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The effect on deep brain stimulation of subthalamic nucleus and dopaminergic treatment in Parkinson disease

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Abstract

Impulsivity is a frequent non-motor symptom in Parkinson disease (PD). It comprises psycho-behavioral alterations that negatively impact quality of life. Dopaminergic treatments underpin many impulsive controls disorders however, side effects, such as increased impulsivity, are described also after neurosurgical procedure of deep brain stimulation (DBS). We investigated the effect of deep brain stimulation on psycho-behavioral alterations and quality of life (QoL) in PD patients, analyzing, also, the role of dopaminergic therapies.

Twenty idiopathic PD patients with and 20 idiopathic PD patients without DBS were included in the study. All patient underwent to neuropsychological assessment for a screening of executive functions, impulsivity, anxiety and depressive symptoms and QoL.

Differences were found between DBS and no DBS groups and in term of dopaminergic therapies. The comparison between 2 groups showed a greater motor and attentional impulsivity in DBS patients. Moreover, this impulsivity worse QoL and interpersonal relationships. The combination of Levodopa and dopamine agonists exerted a great impact on impulsivity behavior.

The emergence of postoperative impulsivity seems to be a neurostimulator phenomenon related to the computational role of the subthalamic nucleus in modulation of behavior.

Abbreviations: AD = Lactivities of daily living, AI = attention impulsivity, BDI-II = beck depression inventory, COM = communication, DA = dopamine agonists, DBS = deep brain stimulation, EMO = emotional well-being, HAM-A = Hamilton anxiety rating scale, L-Dopa = Levodopa, MI = motor impulsivity, PD = Parkinson disease, PDQ-39 = Parkinson disease questionnaire, QoL = quality of life, SS = social support, STN DBS = deep brain stimulation of subthalamic nucleus, WCST = Wisconsin card sorting test.

Keywords: deep brain stimulation, impulsivity, Parkinson disease, quality of life

1. Introduction

Impulsivity is a non-motor symptom in Parkinson disease (PD) commonly defined as the lack of behavioral inhibition and premature decision making. It is characterized by compulsive or repetitive engagement in certain activities, closely associated with the inability to foresee or learn from negative outcomes.[1,2] It comprises a class of psycho-behavioral disorders influenced by a complex interaction of multiple factors that negatively impact quality of life (QoL).[3]

It is now well-recognized that dopaminergic treatments, especially dopamine agonists (DA) and levodopa (L-Dopa) are strictly correlated with impulsive controls disorders. Functional Magnetic Resonance Imaging research showed alterations in striatal regions and limbic cortex suggesting a dysregulation of mesolimbic dopaminergic pathways in these disorders.[4] Side effects, such as increased impulsivity in PD, are be described also after deep brain stimulation of the subthalamic nucleus (STN DBS). STN DBS is a specific advanced therapy for PD that reduces motor symptoms and improves QoL.[5] However, after STN DBS some patients become more impulsive and present a predisposition toward rapid, unplanned actions to internal or external stimuli.[6,7] Several authors also described the association between impulsivity and cognitive functions due to mesocortico-limbic overstimulation that alter prefrontal networks affecting executive abilities, affectivity and motivation.[8] In particular, impulsivity seems to act on interference control, cognitive, and behavioral inhibition that represents a set of abilities related to executive functions.[9] PD patients with STN DBS could show difficulty in situations that need a fast cognitive and behavioral adjustment to novel or shifting requests of the

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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environment, poor ability to inhibit responses when these are no longer functional and enhanced reactivity to environmental cues especially in terms of response's perseverance.[10,11]

Furthermore, when faced with a difficult choice, PD patients generally speed rather than slow their decision-making after STN DBS.[12]

In this study we investigated the effect of STN DBS on impulsivity, executive functions and QoL in PD patients. Contrary to the literature, moreover, we also analyzed the impact of dopaminergic therapies in the pathology of impulsive disorders, investigating the role of L-Dopa and DA on the onset of specific symptoms and the appearance of side effects after DBS.

The first section of this study explains the recruitment of patients, the methods used and the tests administered. The results explain the statistical analysis and, in the subsections, our findings. These are finally deepened in the discussions, while the conclusions set out the limitations and future investigations.

2. Material and methods

This study included 20 idiopathic PD patients with DBS (10 treated with L-Dopa and DA, 10 treated only with L-Dopa) and 20 Idiopathic PD patients without DBS (10 treated with L-Dopa and DA, 10 treated only with L-dopa); Hoehn and Yahr stages 2 to 3; stable pharmacological treatment in the last 6 weeks. Exclusion criteria were: atypical Parkinsonisms; PD with dementia according to diagnostic and statistical manual of mental disorders criteria; other neurological or psychiatric disorders. The approval of an ethics committee (or institutional review board) was not necessary because the study was retrospective. All subjects gave written informed consent for participation in the study. Research methodology is resumed in Figure 1.

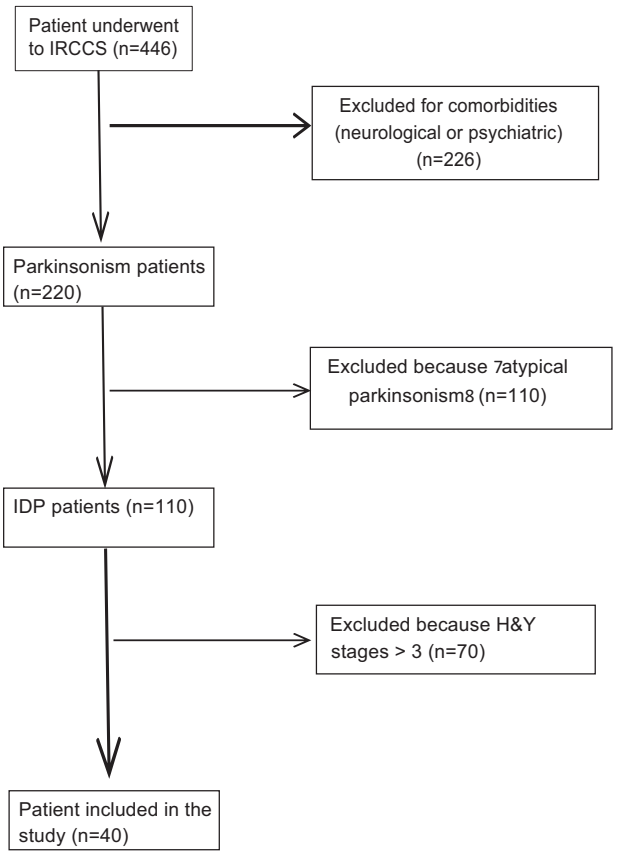

Figure 1. Research methodology.

The neuropsychological evaluation was assessed by using The Montreal Cognitive Assessment for a cognitive screening and Wisconsin Card Sorting Test (WCST) for executive functioning referring to a set of cognitive processes that control goal-directed behaviors from goal formulation and formation of intentions to successful execution and outcome processing.[13] The Barratt impulsiveness scale-11 was used to measure impulse control through 3 subdomains: attention impulsivity (AI), motor impulsivity (MI), non-planning impulsivity.[14] The Barratt impulsiveness scale-11 measure impulsivity, understood as acting without think represents the tendency to behave without premeditation and forethought in response to environmental stimuli in demanding or stressing situations.[15]

We administered Beck Depression Inventory (BDI-II) to assess depression symptoms; instead anxiety was evaluated by Hamilton anxiety rating scale (HAM-A) Parkinson disease questionnaire (PDQ-39) was used to assess QoL across 8 dimensions: mobility; activities of daily living (ADL); emotional well-being (EMO); stigma; social support (SS); cognitions; Communication (COM); bodily discomfort.

3. Results

3.1. Statistical analysis

Continuous variables were expressed as Mean ± standard deviation. A parametric analysis was carried out since Shapiro–Wilk normality test results indicated that most of the target variables were normally distributed. The numerical data are presented in median, and first-third quartile in no normal distribution. The comparison of clinical variables between the 2 groups was performed with the unpaired Student *t* test or Mann–Whitney *U* test for inter group analysis. Correlation Pearson or Spearman Rank correlation was used for intra group analysis in order to assess the relationship between clinical scores. Finally, we performed a multiple regression analysis on sub-item PDQ-39 scores (dependent variables). At first, we focused on the influence of demographic and clinical variables, by using patient's age and disease duration, education, BDI-II, HAM-A, AI, MI, non-planning impulsivity. We applied a backward elimination stepwise procedure for the choice of the best predictive variables according to the Akaike information criterion. Subsequently, each group was divided into 2 subgroups according to the therapy (Levodopa+DA or Levodopa). The inter and intra group analysis have been performed in these subgroups using an open source R3.0 software package (R Foundation for Statistical Computer, Vienna, Austria). A 95% of confidence level was set with a 5% alpha error. Statistical significance was set at $P < .05$.

3.2. DBS and no DBS group

The groups were homogeneous in terms of age, disease duration and education level (Table 1). Inter-group analysis showed a significant difference in MI ($P = .05$) and in PDQ-39 sub-item: mobility ($P = .005$), EMO ($P = .02$), stigma ($P = 0.05$), SS ($P = .02$), and COM ($P < .001$).

In DBS group, intra-group analysis showed a significant trend between AI and WCST Perseverative errors ($r = 0.39$; $P = .08$). In

Table 1

Socio-demographic and clinical characteristics of deep brain stimulation and no deep brain stimulation group.

	DBS Mean±SD	No DBS Mean±SD	P
Age	60.85±8.55	63.05±7.96	.4[+]
Education	10.60±3.62	9.70±3.87	.35[°]
DD	10.75±3.85	9.75±3.19	.61[+]
Moca	26.45±2.61	26.2±1.00	.37[°]
WCST			
Global score	97.46±22.11	86.91±27.97	.19[+]
Perseverative errors	42.87±7.11	37.73±13.10	.16[+]
BDI-II	26.80±10.15	20.9±8.73	.06[+]
HAM-A	24.25±10.90	22.10±10.84	.77[°]
PDQ-39			
M	69.12±19.82	45.28±26.90	.005[°,*]
ADL	51.79±27.12	38.94±24.35	.15[+]
EMO	54.79±12.63	44.08±18.65	.02[+,*]
STI	37.81±23.95	22.19±20.53	.05[°,*]
SS	34.13±22.55	18.71±18.02	.02[°,*]
C	37.12±20.90	29.38±21.06	.42[+]
COM	59.57±15.60	23.66±21.71	<.001[°,*]
BD	45.40±13.36	41.64±22.86	.7[°]
BIS-11			
AI	20.70±5.69	18.65±5.70	.29[°]
MI	29.40±8.08	24.45±5.12	.05[°,*]
NPI	29.70±6.11	28.90±4.58	.83[°]

ADL = activities of daily living, AI = attentional impulsivity, BD = bodily discomfort, BDI-II = beck depression inventory, C = cognitions, COM = communication, DD = disease duration, EMO = emotional well-being, HAM-A = Hamilton anxiety scale, M = mobility, MI = motor impulsivity, NPI = non planning impulsivity, PSDI = Parkinson disease summary index, SS = social support, STI = stigma, TOT BIS = total score.

[+]Unpaired Student *t* test.

[°]Mann–Whitney *U* test.

[*] $P < .05$

no DBS group, AI correlates positively with BDI-II (r = 0.46; $P = .04$)and HAM-A (r = 0.57; $P = .009$), while MI is positively correlated with HAM-A (r = 0.45; $P = .04$) (Fig. 2).

3.3. Subdivision of each group (DBS and no DBS) by therapy

In DBS group, we found a significant difference between L-Dopa +DA therapy subgroup and only L-Dopatherapy subgroup in PDQ-39 sub-item: ADL ($P = .04$), SS ($P = .03$), bodily discomfort ($P = .03$), (Table 2). In DBS Group, Pearson correlation analysis showed a significant trend between AI and WCST scores both in Levodopa+DA subgroup (r = 0.59; $P = .07$) and L-Dopa subgroup (r = 0.61; $P = .06$).

Table 2

PDQ-39 of subdivision of each group by therapy.

	DBS Mean±SD	No DBS Mean±SD	P
M			
Levodopa+DA	68.50±22.40	38.29±28.74	.03[°,*]
Levodopa	72.25±14.46	55.50±23.80	.09[°]
P	1[°]	.16[+]	
ADL			
Levodopa+DA	60.78±18.86	29.99±24.28	.006[+,*]
Levodopa	36.24±25.23	44.53±21.21	.3[°]
P	.04[°,*]	.17[+]	
EMO			
Levodopa+DA	56.25±13.36	41.24±15.90	.03[+,*]
Levodopa	53.33±12.39	44.58±22.22	.29[+]
P	.62[+]	.7[+]	
STI			
Levodopa+DA	33.75±16.98	17.50±18.59	.06[+]
Levodopa	41.88±29.76	26.88±22.25	.27[°]
P	.19[°]	.32[+]	
SS			
Levodopa+DA	23.27±20.93	14.99±16.58	.34[+]
Levodopa	45.00±19.32	22.43±19.50	.01[°,*]
P	.03[°,*]	.37[+]	
C			
Levodopa+DA	42.43±17.26	25.00±18.87	.04[+,*]
Levodopa	24.43±21.69	31.20±21.88	.79[°]
P	.06[°]	.51[+]	
COM			
Levodopa+DA	59.13±18.61	19.99±22.29	.002[°,*]
Levodopa	60.00±12.91	25.80±21.27	.002[°,*]
P	.85[°]	.57[°]	
BD			
Levodopa+DA	52.50±7.90	35.79±27.49	.09[+]
Levodopa	38.30±14.22	46.67±13.15	.18[°]
P	.03[°,*]	.28[+]	

ADL = activities of daily living, BD = bodily discomfort, C = cognitions, COM = communication, EMO = emotional well-being, M = mobility, PSDI = Parkinson disease summary index, SS = social support, STI = stigma.

[+]Unpaired Student *t* test

[°]Mann–Whitney *U* test

[*] $P < .05$.

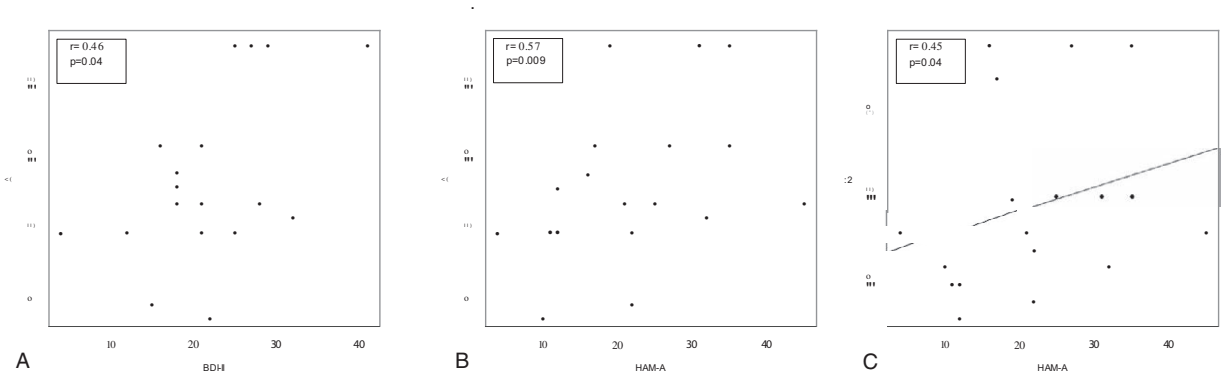

Figure 2. Correlation between clinical scores. (A) Scatter plot of beck depression inventory score and IA in no deep brain stimulation (DBS) group. (B) Scatter plot of Hamilton anxiety rating scale score and IA in no DBS group. (C) Scatter plot of Hamilton anxiety rating scale score and motor impulsivity in no DBS group.

Table 3

Subdivision of Parkinson disease groups (DBS and no-DBS) by pharmacological therapy.

Variables	Teraphy	DBS Mean ± SD	No DBS Mean ± SD	*P*
Age	Levodopa+DA	58.60 ± 10.70	59.60 ± 7.59	.81[+]
	Levodopa	63.10 ± 5.34	66.50 ± 7.04	.24[+]
	P	.25[+]	.05[+,*]	
Education	Levodopa+DA	11.50 ± 3.37	9.90 ± 3.54	.27[°]
	Levodopa	9.70 ± 3.80	9.50 ± 4.35	.78[°]
	P	.21[°]	.82[+]	
DD	Levodopa+DA	12.60 ± 4.14	10.0 ± 4.05	.17[+]
	Levodopa	8.90 ± 2.56	9.50 ± 2.22	.58[+]
	P	.03[+,*]	.74[+]	
Moca	Levodopa+DA	26.00 ± 2.91	26.40 ± 1.07	.69[+]
	Levodopa	26.90 ± 0.99	26.0 ± 0.94	.05[°]
	P	.37[+]	.4[°]	
WCST				
Global score	Levodopa+DA	102.16 ± 21.65	73.98 ± 30.53	.03[+,*]
	Levodopa	92.75 ± 22.68	99.84 ± 18.63	.45[+]
	P	.35[+]	.04[+,*]	
Perseverative errors	Levodopa+DA	46.52 ± 7.31	35.09 ± 15.96	.06[+]
	Levodopa	41.07 ± 8.21	42.73 ± 10.72	.7[+]
	P	.13[+]	.23[+]	
BDI-II	Levodopa+DA	30.90 ± 10.34	20.80 ± 12.15	.06[+]
	Levodopa	22.70 ± 8.55	21.0 ± 3.65	.57[+]
	P	.07[+]	.96[+]	
HAM-A	Levodopa+DA	28.40 ± 13.87	22.20 ± 11.22	.29[+]
	Levodopa	20.10 ± 4.48	22.0 ± 11.04	.62[+]
	P	.1[+]	.97[+]	
BIS-11				
AI	Levodopa+DA	21.10 ± 6.40	21.30 ± 6.07	.93[°]
	Levodopa	20.30 ± 5.21	16.00 ± 4.00	.05[+]
	P	.76[+]	.13[°]	
MI	Levodopa+DA	31.40 ± 8.14	25.20 ± 5.07	.11[°]
	Levodopa	27.40 ± 7.92	23.70 ± 5.33	.24[+]
	P	.28[+]	.32[°]	
NPI	Levodopa+DA	31.60 ± 6.75	28.70 ± 4.55	.42[°]
	Levodopa	27.80 ± 5.03	29.10 ± 4.84	.49[°]
	P	.32°	.85°	

AI = attentional impulsivity, BDI-II = beck depression inventory, DD = disease duration, HAM-A = Hamilton anxiety scale, MI = motor impulsivity, NPI = non planning impulsivity, TOT BIS = total score.
[+]Unpaired Student *t* test
[°]Mann–Whitney *U* test
[*] $P < .05$

In no DBS group, we found a significant difference between L-Dopa+DA therapy subgroup and only L-Dopatherapy subgroup in WCST Global score ($P = .04$) (Table 3). Moreover, in L-Dopa +DA subgroup significant correlation between AI and BDI-II ($r = 0.74$; $P = .01$) and between AI and HAM-A ($r = 0.77$; $P = .008$) were found. No correlation significant were found in L-Dopasubgroup.

3.4. Inter-group analysis based on therapy

In both DBS and No DBS groups, L-Dopa+DA subgroups showed a significant difference in WCST Global score ($P = .03$), (Table 3) and in PDQ-39 sub-item: M ($P = .03$), ADL ($P = .006$), EMO ($P = .03$), C ($P = .04$), COM ($P = .002$) (Table 2). Treatment only with L-Dopa(DBS and no DBS) showed a significant difference in sub-item PDQ-39: SS ($P = .01$) and COM ($P = .002$) (Table 3).

4. Discussion

The relationship between PD and impulsivity is complex and the studies showed conflicting results. Impulsivity frequently occurred after dopaminergic treatment initiation or dosage increase.[16,17] However, impulsive disorders have been described also after STN DBS independently by dopaminergic medication status. In particular, STN DBS seems to be related to decision-making impairment and adverse influences on the reward processing function, in situations of high conflict. Indeed, after STN DBS, PD patients showed failures of motor inhibition,[18] action cancellation,[19] as well as showing a failure of verbal inhibition.[20]

Studies on impulsivity in PD patients highlighting conflicting results. Literature showed that DA seems to represent main risk factor leads to "reflection impulsivity." Indeed, impulsive controls disorders predominantly occurred subsequent to treatment initiation or dosage increase particularly related to the effects of the DA.[17,21] However, increase of impulsivity has been reported also after STN-DBS independently by dopaminergic medication status.[22]

In the present study there was no significant difference between DBS and no DBS groups at the baseline level according to main clinical symptoms, anxiety and depression and cognitive status. However, the comparison between 2 groups showed a more prominent motor (acting without thinking), and attentional (inability to focus attention or concentrate) impulsivity in DBS patients.

Impulsivity had a significant impact on QoL and strain interpersonal relationships.

It is known that problems with the control of information processing or executive functioning can increased impulsive behaviors. In both groups, indeed, measures of poor cognitive flexibility and perseveration were associated with a more impulsivity. In addition, impulsivity worsened executive functions in relation of L-Dopa+DA therapy.

Dysregulation of mesocorticolimbic dopamine system is thought to be the major neurobiological substrate for impulsivity in PD. However, functional and structural brain imaging support also the role of STN in motor and attentional inhibition.[23] Frontostriatal networks, including the dorsolateral prefrontal cortex and the medial prefrontal cortex, are indeed involved in executive functioning, decision-making, impulse control, perseveration.[24] Therefore, the emergence of postoperative impulsivity could be a neurostimulator phenomenon related to computational role of STN in modulation of behavior[25] through connections with frontal lobe and basal ganglia.[26] There is a difficult adjustment of the excitation level in response to environmental stimuli. The failure to initiate a clear beginning or end of sensory events lead to the inability to distinguish relevant environmental stimuli and provide adaptive responses.[27]

5. Conclusions

In recent years, DBS has become a standard evidence-based therapy for severe movement disorders; since it reduces motor symptoms and improves QoL.[5] However, some individuals could become more impulsive and less empathic after DBS, acting recklessly without foresight or concern for others. This form of impulsivity seems to be increase by dopaminergic medication status. Beyond dopamine and DBS other pertinent risk factors have been identified and include gender, country of residence, age

of PD onset, disease duration, alcohol/tobacco use, family history of impulsivity, genetic factors, non-dopaminergic medications, deep brain stimulation, personality traits, and more.[3]

At present, there is a clear need for more conclusive data on the effects of DBS on impulsivity in PD patients. According to the major literature data, this study confirmed that DBS plays a role in the onset of impulsivity especially when accompanied by DA.

The present research has some limitations, which will be addressed in future studies. Among others, 1 limitation of this research is the small sample size that did not allow a generalization of clinical results. It is suggested to undertake more in-depth research on larger samples. Further studies with greater methodological refinement should establish whether impulsivity is associated with a specific pathophysiological process in order to improve the QoL of life and decrease functional disability. Might be interesting for future investigations to deepen the influence of premorbid personality. For example, having positive beliefs about own ability to perform correctly tasks, increase the individual's abilities and lead to positive results in different aspects of life.[28] Differences in personality, values, or norms and premorbid cognitive functioning must therefore be considered.[29,16] These features could determine a greater susceptibility to impulsiveness.

Author contributions

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