Deep brain stimulation in Parkinson's disease: analysis of brain fractional anisotropy differences in operated patients

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Introduction. Deep brain stimulation (DBS) of the subthalamic nucleus is currently an evidence-based therapeutic option for motor symptoms in patients with Parkinson's disease (PD), although other non-motor symptoms can be affected by stimulation.

Aim. Our objective is to evaluate the global changes in the connectivity of the large-scale structural network in PD patients that have obtained a benefit from subthalamic DBS.

Subjects and methods. Retrospective study of 31 subjects: 7 PD patients with subthalamic DBS (group A), 12 age and gender-matched non-operated PD (B) and 12 healthy controls (C). All subjects had undergone a 1.5 T brain MRI with DTI. DICOM images were processed with the FSL5.0 software and TBSS tool.

Results. The study group comprised 23 men and 8 women. No statistically significant differences in age, gender, scores on the H&Y scale and mean follow-up between group A and B were found, and in age and gender between groups A and C. Statistical analysis revealed differences in the fractional anisotropy of the different groups in certain areas: bilateral corticospinal tract, anterior thalamic radiations, bilateral fronto-occipital fascicle, both superior longitudinal fascicles, and left inferior longitudinal fascicle.

Conclusions. In our series, PD patients treated with bilateral subthalamic DBS showed a significantly higher fractional anisotropy in widespread areas of the cerebral white matter; suggesting that neuromodulation produces connectivity changes in different neural networks.

Key words. Connectivity. Deep brain stimulation. Movement disorder's surgery. Neuronal networks. Parkinson's disease. Tractography.

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Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative syndromes, causing a variety of motor and non motor syntoms [1,2]. Imaging and neurophysiological studies in PD patients have demonstrated alterations in volume, diffusion properties and function in different cortical and subcortical structures, suggesting the disease may arise from dysfunction of different network components [2].

Deep brain stimulation (DBS) is a highly effective therapy for PD; effectively restores motor function, reduces the levodopa dosage and motor complications, and improves quality of life for patients with PD [3]. An important but unanswered question is how STN-DBS modulates brain activity, thereby leading to its significant therapeutic effects on PD. A theory based in an abnormal striato-thalamo-cortical (STC) pathway was initially proposed, in which DBS would inhibit the STN, restoring the normal balance of these circuits [3,4]. Posteriorly, some studies using functional neuroimaging techniques have tried to analyse the effects of STN-DBS in many different cortical and subcortical regions [5-9]; however, they are very scarce and have led to contradictory results. To our knowledge, there are no DTI studies evaluating the postoperative effects of DBS in the entire brain connectivity. The objective of our study is to analyze changes in connectivity in PD patients following DBS, by comparing their postoperative DTI parameters with DTI in non-operated patients.

Subjects and methods

Retrospective study of 19 PD patients (7 treated with bilateral DBS (group A), 12 patients under medical treatment (group B), matched according to

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Statement of ethics:
This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the Local Ethics Committee of The University Hospital la Princesa, Madrid, Ceim 13/18, number 3350. The subjects included in the study gave their written informed consent.

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age, gender and score on the Hoehn and Yahr scale (H & Y), from our Movement Disorders Unit, and 12 age and gender matched healthy controls (group C). The DTI images of the healthy controls were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).

Diagnosis was based on the criteria of 'UK Parkinson's disease society brain bank' [9]. All patients were screened for the presence of cognitive impairment using Mini Mental State Examination (MMSE). The severity of the disease was evaluated using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and the stage of the disease was evaluated according to the modified staging system of H&Y. The exclusion criteria for cases was lack of improvement after bilateral STN-DBS of at least a 30% reduction in the UPDRS III subscores at the six months follow-up. This study was approved by our local research ethics committee.

Acquisition and processing of images

All images were acquired with a Siemens 1,5T TIM-Trio scanner (12 channel Matrix head coil), DTI data with a spin echo, echo planar imaging sequence with 64 gradient directions and a b-value of 1,000 s/mm$^{2.}$ and 1 mm isotropic voxels. DTI images were converted from DICOM format to NIFTI, and then were processed with FSl 5.0 software, using the eddycorrect function [10], the BET (Brain extraction), Tool [11] and the Dtifit [12] consecutively for the correction and adjustment of distortions. ADNI images were adquired in General Electric 3T scanners, with b = 0 and 1,000 s/mm^2 weighted volumes and using 2.7 mm isotropic voxels.

Voxelwise analysis of the FA data was carried out using the tract-based spatial statistics (TBSS) part of FMRIB Software Library (FSL) [13]. TBSS projects all subjects' FA data onto a mean FA tract skeleton. Between-groups statistical analyses of the data skeletonized using FSL's randomise tool were conducted to measure voxel-wise differences in FA between different groups.

Threshold-free cluster enhancement and multiple comparison correction were carried out, and bidirectional contrasts in each comparison were applied. The loci of intergroup differences in the skeletonized FA data were identified anatomically in MNI space using various atlases among them The Johns Hopkins University white matter tractography atlas (JHU-WM) [14], to correlate the significant areas with anatomical fascicles. Whole brain tractography was first performed using a deterministic streamline approach. FA thresholds for initiating and continuing tracking were set to 0.2, and the tract-turning angle threshold was set to 30 degrees. Fiber-tract pathways of interest were extracted for each subject individually using a seed mask containing the significant voxel clusters from the TBSS group analysis. For all tests, $p < 0.05$ was considered statistically significant. A critical $p < 0.05$ was considered significant without adjusting for multiple comparisons [15]. Given the possibility of error due to the lack of adjustment by multiple comparisons, a verification of the results was performed.

A comparison of the mean FA and number of fibers of the corticospinal tract was carried out in the BrainLab workstation, between the DBS and conservative treatment patients. A probabilistic tractography method, based on a multifiber model, was used in the performance of fiber tracking [16], (5,000 streamline samples, 0.5-mm step lengths, curvature thresholds 0.2) [17]. CSTs for the M1 were determined by selection of fibers passing through seed and target ROIs. Placement of target ROIs was performed according to literature [18]. Of 5,000 samples generated from each seed voxel, results for each contact were visualized, and thresholds and weightings of tract probability at a minimum of 1 streamline through each voxel were set for analysis. Values of FA, and tract volume of the CSTs were measured. Statistical comparisons between groups were performed using the paired Student's *t*-test for normal distributions or the Mann-Whitney Rank sum test if normality failed. Normality was evaluated using the Kolmogorov-Smirnov test. The independent *t*-test was used for determination of the difference in values of tract volume and FA. The significance level for the *p* value was set at 0.05.

Results

The study group comprised 23 men (74,19%) and 8 women (25,08%). There were no statistically significant differences among groups in their following characteristics: Age, gender, disease duration, age at diagnosis, predominant symptoms, laterality of initial symptoms, and follow-up (p = 0,902, p = 1, p = 0.494, p = 0,102, p = 0,384, p = 0,291 and p = 0,820, respectively) (Tables I and II).

Operated patients underwent two surgical unilateral procedures in 87,7% of the cases (6 patients), while only one patient was operated on bilaterally in the same procedure. Mean time between both procedures was 37 days (0-81 days). Average im-

provement of the disease measured by the Schwab & England daily activity scale was 45,7% (30-60). Mean follow-up time was 4.2 years (1-8) in group A and 4.2 years (1-8) in group B.

DTI parameters

Deep brain stimulation patients (group A) versus patients with Parkinson's disease (group B)

Group A showed significantly greater FA/ than Group B. The right corticospinal tract (CT) presented differences in clusters along its trajectory and its passage through the brainstem and the cerebral peduncles. On the other hand, the left CT showed differences only in its passage through the cerebral peduncle brainstem. Differences were also observed in anterior thalamic radiations, certain areas of the corpus callosum (CC) (right minor forceps), bilateral superior longitudinal fasciculus (SLF), and right fronto-occipital fasciculus (FOF) (Fig. 1).

Group B showed greater FA/ than group A in certain areas of the CC, cingulum, and less markedly (scattered clusters) in hippocampus, optical radiations and thalamic association fibers.

Deep brain stimulation patients (group A) versus healthy controls (group C)

Intervened patients (group A) did not show tracts with significantly higher FA. Conversely, we found a significantly greater FA/ in healthy controls in some fibers of the CC (major forceps), cingulum, in the right SLF and in right IFOF (Fig. 2).

Patients with Parkinson's disease (group B) vs healthy controls (group C)

We found a significantly higher FA in group B in the left IFOF, and bilateral SLF. Conversely, significantly higher FA was found in healthy controls in the fibers of the CC and in the fibers of the right cingulum (Fig. 3).

Comparison of density, FA and length of the CT were compared in the BrainLab workstation, between operated and non-operated PD patients FA and density were significantly higher in DBS patients, whereas there were no differences in the length of the tract between both groups. We have summarized the results for a better understanding in the tables III and IV.

Discussion

Previous DTI studies have shown differences in FA

Figure 1. Results of the tract-based spatial statistics analysis showing clusters of voxels with significantly elevated fractional anisotropy in the operated patients. a) and c) In green, analyzed tracts; in red, global representations of statistically significant tracts. b) and c) Corticospinal tract. e) and f) right superior longitudinal tract.

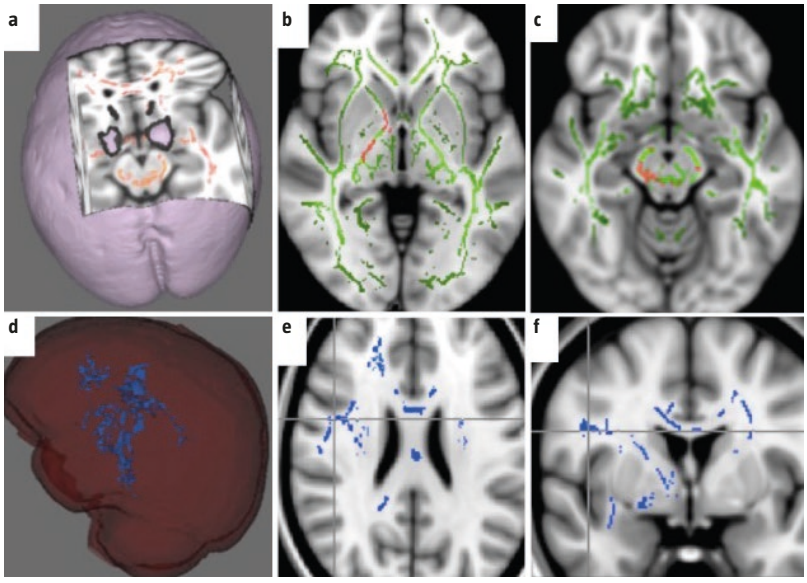


Figure 2. Results of the comparison between operated PD patients and healthy controls showing significantly elevated fractional anisotropy values in healthy controls. a) and b) In red, a representation of the statistically significant tracts: Corpus callosum, cingulum, right superior longitudinal fasciculus and right inferior fronto-occipital fasciculus. c) 3D image of the obtained results.

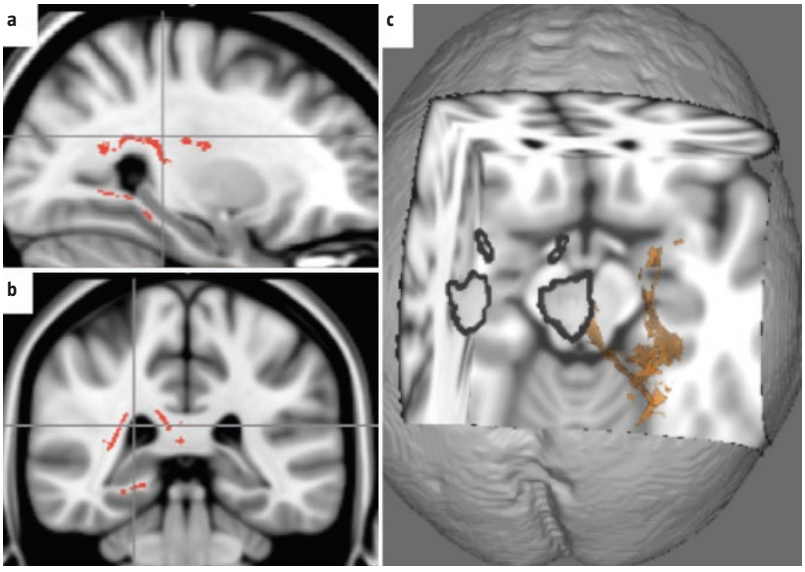


Table I. Main clinical characterisitics or our series of patients with Parkinson's disease that have undergone deep brain stimulation of the subtalamic nucleus.

	Age	Gender	Predominant symptoms	Disease duration	follow-up since surgery (years)	Medication (mg/day)	Preoperatory H and Y ON	Preoepratory Schwab-England Pre ON	Preoperatory UPRDS OFF	Preoepratory UPRDS ON	Postoperatory H and Y	Postoperatory Schwab-England Post
1	70	Female	Rigidity	25	4	Levodopa-carbidopa-entacapone 575. Pramipexole: 0.7, Quetiapine: 25.	2	40	46	8	2	90
2	68	Female	Tremor	18	3.5	Levodopa/carbidopa-entacapone 400, Rasagiline 1, Amantadine 100, Pramipexole 2,8.	2	60	59	19	2	90
3	66	Male	Bradykinesia	10	3.5	Levodopa/carbidopa 1,750, Melatonine 2, Trazodone 150	2	60	43	24	2	90
4	73	Male	Rigidity	23	8.	Rivastigmine 13.3, Mantinex 20. dutasteride 0.5. Levodopa/carbidopa 600 mg Quetiapine 25	2	30	41	11	2	70
5	67	Male	Rigidity, tremor	22	6	Rolpryna 2, Safinamide 50	2	30	26	17	2	90
6	69	Female	Rigidity	7	1	Safinamide 100, Clonacepam 0.5, Propanolol 40, levodopa/carbidopa 75	2	30	42	11	2	70
7	53	Male	Rigidity, tremor	9	3.5	Rasagiline 1 -Levodopa/carbidopa/ entacapone 500	2	40	39	3	2	100
Mean	66.6			20	3.7		2.0	41.4	42.3	13.3	2.0	85.7
SD	6			7	2.5		0.0	13.5	9.8	7.1	0.0	11.3

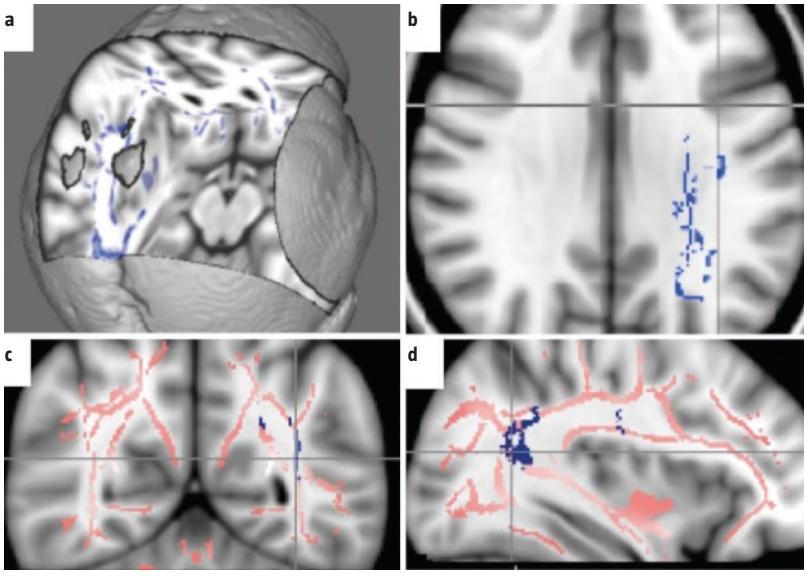
and MD in brain white matter tracts between PD patients and healthy subjects [19]; however, we aimed to analyze changes that might be attributable to the effect of DBS. To our knowledge, this is the first study assessing DTI of FA changes in the entire brain in PD patients treated with DBS.

Our voxelwise analysis by TBSS found significantly greater FA in the CT of DBS patients, as compared with non-operated PD patients, as well as in the anterior thalamic radiations, CC, bilateral SLF and right IFOF. Differences in AF and number of fibers in the CT were confirmed by individually tracing the CT in the surgical and conservative treatment groups in our workstation. When compared with healthy subjects, DBS patients' FA was significantly lower in CC, cingulum, right SLF and right IFOF. On the other hand, the group of PD patients under conservative treatment, showed higher FA than DBS patients in certain areas of CC, cingulum, hippocampus, optic radiations and thalamic association fibers, whereas no areas of higher FA were found in DBS PD patients, in relation with healthy subjects.

Previously reported series, have shown that effective STN stimulation results in changes in the regional cerebral blood flow of primary motor cortex (M1), lateral premotor cortex (PMC), and supplementary motor area (SMA) [5,20,21]. In a very recent study, Hui-Min Chen et al [22] investigated how STN-DBS modulated the brain network using PET/ fMRI dataset. They found that STN-DBS reduced brain activity in the bilateral caudal SMA

Improvement S-E	UPRDS at 6 months FU OFF medicadion	UPDRS at 6 months FU ON medication	UPRDS 1 year FU OFF medication	UPRDS 1 year FU ON medication
50	14	10	14	9
30	18	16	21	14
30	11	9	11	5
40	31	21	31	22
60	25	18	27	19
40	16	12	16	12
60	11	3	14	3
44.3	18.0	12.7	19.1	12.0
12.7	7.5	6.1	7.5	7.0

Figure 3. Results of comparison between non-operated PD patients and healthy controls, showing clusters of voxels with significantly elevated fractional anisotropy values in PD patients. a) 3D image; b) longitudinal fascicles upper left; c) longitudinal fascicles lower left; d) left fronto-occipital fascicle.



and left M1 areas at rest [23]. Moreover, increased activation tends to be seen in the vicinity of the electrode and the surrounding midbrain, together with increased activation in the motor thalamus [24]. These findings support our results of significant improvement in the FA of both corticospinal tracts in operated patients.

The critical involvement of the motor cortex in PD pathophysiology, as our results suggest, has been demonstrated as well by electrophysiological studies. Both levodopa and STN-DBS have shown to normalize cortical beta oscillations, in association with an improvement in motor function [25,26]. Our results agree with these studies, as we have found a higher FA of the CT of operated patients, with respect to the non-operated group, which might be interpreted as a reinforcement in the CT connectivity.

The effects of STN-DBS on cognitive functions and psychiatric side effects may well relate to stimulation effects on these non-motor subdomains [27]. SPECT, PET and functional MRI studies have also shown changes in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), which may be in relation with some of the differences in FA we have obtained among our three groups, in limbic areas such as cingulum and hippocampus [23]. Impairment of verbal fluency is reported in patients that have undergone DBS for PD [28]. In PD, STN stimulations on rCBF while performing verbal fluency tasks have been also associated to impairment of left sided fronto-temporal network [28-30], thus highlighting in surgically treated PD patients the importance of dysfunction in prefrontal rather than temporal areas. The worsening of verbal fluency after STN-DBS has been associated to perfusion reductions in the left dorsolateral prefrontal cortex, anterior cingulate cortex and ventral caudate nucleus ($p < 0.001$) [31]. Since ECD-SPECT is a suitable tracer to measure brain function in patients with parkinsonism [32], it is believed that these results are expression of functional modifications induced by long-term

Table II. Main clinical features of the group of our non-operated patients with Parkinson's disease.

	Age	Gender	Predominant symptoms	Disease duration	Follow-up (years)	Medication (mg/day)	H and Y OFF	H and Y ON	Schwab-England ON	UPRDS OFF	UPRDS ON
1	75	Female	Rigidity	15	9	Levodopa/carbidopa/entacapone: 1150	3	2	50	32	5
2	78	Male	Rigidity	16	12	Levodopa/carbidopa/entacapone 400, Pramipexol 1. Levetiracetam 1000	3	2	60	47	26
3	77	Female	Bradykinesia	15	7	Levodopa/benserazide 800	2	2	60	39	4
4	67	Female	Rigidity	7	6	Rasagiline 1. Levodopa/benserazide 200.	2	2	30	26	16
5	74	Female	Tremor, rigidity	20	8	Duodopa Pump, Levodopa/benserazide 200 Pramipaxole 1.05 Safinamide 100	3	2	30	44	11
6	71	Male	Rgidity	8	12	Ropinirol Prolib: 14, Levodopa/carbidopa/ entacapone 600, Safinamide 100	2,5	2	30	43	16
7	72	Male	Tremor	10	6	Safinamide 100, Levodopa/carbidopa/ entacapone 800, Levodopa/carbidopa 600, Rivastigmine 3	3	2	40	39	12
8	77	Male	Rigidity	14	4	Levodopa/carbidopa 700, Rasagiline 1	4	2	40	45	12
9	72	Male	Tremor, bradikynesia	20	5	Safinamide 100, Levodopa/carbidopa/ entacapone 800,Rasagiline 2	3	2	60	27	17
10	63	Male	Rgidity	15	10	Rasagiline 1. Levodopa/benserazide 200.	3	2	60	40	13
11	56	Male	Bradikinesia	10	6	Levodopa/carbidopa/entacapone: 1150	4	2	50	45	23
12	72	Male	Tremor	20	4	Levodopa/carbidopa/entacapone 800, Safinamide 100,Propanolol,10 Ropirinol 20,	3	2	40	41	10
Mean	71.2			14.2	7.4		3.0	2.0	45.8	39.0	13.8
SD	6.4			4.6	2.8		0.6	0.0	12.4	7.0	6.4

H and Y: Hoehn and Yarh; UPDRS: Unified Parkinson's Disease Rating Scale.

STN-DBS in cortical and subcortical regions engaged in motor and cognitive neural circuitries [33,34].

The SLFis involved in language processing and visual coordination, whereas the superior and inferior FOF are involved in language processing (in relation with the semantic component, the meaning of the things that we hear, read, or say) [35]. We observe a higher FA in these tracts in operated versus non-operated PD patients, and a lower FA in DBS patients compared with healthy controls. These observations, together with changes in CC and cingulum, might be related with the benefit in working memory and language alterations experienced by DBS patients.

Vanegas-Arroyave et al aimed to identify the cortical and subcortical regions most frequently associated with clinically effective contacts in patients with PD treated with DBS, which were the brainstem, thalamus, STN and the superior frontal gyrus [36]. In another interesting study, Acolla et al, conducted whole brain probabilistic tractography seeding from DBS contacts implanted in PD patients, in order to identify the inner organization of the STN in terms of motor and non-motor areas. The authors described projections predominantly to motor and premotor cortical regions additional to connections to limbic and associative areas. More ventral subthalamic areas showed predominant connectivity to medial temporal regions includ-

ing amygdala and hippocampus [37]. In our study, we found a greater FA in operated patients in several tracts, which have multiple connections with the frontal lobe, both in their motor and prefrontal areas. This might suggest that patients who have obtained a good therapeutic outcome, had an increased FA in those areas.

It is noticeable that patients under conservative treatment showed greater FA in the left FOF and bilateral SLF than healthy controls. A correlation between a higher FA in certain tracts and loss of function has been previously reported in PD and other diseases. In William's Syndrome (WS), for example, visuospatial deficits have been associated with a significant increase in the FA of the right SLF, with some reports suggesting that abnormal increases in FA may reliably predict anomalous cognitive function in WS [38]. Similar observations have bee described in other neurological illnesses and in Parkinson's disease [39-42]. Although the cellular mechanisms underlying the increased FA in relation with function decline remain unknown, increased FA potentially reflects compensatory mechanisms [42] and poor cognitive function [43].

Finally, our study has several limitations: First, it is a retrospective study with a small patient population, which prevents establishing correlations between the observed differences in FA and the clinical effects of stimulation. Secondly, the acquisition protocol used by ADNI differed from that performed in our institution, which might affect the results. Finally, we are not comparing the same group of subjects, pre and postoperatively. To minimize biases, the selection of the groups was carried out conscientiously to bring us closer to homogeneity, and we used an age and disease severity matched conservative control group. Despite that, there is certain heterogeneity between subjects, as PD is a multisymptomatic disease.

Conclusions

In our series, patients with Parkinson's treated with bilateral STN-DBS showed a significantly higher FA, compared to patients who were not intervened, in motor and non-motor areas of cerebral white matter, which could be related to the DBS therapeutic and adverse effects observed with DBS. Collectively, remotely modulated areas (M1, SMA, limbic and associate tracts) and those locally affected might constitute an effective STN-DBS network.

Table III. Comparative table showing the analyzed results of the three groups of our study: tracts that have shown statistically significant increases in the anisotropy fraction, resulting from the comparison between the two confluent groups.

	DBS patients	Parkinson´s disease non-operated patients	Healthy controls
DBS patients	–	Corpus callosum Cingulum Hippocampus (scattered cluster) Optical radiations Thalamic association fibers	Corpus callosum (major forceps) Cingulum Right superior longitudinal fasciculus. Right inferior fronto-occipital fasciculus
PD non-operated patients	Right Corticoespinal tract Left Corticoespinal tract Anterior thalamic radiations Corpus callosum (right minor forceps) Right superior longitudinal fasciculus. Left superior longitudinal fasciculus Right inferior fronto-occipital fasciculus	–	Corpus callosum Cingulum
Healthy controls	None	Left fronto-occipital fasciculus Right superior longitudinal fasciculus Left superior longitudinal fasciculus	–

Table IV. Analysis of the number of fibers and mean fractional anisotropy FA of the corticospinal tract (CST) performed in our series of patients with Parkinson's disease (PD).

DBS	Fibers Right CT	FA Right CT	Length Right CT	Fibers Left CT	FA Left CT	Length Left CT
1	12355	0.30	130	6473	0.41	135
2	4271	0.44	137	1548	0.40	149
3	4753	0.47	120	4603	0.46	129
4	4246	0.48	126	3423	0.47	127
5	3517	0.44	135	4228	0.48	126
PD	Fibers Right CT	FA Right CT	Length Right CT	Fibers Left CT	FA Left CT	Length Left CT
1	16	0.20	172	21	0.21	168
2	2205	0.32	124	2085	0.33	122
3	2724	0.38	123	3745	0.27	130
4	2541	0.28	128	2511	0.27	120
5	873	0.3	128	1899	0.39	128
p value	0.0426	0.0178	0.5967	0.0807	0.0025	0.9683

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Estimulación cerebral profunda en la enfermedad de Parkinson: análisis de la anisotropía fraccional cerebral en pacientes intervenidos mediante estimulación cerebral profunda

Introducción. La estimulación cerebral profunda (ECP) del núcleo subtalámico actualmente es una opción terapéutica basada en la evidencia para los síntomas motores en pacientes con enfermedad de Parkinson (EP), aunque otros síntomas no motores pueden verse afectados por la estimulación.

Objetivo. Nuestro objetivo es evaluar los cambios globales en la conectividad de la red estructural a gran escala en pacientes con EP que han obtenido un beneficio de la ECP subtalámica.

Sujetos y métodos. Estudio retrospectivo de 31 sujetos: siete pacientes con EP con ECP subtalámica (grupo A), 12 pacientes con EP no operados de la misma edad y sexo (B) y 12 controles sanos (C). Todos los sujetos se habían sometido a una resonancia magnética cerebral de 1,5 T con imagen del tensor de la difusión. Las imágenes DICOM se procesaron con el *software* FSL5.0 y la herramienta estadística espacial basada en el tracto.

Resultados. El grupo de estudio estuvo compuesto por 23 hombres y ocho mujeres. No se encontraron diferencias estadísticamente significativas en edad, sexo, puntuación en la escala de Hoehn y Yahr y seguimiento medio entre el grupo A y B, y en edad y sexo entre los grupos A y C. El análisis estadístico reveló diferencias en la anisotropía fraccional de los diferentes grupos en ciertas áreas: tracto corticoespinal bilateral, radiaciones talámicas anteriores, fascículo frontooccipital bilateral, ambos fascículos longitudinales superiores y fascículo longitudinal inferior izquierdo.

Conclusiones. En nuestra serie, los pacientes con EP tratados con ECP subtalámica bilateral mostraron una anisotropía fraccional significativamente mayor en áreas extensas de la sustancia blanca cerebral, lo que sugiere que la neuromodulación produce cambios de conectividad en diferentes redes neuronales.

Palabras clave. Cirugía de trastornos del movimiento. Conectividad. Enfermedad de Parkinson. Estimulación cerebral profunda. Redes neuronales. Tractografía.