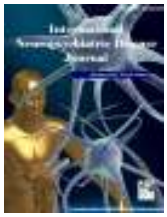

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Personality and Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson's Disease

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Authors' contributions

This work was carried out in collaboration between all authors. Authors ML, LL and SF designed the study and wrote the protocol. Authors GAD and MZ performed the statistical analysis, authors EM and FA managed the literature search, and authors GAD and EM wrote the first draft of the manuscript with assistance from author AM. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: Certain personality features and psychiatric symptoms are often observed in Parkinson's Disease (PD) but the effects of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on psychiatric aspects of PD remain largely unclear. We aimed to evaluate changes in personality and psychiatric symptoms before and after STN-DBS in patients affected by PD. Moreover, motor symptoms and L-dopa equivalent daily dose (LEDD) were also investigated.
Methodology: Eighteen PD patients consecutively admitted at the San Giovanni Battista Hospital of the University of Turin to undergo STN-DBS were recruited. Participants were neurologically assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), and the Hoehn and Yahr scale. They were also psychiatrically evaluated with both self-report and clinician-rated instruments: Temperament and Character Inventory (TCI), Beck Depression Inventory (BDI), State-Trait Anxiety Inventory – Y form (STAI-Y), Hamilton Depression Rating Scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A).

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Results: After STN-DBS, temperament dimensions of the TCI significantly changed whilst character did not. Moreover, both HAM-D and HAM-A improved but BDI and STAI-Y resulted unmodified. We found significant improvements as regards the UPDRS part II and part III scales and L-dopa equivalent daily dose.
Conclusions: The change we found on biological dimensions of temperament after STN-DBS raises the intriguing hypothesis that surgery may entail subtle modifications of personality in PD patients. Further studies are needed to confirm these findings.

Keywords: Parkinson's disease; deep brain stimulation; subthalamic nucleus; personality; reward dependence; temperament.

1. INTRODUCTION

Psychiatric symptoms frequently occur in Parkinson's Disease (PD) and have important consequences on patients' quality of life and daily functioning. Psychiatric symptomatology includes depression (30-40%), anxiety (40%) [1], psychosis (20-50%) [2], and sleep disturbances (88%) [3]. Still, these data might be underestimated inasmuch PD patients often do not mention their non-motor symptoms [4].

Since the late 1990s, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a well-established procedure for advanced PD patients to greatly improve motor symptoms and quality of life [5]. Moreover, notwithstanding the variable risk of adverse events (e.g. surgical site infection, dystonia, gait disturbance), this procedure was found to be more effective than medical management alone [6,7]. Still, STN-DBS has the advantage to reduce L-dopa equivalent daily dose (LEDD; i.e., a useful summary of the total daily antiparkinsonian medication a patient is receiving independently of treatment regimen) [8] possibly limiting its unwanted motor [2] and psychiatric [9] side-effects on the medium and long-run.

The effects of STN-DBS on psychiatric outcome in PD patients remain largely unclear also because of a lack of systematic psychiatric screening [10]. The majority of psychiatric symptoms that occur after surgery are frequently transient and manageable and vary from depression to hypomania [10]. However, this procedure reported encouraging outcomes as regards psychiatric symptomatology [8,11,12].

The motor function of the STN has been well documented [13] but those mechanisms underlying psychiatric symptoms are poorly understood [14] raising the hypothesis of a multifactorial etiology which is thought to include preoperative PD-related aspects, dopaminergic medications, surgical factors, and psychosocial effects [15]. However, basal ganglia and STN represent the substrate not only for complex motor cortico-subcortical loops but also for limbic connections processing thoughts, emotions, and behaviour [11,14] with animal and human studies on PD [16,17] providing intriguing evidence for the role of the STN in these regards.

With respect to personality, a general consensus does not exist as to whether personality features like punctuality, introversion, moral rigidity, and conventionality might be considered as premorbid traits and eventually risk factors of PD [18-20]. These traits are underpinned by both dopaminergic and GABAergic systems [21]; in particular, novelty seeking (NS) is a personality dimension thought to mirror the dopamine function in the brain [22] and it has been often found to be low in PD individuals [23-25].

The available body of literature regarding personality changes in PD individuals who underwent STN-DBS is even scarcer and only two studies [26,27] investigated these aspects. The study conducted by Houeto and Coworkers [26] with the Temperament and Character Inventory-Revised (TCI-R) [28] did not find significant changes in patients' personality traits after surgery. In our previous work, using the Temperament and Character Inventory (TCI) [22], we found that two NS subscales were significantly higher in PD patients who underwent the STN-DBS intervention [27].

The primary aim of this study was to investigate changes in personality and psychiatric symptoms - using self-administered and clinician-rated instruments - in PD individuals treated with STN-DBS, and the secondary aim was to measure also motor symptoms. Both changes in NS scores as well as motor improvement were expected.

2. METHODOLOGY

2.1 Patients

We consecutively enrolled 18 participants affected by PD, according to the UKPD-Brain-Bank criteria [29]. All participants, N=16 (88.9%) males and N=2 (11.1%) females were recruited at the San Giovanni Battista Hospital of the University of Turin, Italy, between September, 1st 2010 and January, 31st 2012. Mean age at intervention was 61.22±6.69 years and at follow-up was 62.47±5.6 years; mean duration of illness was 15.44±4 years.

Exclusion criteria were: a) age > 70 years old; b) severe medical comorbidity (e.g., epilepsy or diabetes); c) severe Axis I psychiatric comorbidity; d) drug dependence; e) cognitive impairment (Mini-Mental state examination <27/30 [30]). Patients were all Caucasian.

2.2 Surgical Procedure

Deep brain stimulation (DBS) is a neurosurgical procedure consisting in placing a brain pacemaker which sends electrical impulses through implanted electrodes to specific parts of the brain to deliver continuous high-frequency electrical stimulation for the treatment of movement and affective disorders. Electrodes are placed deep in the brain and are linked to a stimulator/battery device. The electrodes are placed on both the left and right sides of the brain through small holes made at the top of the skull. A neurostimulator, similarly to a heart pacemaker, uses electric pulses to help regulate brain activity. When turned on, the stimulator sends electrical pulses to modify nerve signals involved in tremors, rigidity, and other symptoms. DBS can be performed on both sides of the brain or in a combination of targets depending on the symptoms to treat and may include thalamus, globus pallidus, or the subthalamic nucleus. The latter is the target we used in previous [27] and current research. A deep brain stimulator system has three parts that are implanted inside the body: A) Lead – a thin, insulated wire with a number of electrodes at the tip that deliver electric pulses to the brain tissue. It is inserted through a small opening in the skull; the tip of the electrode is positioned within the targeted brain area. B) Extension – an insulated wire that is passed under the skin of the head, neck, and shoulder and connects the lead to the neurostimulator. C) Neurostimulator– a programmable battery-powered pacemaker device that creates electric pulses. It is placed under the skin of the chest below the collarbone or in the abdomen.

All procedures involving experiments on human subjects were done in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. All participants provided written informed consent according to the Ethical Committee of the Department of Neuroscience of the University of Turin.

2.3 Neurological Assessment

All participants were clinically assessed one month before (T0) and 6 months after (T1) the STN-DBS intervention by a neurologist using the Unified Parkinson's Disease Rating Scale (UPDRS) [31] parts II and III, and the Hoehn and Yahr scale [32].

2.3.1 Unified Parkinson's disease rating scale (UPDRS)

The UPDRS [31] is a scale that was developed to provide a comprehensive and flexible means to monitor PD-related disability. The scale has four components: part I: mentation, behavior and mood; part II: activities of daily living; part III: motor; and part IV: complications. According to the aims of this study, in order to assess motor functioning only parts II and III of this scale were included in subsequent analysis.

2.3.2 Hoehn and Yahr scale

The Hoehn and Yahr scale [32] is a commonly used system for describing how the symptoms of PD progress with a range of five stages: 1. unilateral involvement only usually with minimal or no functional disability; 2. bilateral or midline involvement without impairment of balance; 3. bilateral disease: mild to moderate disability with impaired postural reflexes, physically independent; 4. severely disabling disease; still able to walk or stand unassisted; 5. confinement to bed or wheelchair unless aided.

2.4 Psychiatric Assessment

After the neurological assessment, all participants were clinically assessed by an experienced psychiatrist one month before (T0) and 6 months after (T1) the STN-DBS intervention using both self-report instruments and semi-structured interviews as follows:

2.4.1 Temperament and character inventory (TCI)

The TCI [22] is divided into seven dimensions. Four of these assess temperament (novelty seeking [NS], harm avoidance [HA], reward dependence [RD], and persistence [P]), defined as partly heritable emotional responses, stable throughout life, mediated by neurotransmitters in the central nervous system. The other three dimensions assess character (self-directedness [SD], cooperativeness [C], and self-transcendence [ST]) which is influenced by both genetic factors and social learning. The TCI showed good properties as regards internal consistency and test-retest reliability [33].

2.4.2 Beck depression inventory (BDI)

The BDI [34] is a self-administered questionnaire used to assess the severity of depressive symptoms and demonstrated good psychometrics [35].

2.4.3 State-trait anxiety inventory – Y Form (STAI – Y)

The STAI-Y [36] is a brief self-report assessment designed to measure and differentiate between anxiety as a trait and a state with good psychometric properties [37].

2.4.4 Hamilton depression rating scale (HAM-D)

The HAM-D [38] rates the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety, and weight loss. Clinicians have to rate each question by interviewing the patient and by observing patient's symptoms. The HAM-D showed good inter-rater and test-retest reliability [39].

Although HAM-D scores were moderately high, when clinically interviewed all patients reported negative anamnesis for mood disorders; only four patients affected by minor depression resulted to be included in this sample.

2.4.5 Hamilton anxiety rating scale (HAM-A)

The HAM-A [40] is a 14-item questionnaire that covers anxiety symptomatology. The test is administered by clinicians who rates patients' answers and the questions are split into seven for psychic anxiety and seven for somatic anxiety. Cronbach's alpha for the HAM-A was .89 [41] and its test-retest reliability was good [42].

2.5 Statistical Analysis

The Statistical Package for Social Sciences, version 17.0 (SPSS, IBM, Armonk, NY) statistical software package was used for data analysis. All scores of psychometric tests before and after the intervention have been compared with the paired sample t-test.

Potential correlations between LEDD and personality changes have been studied running bivariate (Pearson) linear correlations between changes in personality (i.e., NS at T0 – NS at T1 = ΔNS), psychiatric symptomatology, and LEDD (i.e., LEDD at T0 – LEDD at T1 = ΔLEDD).

An alpha level <.05 was considered statistically significant.

3. RESULTS

3.1 STN-DBS and PD Symptomatology

With this study we aimed at assessing changes in PD symptomatology after STN-DBT.

The Hoehn and Yahr scale has been used to describe PD staging before intervention in the off-medication condition. Participants were classified as follows: N=2 (11%) stage II, N=4 (22%) stage III, N=6 (33.5%) stage IV and N=6 (33.5%) stage V.
The UPDRS part II changed significantly from 23.86±6.52 to 10.02±7.93 (P<.001) as well as part III from 51.69±12.05 to 24.58±8.73 (P<.001, Table 1).

LEDD, expressed in milligrams (mg) significantly changed before and after the intervention (Table 1). We showed no correlations between the LEDD difference before and after STN-

DBS (ΔLEDD) and changes in personality, anxiety and depression scores (ΔLEDD vs ΔNS r=.06, P=.79; ΔLEDD vs ΔHA r=.14, P=.55; ΔLEDD vs ΔRD r=.32, P=.18; ΔLEDD vs ΔHAM-D r= -.18, P=.46; ΔLEDD vs ΔHAM-A r= -.12, P=.61).

In synthesis, UPDRS parts II and III as well as LEDD changed significantly after STN-DBS.

Table 1. L-dopa equivalent daily dose (LEDD) and Unified Parkinson's disease rating scale (UPDRS) part II and III before (T0) and after (T1) deep brain stimulation of the subthalamic nucleus (STN-DBS)

	Mean±SD			
	T0	**T1**	**t**	***P***
LEDD (mg)	1169.86±435.71	527.5±283.99	8.76	.001
UPDRS II	23.86±6.52	10.02±7.93	5.64	.001
UPDRS III	51.69±12.05	24.58±8.73	8.76	.001

Legend: LEDD: L-dopa equivalent daily dose (expressed in milligrams, mg)
UPDRS II: Unified Parkinson's Disease Rating Scale, part II
UPDRS III: Unified Parkinson's Disease Rating Scale, part III

3.2 STN-DBS and Personality and Psychiatric Symptoms

With this study we aimed at assessing changes in personality and psychiatric symptoms after STN-DBT. We found significant differences on the TCI; in particular, as regards temperament dimensions, novelty seeking (NS, *P*=.02) and reward dependence (RD, *P*<.001) scores resulted to be higher whilst harm avoidance (HA, *P*=.04) was found to be lower after STN-DBS (Table 2). On the other hand, we did not find any difference on TCI character domains before and after STN-DBS (Table 2).

No significant differences were reported either on BDI or STAI-Y scores (data not shown) whereas both HAM-D and HAM-A scales significantly improved before and after STN-DBS (HAM-D: T0 16.28±8.50 [4 patients resulted to be affected by clinically relevant minor depression] T1 11.94±6.42, P<.001; HAM-A: T0 13.39±5.64 T1 10.50±5.07, P<.001).

In closing, temperament dimensions as well as interviewer-based assessments of anxiety and depression improved significantly after the intervention.

Table 2. Temperament and character domains of the Temperament and Character Inventory (TCI) before (T0) and after (T1) deep brain stimulation of the subthalamic nucleus (STN-DBS)

	Mean±SD			
	T0	**T1**	**t**	***P***
Novelty seeking (NS)	14.78±5.79	18.06±8.01	-2.49	.02
Harm avoidance (HA)	19.28±6.25	16.39±5.21	2.20	.04
Reward dependence (RD)	13.83±3.20	15.28±2.88	-4.57	.001
Persistence (P)	4.72± 1.44	5.17±1.46	-1.28	.21
Self-directedness (SD)	30.44±4.89	30.06±6.62	0.28	.73
Cooperativeness (C)	31.11±4.73	32.61±4.47	-1.74	.01
Self-transcendence (ST)	15.61±4.75	14.11±5.29	1.46	.16

4. DISCUSSION

The primary aim of this study was to investigate changes in personality traits in individuals affected by PD assessed one month before and six months after STN-DBS. Our main finding is that temperament dimensions changed after surgery, differently from character ones that remained stable. It is noteworthy that not only NS but also HA and RD changed after surgery. Temperament has been theoretically [22] and experimentally [43,44] shown to mirror the biological networks in the brain and RD has been shown to reflect the attitude of an individual to react to reinforcements and maintain a certain behavior previously associated to social reward or punishment [22]. All in all, this study raises the possibility that the aforementioned changes may be due to STN-DBS and its effects on those brain networks mostly related to motivational aspects.

NS increased and it has been found to have a major role in PD since dopamine-related [22] and low scores on this subscale in PD patients have been consistently found in literature [23-25]. Broadly speaking, this feature characterizes individuals who are rigid, frugal, stoic, and persistent [27], showing startling similarities with individuals affected by Obsessive-Compulsive Disorder (OCD). Moreover, the STN is a shared target of DBS for both diagnoses [45]; in fact, a double-blind multicenter study conducted on refractory OCD individuals demonstrated the effectiveness of STN-DBS in significantly lowering obsessive-compulsive symptomatology [46]. Accordingly, also in parkinsonian patients [5,47] the stimulation of the STN strongly improved their OCD traits further suggesting a role of the STN in the integration of associative-cognitive, limbic-emotional, and sensorimotor inputs [48]. Therefore, PD and OCD patients may have a partially shared neurobiological substratum that could be measured by this temperament dimension.

HA represents a complex temperament trait that has been found to be linked to the neurotransmitter serotonin in the brain [22], playing indeed a potentially relevant role in the development of anxiety and depression. Since HA changes have been found to correlate with depressive scores [49] our results are in line with previous literature [26,50] and with the improvement we reported on the clinician-rated assessments of anxiety and depression.

In order to better understand the significant change in RD that PD patients showed after surgery, the complexity of the STN should be taken into account. This nucleus is thought to be part of a more distributed cortico-subcortical network involved in the selection, facilitation and inhibition of movements, emotions, and behaviors [50]. The STN can be divided into functionally segregated areas: motor, oculomotor, associative, and limbicand it is involved in decision-making processes [11]. Although the role of STN in the motor cortico-basal ganglia-thalamo-cortical loop has been widely described, its role on limbic functions remains unclear [14]. The medial tip of the STN represents its limbic portion receiving inputs from the anterior cingulate cortex, the medial prefrontal cortex, the limbic part of the striatum (nucleus accumbens), the ventral tegmental area, and the limbic ventral pallidum. The limbic portion of the STN sends projections to the limbic sections of substantia nigra and the ventral tegmental area. This circuit could be involved in linking the STN to the mesolimbic dopaminergic network and to limbic cortical structures, potentially explaining limbic impairments (e.g. apathy and depression) possibly observed after DBS [10,15]. Moreover, research on human [16] and animal models [17,51] suggested the STN as involved in reward and motivational functions. The change on RD we found raises the intriguing possibility of a surgery-related change in these networks but larger studies with control groups may want to replicate this finding.

Given the dearth of systematic psychiatric evaluations of PD patients presenting to STN-DBS, we aimed also at assessing depression and anxiety symptomatology before and after surgery with both self-report and clinician-rated instruments. In line with previous literature [12,50,52] we found encouraging results although we reported mixed findings using objective and subjective assessment tools with significant improvement only on the clinician-rated evaluations. Since many psychosocial factors may be taken into account in self-administered reports of anxiety and depression levels, our study is in line with previous literature questioning the reliability of patient-rated assessments [10] potentially generating mixed findings [1].

It is of interest that the changes on TCI, HAM-A and HAM-D were not linearly correlated with LEDD modifications since chronic replacement medication has been called into question in the development and worsening of psychiatric symptoms [9,53].

Our data are only partially in line with previous literature. In fact, our group previously reported [27] higher scores on some NS sub-dimensions after STN-DBS; however, it should be borne in mind that the design of our earlier study was profoundly different from the current one. In fact, a longitudinal approach had not been undertaken in our previous work and a different sample composition had been considered. Hence, the results may be not fully comparable. Moreover, Houeto and Cowokers [26] did not find any change in personality before and after surgery. This difference could be better understood with the following considerations: 1) two different instruments were used (TCI versus TCI-R); 2) they excluded personality disorders on the basis of a different a priori hypothesis; and 3) sampling biases may account for the lack of significance of NS scores.

As a secondary aim, we investigated motor symptoms after STN-DBS and as expected our positive results are in line with previous literature [5-7,54].

5. CONCLUSION

In closing, STN-DBS resulted to be effective in PD on one hand as regards those temperament traits mostly related to limbic and reward circuits and on the other hand in improving anxious and depressive symptomatology with no correlations with replacement therapy. Improvement of motor function after this intervention was also confirmed. However, the present findings should be taken with caution since our work suffers from small sample size, lack of control group, and relatively short follow-up. Finally, notwithstanding an accurate psychiatric evaluation at baseline, four patients affected by clinically relevant minor depression were included. Future studies are indeed warranted to confirm our findings.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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