Deep brain stimulation electrode position impact on parkinsonian non-motor symptoms

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Background. In this study we evaluated the impact of location of deep brain stimulation electrode active contact in different parts of the subthalamic nucleus on improvement of non-motor symptoms in patients with Parkinson's disease.
Methods. The subthalamic nucleus was divided into two (dorsolateral/ventromedial) and three (dorsolateral, medial, ventromedial) parts. 37 deep brain stimulation electrodes were divided according to their active contact location. Correlation between change in non-motor symptoms before and one and four months after deep brain stimulation electrode implantation and the location of active contact was made.
Results. In dividing the subthalamic nucleus into three parts, no electrode active contact was placed ventromedially, 28 active contacts were located in the medial part and 9 contacts were placed dorsolaterally. After one and four months, no significant difference was found between medial and dorsolateral positions. In the division of the subthalamic nucleus into two parts, 13 contacts were located in the ventromedial part and 24 contacts were placed in the dorsolateral part. After one month, significantly greater improvement in the Non-motor Symptoms Scale for Parkinson's disease (P=0.045) was found on dorsolateral left-sided stimulation, but no significant differences between the ventromedial and dorsolateral positions were found on the right side.
Conclusion. This study demonstrated the relationship between improvement of non-motor symptoms and the side (hemisphere, left/right) of the deep brain stimulation electrode active contact, rather than its precise location within specific parts of the subthalamic nucleus in patients treated for advanced Parkinson's disease.

Key words: non-motor symptoms, Parkinson's disease, deep brain stimulation

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INTRODUCTION

The subthalamic nucleus (STN) and internal globus pallidus are the most common targets for deep brain stimulation treatment (DBS) in patients suffering from Parkinson's disease (PD). The effect on motor symptoms in advanced stage of PD are comparable[1-3]. Detailed segmentation of the subthalamic nucleus has been the object of several studies. Recent findings mostly suggest that the subthalamic nucleus should be divided into three anatomical/functional parts: sensorimotor and limbic which are probably located in dorsolateral and ventromedial portions respectively and the associative part between them; with the motor region having its own somatotopic organization[4,5]. The exact borders between them have not been established yet. The definite functions of each part are still the object of research, but it appears that stimulation of different parts of STN provide different impact on PD symptoms.

Recently, Dafsari et al.[6] used coordinates of the active electrodes and suggested that more anterior, medial and ventral subthalamic nucleus deep brain stimulation (STN-DBS) is related to more beneficial non-motor outcomes in patients with PD. Petry-Schmelzer et al.[7] also support the hypothesis that location of neurostimulation in PD on non-motor outcomes has an impact. In their study of mood/apathy and attention/memory domains of the non-motor symptom scale for Parkinson's disease, voxels associated with less improvement were mainly located dorsal to the subthalamic nucleus. The better improvement for mood/apathy was observed in the ventral border region of the subthalamic nucleus in the sensorimotor subregion and for attention/memory in the associative subregion. For the sleep domain, a trend was observed

showing voxels with above average improvement located ventral to the subthalamic nucleus.

The aim of this study was to test the effect of precise location of DBS electrodes within the STN on non-motor symptoms and was based on prior results from examination of the initial effect of STN-DBS on non-motor and motor symptoms; STN-DBS in patients with advanced PD clearly improved not only motor symptoms, but also several domains of non-motor functions, namely sleep, autonomic functions and quality of life[8].

MATERIAL AND METHODS

This prospective single institutional study was approved by the local ethics committee and was conducted according to the latest Declaration of Helsinki principles. The data from 24 patients who underwent bilateral STN-DBS were used. All patients gave their informed consent with the inclusion into the study and with the data analysis. All demographical data of the cohort were described in our previous paper[8].

The pre-surgery brain magnetic resonance and post-surgery computed tomography scans were uploaded into SureTuneTM (Medtronic Inc, Fridley, Minnesota, USA) system and then merged[9]. This process enabled us to directly visualize the subthalamic nucleus, DBS electrodes and their leads and provided exact location of each contact within the parts of subthalamic nucleus (Fig. 1). The longest axis of each nucleus was divided into parts with the same length; then each subthalamic nucleus from each patient was divided into parts by perpendicular lines. It has been decided to use the STN subsegmentation into three parts which was presented in the recent anatomical papers and then also use a simpler division into just two parts: ventromedial and dorsolateral. When STN was divided into three parts, the dorsolateral part represented the sensorimotor part, the medial part represented the associative and the ventromedial part represented the limbic part of the subthalamic nucleus[4,5]. Both abovedescribed processes were done manually using SureTuneTM software. Then the DBS electrodes were divided into groups according to the location of their active contacts. Electrodes with active contacts placed outside the subthalamic nucleus were excluded and also the electrodes in which the active contact (and thereby its location) was changed during the initial four months programming were excluded (six on the right side and five on the left side). The non-motor and motor symptoms have been evaluated using the dedicated questionnaires, as described into detail in our previous paper[8]. These were:

- Movement Disorder Society Unified Parkinson's Disease Rating Scale, (MDS UPDRS) part III: Motor Examination[10,11]
- Non-motor Symptom Scale for Parkinson's Disease (NMSS) (ref.[12])
- The Parkinson's Disease Questionnaire (PDQ-39) (ref.[13,14])
- Scales for Outcomes in Parkinson's Disease - Autonomic (SCOPA-Aut) Questionnaire[15]

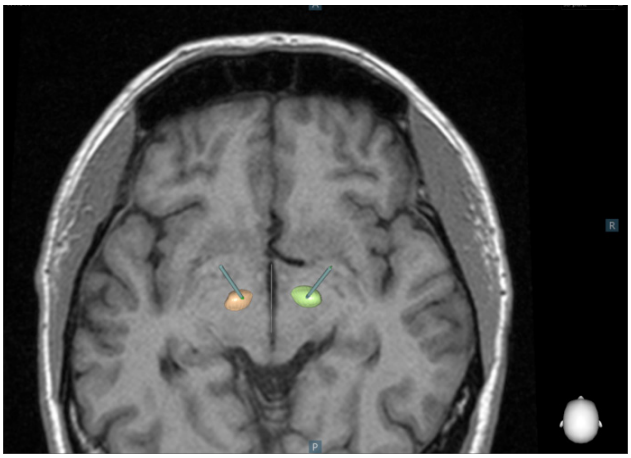

Fig. 1. Subthalamic nucleus (SureTune).

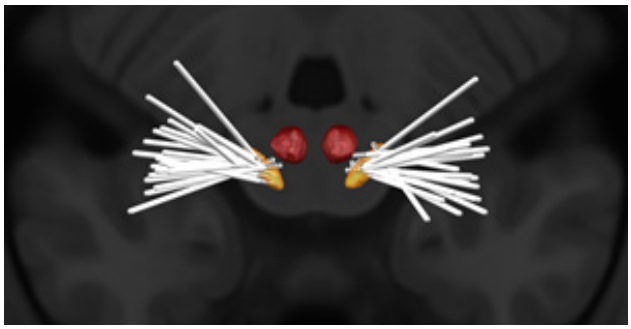

Fig. 2. Group level visualisation (Lead-DBS toolbox v2.2.3).

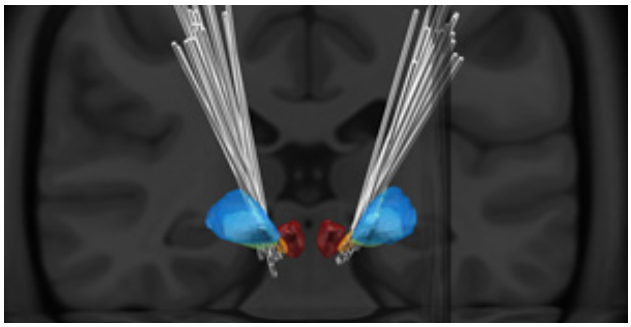

Fig. 3. Group level visualisation (Lead-DBS toolbox v2.2.3).

- The Parkinson's Disease Sleep Scale (PDSS) (ref.[16])
- International Index of Erectile Function (IIEF) (ref.[17])
- The Female Sexual Function Index (FSFI) (ref.[18])

The data were collected before the surgery, one month after the STN-DBS system implantation (just before the adjustment of initial stimulation parameters and the start of DBS treatment), and three months after the start of DBS treatment, i.e., four months following the implantation. Finally, the correlations between position of the active contact of the DBS electrode and change of non-motor symptoms and motor symptoms for each side were calculated, using the Mann-Whitney U tes and Fisher's test). Group level visualisation was performed using Lead-DBS toolbox v2.2.3 (https://www.leaddbs.org/) in MATLAB R2019b (MathWorks, Natick, MA) (Fig. 2, 3).

Table 1. Change in clinical scales after 1 month – left side, division into two parts.

	Left side – change after one month						
	ventromedial			dorsolateral			
	Median	Min	Max	Median	Min	Max	*P*
PDSS	8.0	-2	27	6.0	-24	37	0.567
PDQ-39	-11.5	-47	8	-9.0	-35	37	0.438
NMSS	**-10.0**	-41	5	**-28.0**	-46	-8	**0.045**
SCOPA-AUT	-2.0	-7	3	-2.0	-12	2	0.934
FSFI/IIEF	-0.1	-54	8	-1.0	-9	10	0.743
MDS-UPDRS	-4.0	-17	2	-4.0	-17	2	0.902

Table 2. LEDD (mg) before the onset of stimulation, after primary programming and after four months for all patients.

Patient.	LEDD before stimulation	LEDD after primary programming	LEDD after 4 months
1	1220	760	660
2	920	532	852
3	1365	1150	910
4	1810	692	692
5	1544	532	798
6	1318	798	798
7	1208	532	532
8	1388	500	500
9	1720	1410	1730
10	2076	998	998
11	753	426	426
12	1671	710	710
13	1746	998	998
14	480	240	240
15	1310	660	660
16	426	0	0
17	1160	798	798
18	1345	692	852
19	1145	692	426
20	1517	692	692
21	1238	692	692
22	1118	160	426
23	1038	958	1158
24	1810	692	692

Levodopa equivalent daily dose (LEDD) after one month (before primary programming and after) and at fourt month after the implantation was calculated for each patient and is shown in Table 2; the stimulation parameters are shown in the Table 3.

RESULTS

Originally, the data from 24 patients were included. After exclusion of electrodes with the active contact outside of the anatomical borders of STN and electrodes which could not be evaluated for other reasons (change of active contact during deep brain stimulation programming, etc.), the data from 37 electrodes were evaluated.

STN division into three parts

No electrode active contact was placed ventromedially, where limbic area is supposed to be located, 28 active contacts were located in the medial part of the STN and 9 contacts were found in the dorsolateral part of the STN. Finally, for each side the correlation of change in all used non-motor scales and the position of the active electrode contact were calculated.

After one month, no significant difference between active electrode contacts in the medial and dorsolateral position was found. After four months, no significant difference between active electrode contacts in the medial and dorsolateral position was found.

Table 3. Stimulation parameters after primary programming (month 1) and after four months (month 4) for each patient (active contact or contacts on the first row followed by intesity/frequency/pulse width).

Patient	Left side, month 1	Right side, month 1	Left side, month 4	Right side, month 4
1	1-2- 3.0V/130Hz/60μs	9- 2.0V/130Hz/60μs	1-2- 2.5V/125Hz/60us	9- 2.0V/125Hz/60μs
2	1- 3.8V/130Hz/60μs	9- 1.5V/130Hz/60μs	1- 3.8V/130Hz/60us	9- 1.8V/130Hz/60μs
3	2- 2.8V/130Hz/60 μs	9- 2.0V/130Hz/60μs	2- 3.1V/130Hz/60us	9- 2.3V/130Hz/60μs
4	2- 2.8V/130Hz/60μs	9- 2.3V/130Hz/60μs	2- 3.1V/130Hz/60μs	9- 3.1V/130Hz/90μs
5	1- 2.4V/130Hz/60μs	10- 3.0V/130Hz/60μs	1- 2.7V/130Hz/60μs	10- 3.3V/130Hz/60μs
6	1- 3.0V/130Hz/60μs	10- 3.0V/130Hz/60μs	1- 2.8V/130Hz/60μs	10- 3.2V/130Hz/60μs
7	2- 2.0V/130Hz/60μs	9- 1.7V/130Hz/60μs	2- 2.7V/145Hz/60μs	9- 1.9V145Hz/60μs
8	1- 1.5V/130Hz/60μs	10- 2.2V/130Hz/60μs	1- 2.0V/130Hz/60μs	10- 3.5V/130Hz/60μs
9	0- 3.4V/100Hz/60μs	8- 3.4V/100Hz/60μs	0-1+ 2.0V/100Hz/60μs	8-9+ 2.0V/100Hz/60μs
10	2- 3.0V/130 Hz/60μs	9- 2.0V/130Hz/60μs	2- 3.3V/130Hz/60μs	9- 2.5V/130Hz/60μs
11	1- 2.0V/130Hz/60μs	9- 2.4V/130Hz/60μs	1- 1.9V/130Hz/60μs	9- 2.3V/130Hz/60μs
12	2- 3.0V/145Hz/60μs	9- 2.6V/145Hz/60μs	2- 3.8V/145Hz/60μs	9- 2.6V/145Hz/60μs
13	2- 2.5V/130Hz/60μs	9- 2.0V/130Hz/60μs	1- 2.8V/130Hz/90μs	9- 2.3V/130Hz/60μs
14	2- 2.8V/130Hz/60μs	9- 2.0V/130Hz/60μs	2- 3.4V/130Hz/60μs	9- 2.2V/130Hz/60μs
15	2- 1.3V/130Hz/60μs	10- 1.0V/130Hz/60μs	2- 2.6V/130Hz/60μs	10- 1.1V/130Hz/60μs
16	1- 1.9V/130Hz/60μs	9- 1.3V/130Hz/60μs	1- 3.5V/145Hz/60μs	9- 1.3V/145Hz/60μs
17	2- 1.7V/130Hz/60μs	10- 0.8V/130Hz/60μs	2- 1.7V/130Hz/60μs	10- 0.8V/130Hz/60μs
18	1- 2.0V/130Hz/60μs	8- 1.6V/130Hz/60μs	1- 2.0V/130Hz/60μs	8- 1.8V/130Hz/60μs
19	0- 1.9V/130Hz/60μs	8- 1.2V/130Hz/60μs	0- 1.7V/130Hz/60μs	8- 1.0V/130Hz/60μs
20	2- 2.0V/130Hz/60μs	10- 0.8V/130Hz/60μs	2- 2.3V/130Hz/60μs	10- 1.1V/130Hz/60μs
21	1- 2.5V/130Hz/60μs	9- 2.5V/130Hz/60μs	1-2+ 1.8V/130Hz/60μs	9-10+ 1.8V/130Hz/60μs
22	1- 2.0V/130Hz/60μs	10- 2.5V/130Hz/60μs	1- 2.0V/130Hz/60μs	10- 2.5V/130Hz/60μs
23	1- 2.4V/130Hz/60μs	10- 1.4V/130Hz/90μs	1- 1.5V/130Hz/60μs	10- 1.2V/130Hz/60μs
24	3- 1.5V/130Hz/60μs	9- 1.5V/130Hz/60μs	1+2- 2.0V/130Hz/90μs	9- 1.6V/130Hz/90μs

STN division into two parts

Out of the 37 evaluated electrodes, 13 electrodes were located in the ventromedial part and 24 DBS electrodes were placed in the dorsolateral part of STN. After one month, on the left side, statistically significant improvement was found in the dorsolateral location of DBS electrode (P=0.045) in NMSS; however, no significant difference between the ventromedial and dorsolateral position on the right side was found (Table 1, Fig. 4).

After four months, no significant difference in non-motor symptoms between the ventromedial and dorsolateral position was found.

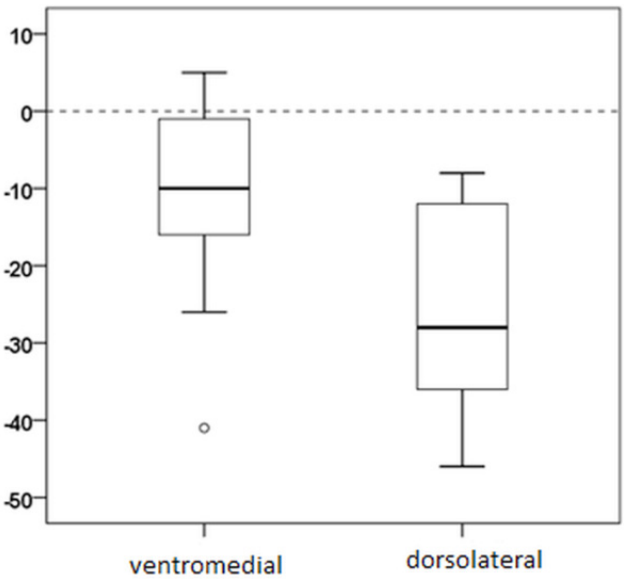

Fig. 4. Change in NMSS after 1 month – left side, division into two parts.

DISCUSSION

Temel et al. suggested that STN has anatomically a central position within the basal ganglia thalamocortical associative and limbic circuits and acts as a potent regulator of these pathways[19]. Its impact on PD symptoms has been extensively studied[8,20,21]. However, to our knowledge, only a few studies have systematically studied the correlation of DBS active contact location within the STN and the involvement of the non-motor symptoms. Dafsari et al. used coordinates of the active electrodes and suggested

that more anterior, medial and ventral location within the STN might be related to more beneficial non-motor outcomes[6]. In the study of Petry-Schmelzer et al. the voxels associated with a minimal improvement for mood/apathy and attention/memory were mainly located dorsal to the subthalamic nucleus. The voxels associated with above average improvement for mood/apathy were localised into the ventral border region of the subthalamic nucleus and in its sensorimotor subregion and for attention/memory in the associative subregion. For sleep domain, an improvement trend was observed in the voxels located ventral to the subthalamic nucleus[7].

The present study showed only the relationship between the side (or hemisphere, left/right) of the DBS electrode active contact rather than its precise localization within the STN. The beneficial effect on non-motor symptoms, which was present at Month 1, fall under the statistical significance at Month 4. This should be explained by the lesional effect after the implantation, nonetheless, the habituation of the stimulating effect may be also the plausible explanation. Different results from previously mentioned studies[6,7] could be explained in several ways:

1) Unlike Dafsari et al. and Petry-Schmelzer et al, our study used topographicall division of STN into three/two parts while Dafsari used the coordinates of the active electrodes[6]. Our division does probably not exactly represent the somatotopic organization of subthalamic nucleus which is still object of research and varies depending on methodology of each study[4,5] and can also differ interindividually. The subdivision into three parts itself is still under debate[22,23]. This fact is supported by the work of Keuken et al., who compared the results of 33 studies of human and non-human primates STN concluding that the variability across studies is surprisingly large, both in the number of methods used for the subdivision and the final anatomical borders within the STN (ref.[24]).

2) The stimulation field probably covers a larger area than just one subsegment of STN. Work of McIntyre et al. showed that stimulation can result in activation of large diameter (5.7 μm) myelinated axons over a volume that spreads outside the borders of the STN (ref.[25]).

3) Unlike motor effect which almost strictly depends on contralateral stimulation, the non-motor symptoms depend on the impulses from both electrodes.

CONCLUSION

Our study showed that the location of stimulating spot of DBS electrode contact within the subthalamic nucleus may have different impact on the non-motor symptoms of Parkinson´s disease depending on the hemisphere (left/right) in which the electrode is located.

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Author contributions: JB, SK: provided the original idea, designed the study, examined the patients, gathered the data and wrote the first draft; PK, MN, PO: designed the study, participated on the SureTune® analyses and critical reading of the manuscript; MC, LH, MV, MK, KM, MV, KS: gathered the clinical and neuropsychological; DK: planned, prepared and performed all DBS surgeries; JV: provided data visualizations in MATLAB; PH, SS, EG: did the critical reading and revisions of the manuscript.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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