder, with time, the patient's condition measured with the H–Y Scale gets poorer. It has been reported by Schuepbach[22] that qualification for DBS at the early stage of the disease gives better results in the aspect of motor symptoms of PD. Better results measured with NMS were reported in the presented study, in patients with a shorter history of PD and in better clinical conditions measured with the H–Y Scale.[18,22,5]

The impact of STN DBS on the global score of the NMS Scale has been previously reported. This study confirms the positive effect of STN DBS on NMS.[23,7,8,9,10] The results for patient domains of the NMS Scale vary. In contrast to Dafsari et al, who reported no significant difference at a three years follow-up in domain I (Cardiovascular including falls) in the short - term study (three to six months) presented here, an improvement was registered in this domain mainly due to a decreased number of falls.[7] In the presented study improvement in domain II (Sleep/fatigue) was less significant and this result is in line with the study by Choi et al.[15] Improvement of domain II is mainly related to the improved quality of sleep. Lilleeng in contrast reported a decreased domain II score as a result of the worsening of fatigue.[19] However, this result might be limited by the fact that the conservative treatment remained high in his study at postoperative follow-up and sleep alterations and fatigue are common side effects of pharmacological treatment. On the other hand, DBS, by influencing cortical-basal-thalamic-cortical loops, might reduce directly nocturnal motor symptoms of PD. In contrast to previous evidence,[2] ~~at~~ in the presented study improvement in domain III (Mood/-Cognition) has been reported. The subjective improvement of those aspects in a short - term follow-up might be related to the motor improvement of the patients and their positive, high expectations regarding another DBS- related "honeymoon" (mood improvement has not been confirmed by objective, dedicated psychological tests).[2] The most significant improvement in domain IV in this study (Perceptual problems/hallucinations) that has been previously observed and reported by Yoshida et al might be related to the reduction of conservative treatment whereas hallucinations are reported to be one of its adverse effects.[24] Additional analysis needs to be undertaken to establish the relationship between hallucination outcome and conservative dopaminergic and psychotropic treatment, and its dependency ~~to~~ on other neuropsychiatric aspects of PD. Slight improvement in the presented study in domain V (Attention/Memory) further supports Zangaglia's results, however in the same study Zangaglia also reported verbal fluency performance deterioration after DBS.[20] Zangaglia indicated that logical executive function tasks might be impaired transiently after DBS as well. No significant changes in the domain VI (Gastrointestinal tract) in this, short-term study stay in opposition to Lilleng's study, who reported a lower prevalence of constipation in 24 months follow up.[17,19] Lilleng however, did not employ validated scales in his study. In the presented study deterioration of VII domain (Urinary) stays in opposition to Herzog's study. Herzog et al analyzed ameliorations of bladder functions in a short-term follow-up along with modulation of blood flow of the thalamus and brain cortex.[25] No significant improvement in domain VIII (Sexual function) goes in line with the results of Kurcova et al.[26,17] It is assumed that the impact of STN-DBS on sexual function mainly depends on demographic parameters like sex and age of the subjects.[17] In the presented study the most significant deterioration was recorded in domain IX (Miscellaneous). No pain reduction, and no changes in smell or taste were reported. A group of patients from the presented study reported increased sweating and decreased body weight and those might be related to increased involuntary movements (dyskinesias) observed in the short-term follow-up as a result of microleasion effect after surgery that fade away after several weeks.[6,7,4,10]

Adverse events related to the implantation of DBS are primarily intracranial bleeding (average risk is estimated at 2% in most reports) and infection (4%). STN DBS can harm speech and gait in a group of PD patients that require an adjustment of stimulation. STN DBS can affect mood, especially if mood alterations were reported before surgery-~~the~~ depression tends to worsen.[1] Several authors report that neuropsychiatric symptoms might appear after STN DBS (~~hipomania~~ hypomania, pathological gambling); however, those symptoms are usually transient if managed appropriately. While keeping those adverse events in mind, STN DBS is believed to give great symptomatic benefits in cognitively and psychiatrically intact PD patients.[1]

5. Conclusions

The study confirms that STN DBS has a positive effect on non-motor symptoms in Parkinson's disease measured with the Non-Motor Symptoms Scale. The most important factors that influence improvement measured with The Non-Motor Symptoms Scale after subthalamic deep brain stimulation among Parkinson's disease patients are: young age, short disease duration, and good clinical state measured with the Hoehn Yahr Scale. Non-Motor Symptoms Scale domains that tend to respond the best are domain IV (Perceptual problems/hallucinations), domain I (Cardiovascular including falls) and domain III (Mood/Cognition). The domains that might tend to deteriorate are: domain IX (Miscellaneous)- and domain VII (Urinary).

CRediT authorship contribution statement

Victor H. Mandat: Writing – original draft, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Paweł R. Zdunek:** Resources, Data curation. **Bartosz Krolicki:** Resources, Methodology. **Tomasz Mandat:** Writing – review & editing, Validation, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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