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Neuropsychological balance in Parkinson's patients after deep brain stimulation: total electrical energy delivered or led positioning?

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Abstract

Introduction

Parkinson's Disease (PD) is characterized by some cardinal motor signs: 4-6 HZ resting tremor, rigidity, and bradykinesia. Furthermore, most patients may experience neuropsychiatric disturbances throughout their disease, including depression, anxiety, sleep disturbances, psychosis, and behavioral and cognitive changes. The Deep Brain Stimulation has so far proved to be a successful neurosurgical procedure in controlling the motor symptoms associated with PD. However, since 2013, some authors have highlighted a possible correlation between the occurrence of mood disorders such as apathy, depression, and suicidal ideation, and deep brain stimulation surgery. Therefore, to date, several prospective and retrospective studies investigated this phenomenon showing conflicting results, mainly due to differences in population characteristics and study designs.

Our study appraised the neuropsychological balance after one-year DBS.

Methods

From 2011 to 2020, the Neurosurgery Division at Federico II University of Naples performed 53 procedures. Of these patients, fourteen (26%), seven females, and seven males underwent a comprehensive neuropsychological examination at baseline and one year following STN-DBS. The *Suretune™ Medtronic®* software ensured a detailed evaluation of the lead position, whereas total electrical energy delivered was estimated using the Koss formula.

Results

There was no difference in the baseline characteristics. The leads were positioned within the dorsolateral area of the NST for all patients. Evaluation at 12 months in the 14 patients showed a significative clinical improvement in the post-operative UPDRS (*p*-value = 0,004). The Student's t-test performed between preoperative and postoperative data turned out statistically significant for two psychological tests: HAM-A (*p*-value 0,0410) and BIS-11(*p*-value= 0,0483); no significant differences were found in the remaining tests administrated. TEED was not correlated to behavior modifications.

Conclusions

A tailored and multidisciplinary patient evaluation, alongside a correct target selection, and maximal accuracy, guarantees the best efficacy and safety, without permanent alterations in the neuropsychological asset, following the Deep Brain Stimulation Surgery.

State of art

Parkinson's disease (PD) is the second most common neurodegenerative disorder.

It occurs in approximately 7 million people worldwide, with 0,3-1% prevalence in the 60-80 year range. It is characterized by dopaminergic neurodegeneration of the nigrostriatal pathway, resulting in both motor and non-motor symptoms[1-4].

The ancient medical system of the Ayurveda, born and developed in India between 4500 and 2000 BC, recognized already the first signs of this disease, using the term "*Kampavata*" to refer to a clinical picture characterized by tremor, akinesia, depression. They also identified some herbal preparations, containing levodopa, for treating the disease. [5]

In the early 70' bestseller "The Terminal Man" highly anticipated the revolutionary treatment for Parkinson's Disease: deep brain stimulation (STN-DBS), approved in 1997. The main character of the romance was treated by an experimental psychosurgical procedure known as "Stage Three" with the positioning of electrodes in his brain.

Deep Brain Stimulation (STN-DBS) so far proved to be highly effective in treating many of PD's motor symptoms and often allows medication reductions [6].

However, since 2013, some authors have highlighted a possible relationship between mood disorders and deep brain stimulation.

DBS and mood disorders

Parkinson's disease and its treatments impact on frontal–striatal systems, a critical pattern for behavioral regulation. [7]

DBS induces controversial effects on mood disorders. [8] Several authors demonstrated its efficacy on treatment of depression and anxiety. Many others underlined the worsening of mood state with a higher risk of suicide. There are several cohort studies concerning behavioral changes following DBS, including the onset of mania, depression, suicidal ideation, apathy and impulsivity, as well as effects of this treatment on global cognitive abilities, attention, executive functions, and memory.[9, 10] [11-13]

Nowadays, the conclusions about mood disorders outcome after DBS are unclear probably due to the relative heterogeneity of the scales to evaluate the outcome.[14-19]

Euphoria, hypomania, and mania

Postoperative euphoria and hypomania have been described in 4–15% of patients and usually are observed within the first 3 months after surgery. Manic psychosis occurs in 0.9–1.7% of patients.[20, 21]

These conditions typically develop in close association with DBS initiation; thus, such states seem to be a direct consequence of neuromodulation affecting the limbic basal ganglia pathways. This is supported by the electrode position within the anteromedial limbic territory of the STN.[22-24] and by inadvertent axonal activation in the medial forebrain bundle, which runs close to the anteromedial STN. Indeed, The medial forebrain bundle is an important pathway of the mesolimbic dopamine system and belongs to the reward circuitry, which has been implicated in affective disorders, addictive behavior, and learning. [15, 16]

In the long term, the stimulation threshold for induction of these phenomena gradually increases and, eventually, the contact that initially caused the adverse effect can be used for chronic stimulation. [25]

Depression

Depression is observed in 20–25% of patients with PD following subthalamic surgery, and that such symptoms typically develop within the first 2 months of undergoing this procedure. [26, 27] The effect of psychological components must not be underestimated. Risk factors for postoperative depression include rapid or excessive withdrawal of dopaminergic medication, a previous history of depression, and problems adjusting to a reduction in disability level. [10]

Castelli et al. found no differences in mood or anxiety in patients with PD following 3 years of treatment with either STN-DBS or best medical management.[17] This is in line with a 5 year follow-up study, in which only one of 49 patients with PD who underwent STN-DBS developed clinically relevant depression at the end of the observational period.[28] Another prospective study evaluated mood and psychosocial functioning in such patients for 3 years after STN-DBS and also found no marked changes in these states over the study period.

In a case report by Tommasi and colleagues,[29] acute transient depression was induced by DBS through several contacts of the quadrupolar electrodes, these contacts covered a large subthalamic volume including the zona incerta, STN and substantia nigra. The stimulation-induced mood changes subsequently adapted with time, indicating that the micro traumatic effect of the implantation procedure contributed to the appearance of these changes. [30]

The involvement of ventral contacts in the stimulation and its relationship with mood disorders was further corroborated by the ComPare trial, [31] in which 22 patients with PD rated themselves on average ‘less happy’, ‘less energetic’ and ‘more confused’ when stimulated ventrally (below the optimal motor target) than when stimulated by a more distal contact within the sensorimotor region of the STN. No patients in this trial, however, exhibited acute depressive symptoms.

Ventral subthalamic stimulation might reproduce a mild depressive syndrome through limited current spread into this region. Studies evaluating acute mood changes with stimulation inside the STN through contacts providing optimal motor control-have consistently reported acute anti-depressive and mood-elevating effects in patients. [32, 33]

Anxiety

Anxiety (up to the level of panic attacks) is a frequent nonmotor symptom during off periods in medically treated PD patients. In a controlled study of patients with PD, individuals who underwent DBS-STN had markedly lower Beck anxiety inventory scores after 6 months of therapy than individuals receiving best medical treatment. Caution is warranted in the interpretation of this finding, however, as the Beck anxiety inventory includes several items with a strong somatic connection (such as an inability to relax and tremor of the hands) that improve considerably after DBS. [10] However, reductions in anxiety following sub-thalamic neurostimulation have been reported in studies using other scales and measures of state anxiety during stimulation challenges. [32, 34] Whether reductions in anxiety occur secondarily to improvements in motor fluctuations or are a genuine nonmotor effect of DBS-STN remains unknown. [35, 36]

Apathy

Apathy is the most frequent long-term psychiatric adverse effect of subthalamic neurostimulation. Clinically, apathy is defined as a decrease in motivation and interest that cannot be ascribed to emotional or cognitive disorders, or to an impairment of consciousness. The proportion of patients with PD who exhibited apathy was documented to be 8.7% before surgery and 24.6% in the third postoperative year. [24]

In individuals with PD, apathy is more frequently associated with a frontal dysexecutive syndrome or dementia than with depression, indicating that this symptom is at least in part attributable to an advanced stage of disease characterized by widespread neurodegeneration. [37] In other studies apathy was associated with the spectrum of hypodopaminergic nonmotor symptoms of PD because in some patients this symptom responds to dopaminergic treatment. [38]

Disease progression might explain the increasing incidence of apathy seen in long-term follow-ups after DBS surgery. However, a marked deterioration in apathy scores has been noted as early as 3–6 months post-operatively, indicating that apathy is associated with either neurostimulation itself or medication withdrawal in the immediate postoperative period. [18]

These preliminary data indicate that subthalamic neurostimulation might inadvertently modulate a frontal motivational network that is connected to the limbic and associative territories of the STN, thereby causing apathy. This etiological concept is still controversial, however, as a study comparing apathy in the stimulation-on and stimulation-off states found an improvement in self-reported apathy with STN-DBS. [39]

Suicide

The risk of suicide in patients post-DBS is estimated to be higher than the average for the general population and higher than the average for those with Parkinson's disease who had not sought DBS. [40]

According to Burkhard et al.[41], pre-operative risk factors include history of severe depression and multiple DBS surgeries, despite successful post-operative motor outcomes. Conversely, a later study, of 200 STN-DBS patients with PD found that post- operative depression or impulsivity was associated with suicidality, with no evident difference in pre-operative depressive or cognitive status between suicidal and non-suicidal patients. [42]

The frequency of suicide, reported in a multicenter survey, among patients undergoing STN-DBS for advanced PD is 0.45% of surgically treated patients (24 of 5,311 individuals). The rate of attempted suicides in such patients was reported to be 0.90%. Postoperative depression, being single, and a previous history of iCDs were found to be independent risk factors for suicide in these patients (together, these factors accounted for 51% of the postoperative suicide risk). [43]

Another study revealed that suicide attempts can occur in surgically treated patients with PD who have no previous or present psychopathology and under circumstances that underline the impulsive nature of this behavior. [44]

Relationship between neuropsychological outcome and led position

The subthalamic nucleus (STN) is a highly organized structure, and several studies examineted its spatial and functional organization. It can be distinguished in three functionally distinct territories: a dorsolateral component, involved in somatomotor functions, an anterior component, ventromedial, with associative functions in communication with the limbic system, and a pure medial part, involved in the limbic circuits although documented only in primatesv[45]. Therefore, the best target for DBS procedure, to lessen the risk of interference with the limbic circuits and neuropsychological sequelae, would be represented by the dorsolateral portion [45]. However, it is not always easy an easy task to obtain. Indeed, the STN is a very small structure and the discrimination among emotional, cognitive, and motor areas is very difficult. York et al. evaluated the led positioning using software (Framelink 5.1TM) for achieving the approximated localization within the STN with several different parameters such as the superomedial distance (distance to target) and inferolateral (distance past target). They reported cognitive and emotional changes six months after bilateral STN DBS, suggesting that the angle of surgical trajectory and electrode placement can play a role in cognitive and emotional functioning [46]. This is supported by Tsai et al. that demonstrated the relationship between the worse psychiatric outcome with a more anterior and ventromedial led localization [47].

Postoperative onset of the psychiatric disorders, represented by opposite conditions such as apathy and depression with suicide and suicide attempts on one hand, or mania and impulse control disorders on the other with significant social life changes, have been widely underlined. It led to a flourishing bloom of studies showing conflicting results, mainly due to differences in population characteristics and study designs.[18, 48-51] Our study aims to evaluate the neuropsychological balance after Deep brain stimulation, considering a homogenous sample of patients selected by a multidisciplinary team, enriched by the neuropsychiatric specialist.

Patients and Methods

This prospective study aimed at assessing the relationship between neuropsychiatric disorders and Deep Brain Stimulation.

Patients

From 2011 to 2020, 53 patients affected by Parkinson's Disease were enrolled at the Neurosurgery Department of the University of Federico II of Naples and treated with Deep Brain Stimulation, with selective targeting the dorsolateral region of the Subthalamic Nucleus (STN).

All patients were evaluated by a multidisciplinary team of neurologists, neurosurgeons, psychiatrists who assessed the eligibility for surgery by administering the Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD) (Table 1).[52]

Of these patients, fourteen (seven females, and seven males with an average age of 55,7 years old) have been prospectively exanimated at baseline and one year following STN-DBS on a comprehensive neuropsychological examination. Eight of them were already in treatment with antidepressant drugs (fluoxetine and duloxetine), while six of them were treated with benzodiazepines (lorazepam, alprazolam) or mild sedatives (melatonin-based drops) at the same time. The characteristics related to the patients are summarized in Table 2

General and mood evaluation	Mattis Dementia Rating Scale	**MDRS**
	Montgomery and Asberg Depression Rating Scale	**MADRS**
Executive function	Verbal fluency: letters F, A, and S	**FAS**
	Paced Auditory Serial Addition Test	**PASAT**
	Odd Man Out	**OMO**
	Modified Brown Peterson Paradigm	**MBPP**
Explicit memory	Rey Auditory and Verbal Learning Test	**RAVLT**
	Visual amnesic battery of Signoret	
Procedural memory	Short version of Tower of Hanoi	

Table 1.

Core assessment program for surgical interventional therapies in Parkinson's disease CAPSIT-PD.

Patients Characteristics	
Subjects	14
Sex (% female)	50%
Age	55,7±9.12
Duration of disease(years)	9.78±2.51
Depression	8

Table 2.

Patients Characteristics

Clinical Assessment

Neurological Evaluation:

The patients were evaluated by the same neurologic team 3 months before the operation and every three months following the STN-DBS. The neurological assessment was performed in off-medication condition, after a 12-hour withdrawal from drugs, and in the on-medication condition with Unified Parkinson's disease rating scale (UPDRS).

It was the neurologist's task to gradually reduce L-dopa treatment to the maximum extent permitted by patients' motor state starting from the day following surgery. About two weeks after the surgery, the pulse generator was activated, and in the following months, the optimal settings for all patients were reached.

Neuropsychological Evaluation:

The patients have been prospectively exanimated at baseline and one year following STN-DBS on a comprehensive neuropsychological examination that explored 5 psychological domains with the following self and hetero-evaluation scales:

- ***Depression:***

The hetero-evaluation scales used were the Hamilton Scale for Depression (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS). HAM-D indicates the absence of depression if the score is </ = 7, mild depression for a score between 8 and 17, moderate between 18 and 24, and severe if> / = 25) and it represents the reference standard; whereas for MADRS there is absent depression with scores between 0-6, mild 7-19, moderate 20-34, severe> 35. The self-assessment scale administered was the Beck Depression Inventory (BDI) that states minimal depression if the score is less than 9, mild between 10-18, moderate 19-29, severe if> 30.

- ***Anxiety:***

The hetero-evaluation scales used were the Hamilton Rating Scale for Anxiety –(HAM-A) and the Anxiety Status Inventory (ASI). HAM-A scores are characterized by: <17 mild anxiety, 18-24 moderate, 25-30 severe,> 30 persistent anxiety). ASI, instead, has for cut off a score of 45 to discriminate the presence or absence of anxiety. As self-assessment scales, the Self-rating Anxiety State scale (SAS) and the Beck Anxiety Inventory scale were used. SAS has a single cut-off of 45 to discriminate the presence or absence of anxiety; BAI (<21 mild anxiety, 22-35 moderate anxiety,> 36 severe anxiety).

- ***Apathy:***

The scale used was the Apathy Evaluation Scale (AES) which is characterized by a cut off 38/72 (a higher score indicates a more severe apathy level) and treats apathy as a psychological dimension defined by several aspects:

1. Cognitive apathy: Reduction of initiative followed by executive deficits in attentional supervision, planning, scheduling of activities (lesions of the dorsolateral prefrontal circuit)
2. Emotional-affective apathy: Affective flattening and difficulty in associating and in the interpretation of emotional signals with behavior (Lesions of the orbito-medial prefrontal circuit)
3. Behavioral apathy: difficulty in reaching the activation/initiative threshold necessary to generate the motor programs aimed at completing the targeted behavior, which can be overcome with external stresses

- ***Impulsiveness:***

For its evaluation, the Barratt Impulsiveness Scale-11(BIS-11) was used. It discriminates the presence or absence of impulsivity with a cut-off of 63.8±10.

- ***Suicidal ideation and attitudes:***

The scales used were the Reason for Living Inventory (RFL-48), the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Scale for Suicide Ideation (SSI).

These tests were administered to patients 3 months before the surgical procedure (time 0-t0) with the patients in "ON" state, approximately one hour after taking the drug, and then again 12 months following the surgery (time 1 -t1), in the same conditions. The overall examination lasted for an hour and a half for each patient; the presence of family members or relatives that could have influenced the patient's responses was avoided.

Surgical technique and programming

Patients underwent the bilateral implantation of a Deep Brain Stimulation system with a selective targeting on the dorsolateral region of the Subthalamic Nucleus (STN). [53] To ensure the correct placement of the electrodes, accurate preoperative planning was performed and a postoperative CT was done to check the right position of the electrodes.

Imaging Evaluation:

Each patient performed a preoperative MRI with sequences specific for our Parkinson protocol (FLAIR, MP-RAGE, MP2-RAGE) . On the first postoperative day, a CT scan of the skull, integrated with radiography extended to the right subclaviclear region, was performed to show the correct positioning of the leads and the components of the deep brain stimulation system.

Moreover, the *Suretune™ Medtronic®* software ensured a detailed evaluation of the electrodes' localization (Fig 4 and 2). It is an innovative system that allows an extremely accurate tridimensional evaluation of the electrical contact. This novel technology was a fundamental support in verifying the extent of the postoperative stimulated area in order to correlate the relationship between postoplerative mood disorders onset with the leads localization.

TEED estimation

Total electrical energy delivered (TEED) per second through the STN-DBS leads was estimated using the KOSS formula. [54] The stimulation parameters and the contact impedance were read at 12 months after DBS, and TEED values were calculated without side distinction.

Statistical Analysis

All data analyses were performed using R Studio software™ (version 1.3.959). Data were summarized in terms of size and frequency for categorical data by mean scores±standard deviation for quantitative data. The data have been analyzed by performing a paired *t*-test (Student's *t*-test) comparing preoperative and postoperative data. A *p-value* <0.05 was considered significant.

TEET analysis was performed with the Koss formula.

Results

14 patients were enrolled in the study and the data are summarized in Table 2. There was no difference in the baseline characteristics. 8 patients were already in treatment with antidepressant drugs (fluoxetine and duloxetine), while six of them were treated with benzodiadepines (lorazepam, alprazolam) or mild sedatives (melatonin-based drops) at the same time. Evaluation at 12 months in the 14 patients showed a significative clinical improvement in the post-operative UPDRS (*p*-value = 0,004) (Fig 1). The Student's t-test performed between preoperative and postoperative data turned out statistically significant for two psychological tests: HAM-A (*p*-value 0,0410) and BIS-11(*p*-value= 0,0483)(Fig. 2-3); no significant differences were found in the remaining tests administrated. Table 3 (Table 3) summarizes the t-Student tests carried out for each neuropsychiatric test. The electrodes were located within the NST for all patients (Fig. 4-5). We did not observe any significant correlation between TEED and neuropsychological modifications.

Test	Average + Standard Deviation		*P-value*
	T0	T1	
HAM-D	10,64±6,11	8,78±6,67	*0.4241*
MADRS	12,78±7,04	11,21±6,36	*0.5460*
BDI	12,64±5,27	10,5±6,58	*0.2856*
HAM-A	14,36±6,40	10,29±5,46	***0.0410****
BAI	15±6,67	11,71±8,79	*0.1717*
ASI	45,14±8,18	45,5±17,93	*0,9485*
SAS	50,07±7,21	48,86±11,99	*0.721*
RFL-48	4,64±0,47	4,47±0,35	*0.2511*
SSI	0,5±1,87	0,36±0,63	*0.8003*
AES	29,35±6,68	29,71±6,68	*0,8781*
BIS-11	60,14±8,72	66,07±8,76	***0.0483****

Table 3. Neuropsychological tests result

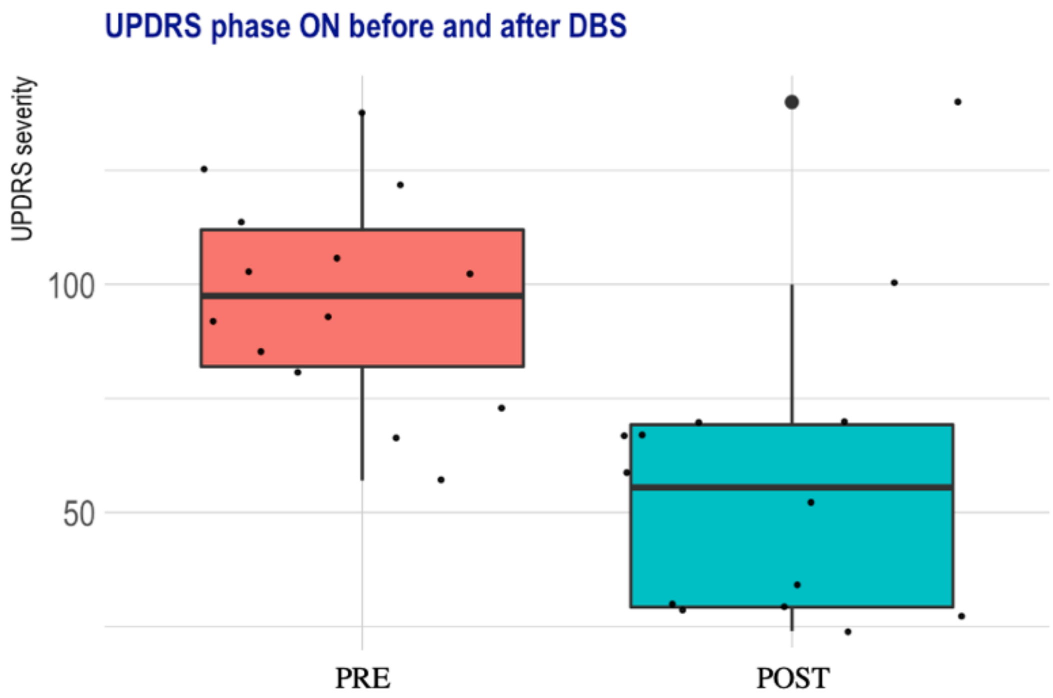

Figure 1. UPDRS score before and after DBS surgery

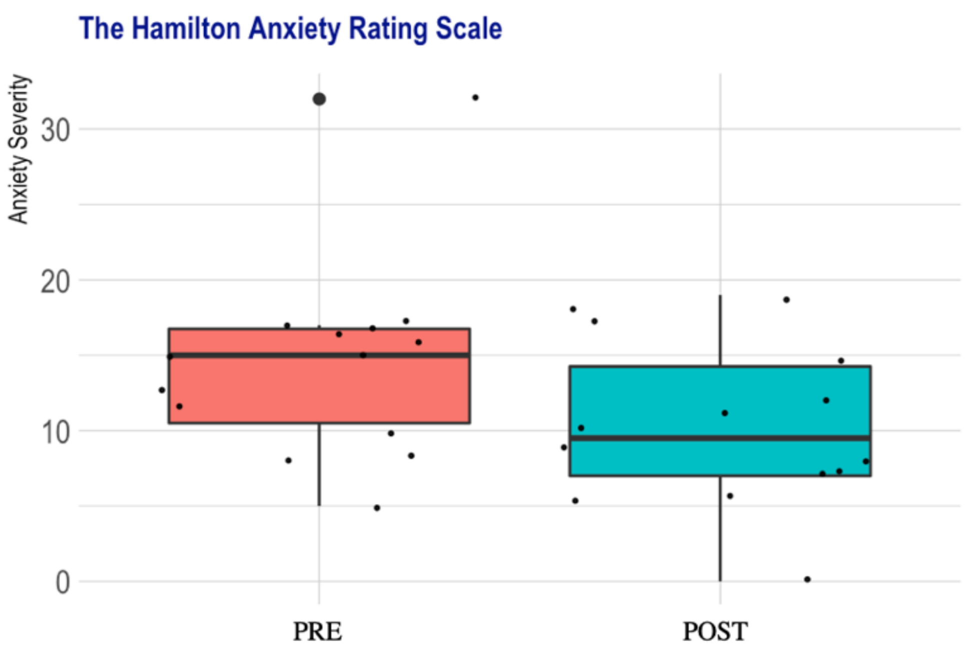

Figure 2. Preoperative and postoperative BIS-11 box plot

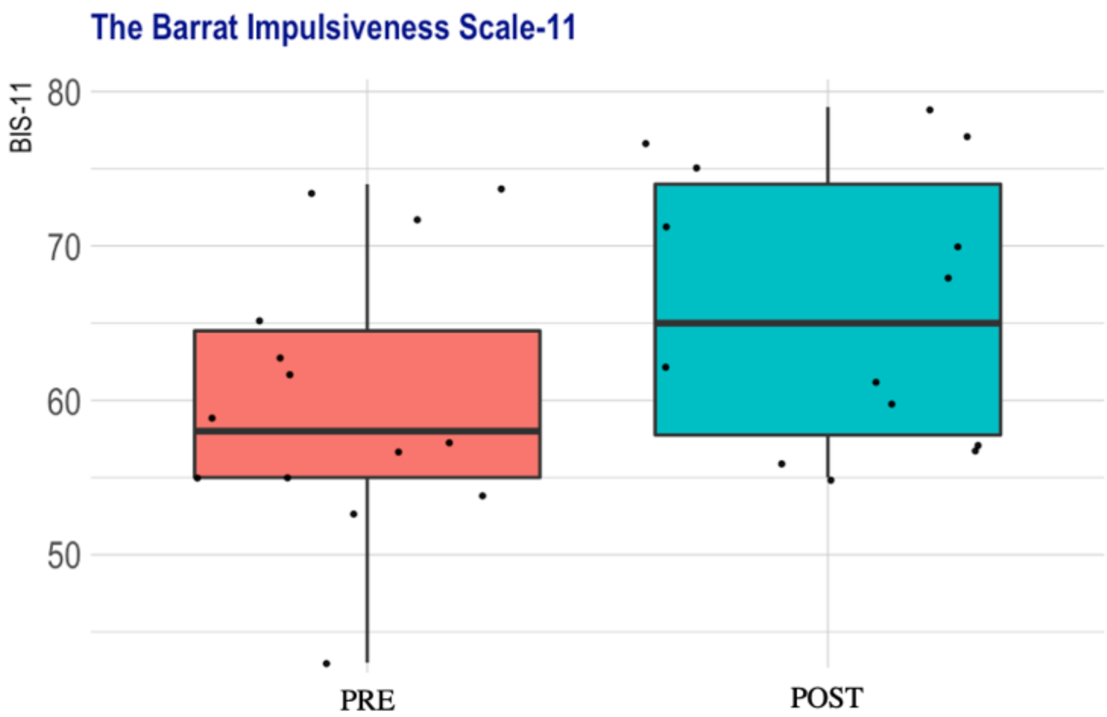

Figure 3. Preoperative and postoperative HAM-A box plot.

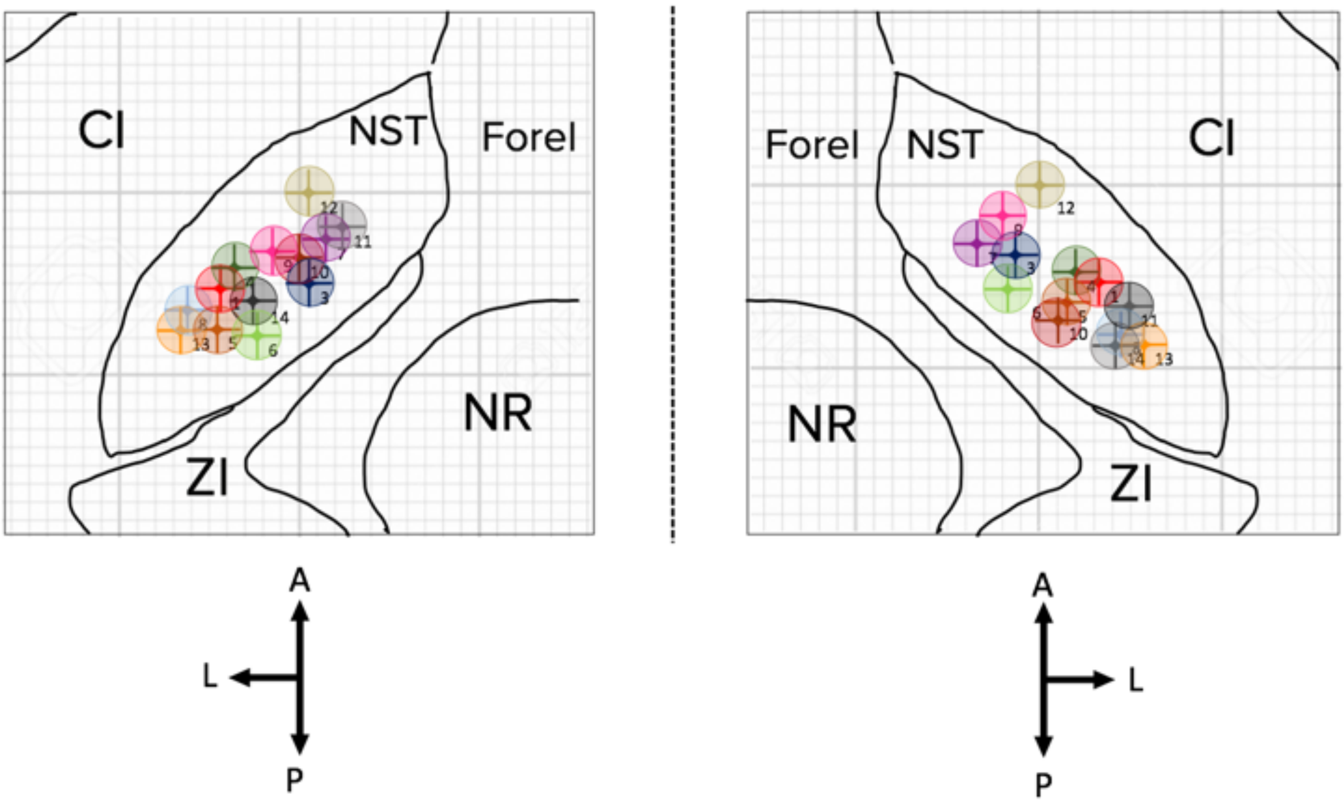

Figure 4. Leads position within the STN.

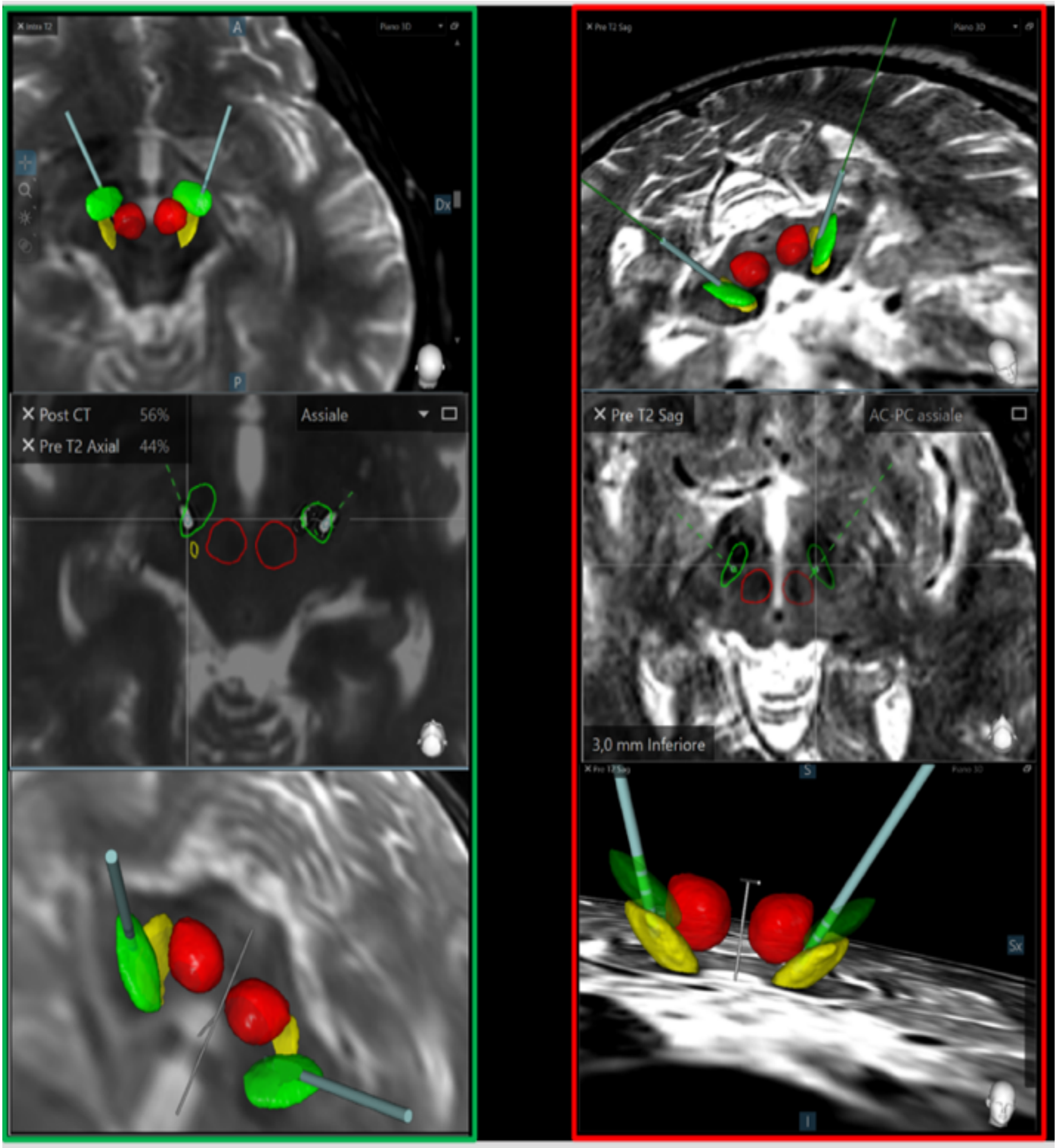

Figure 5. Tridimensional representation with Suretune™.

Discussion

Deep brain stimulation (DBS) is a very well-established and effective treatment for patients with extrapyramidal diseases. However, some undesirable neuropsychological outcomes have been reported after surgical procedure and are still a matter of discussion.

In our series, we investigated the relationship between the DBS and the neuropsychiatric outcome through a comprehensive neuropsychological evaluation before and 1 year after the surgery. Moreover, we focus our attention on the possible correlation between the impact of the total energy delivered and the led positioning within the STN with the mood status of the Parkinson patients.

Several hypotheses have been formulated to explain the complex mechanisms behind the possible onset of neurophysiological disorders after DBS [55-58].

Inevitably, it could be related to the patient. Indeed, some patients with PD are more prone to develop psychiatric disorders after DBS than others. In this scenario, the family history, pre-existing non-motor fluctuation, disability grade, and length of duration disease play a crucial role. [6]

In this regard, it is important to consider the difficulty in identifying a depressive state in patients with PD. It is not an easy task to accomplish; depression or apathy and PD have several symptoms and signs in common, and this symptomatologic overlap makes harder the diagnostic process, especially in the initial stages of the disease. Bradykinesia, identified as the difficulty in initiating actions and carrying out the normal activities of daily life, inexpressiveness, and facial amimia are reminiscent of the psychomotor slowdown, reduction or loss of initiative, and affective dulling that characterize depression or apathy. Therefore, it is difficult to differentiate among somatic and vegetative Parkinson symptoms such as fatigue, sleep, and appetite alterations with possible expressions of depression. Consequentially, it has been suggested that reduced appetite and early awakening in the morning are more specific to PD; hence, these would be the signs and symptoms that should be researched when counseling the PD patient about depression.

However, considering that the tests administered on a daily basis are aimed at assessing the presence and severity of depressive symptoms in the general population, it is challenging to ensure a result that is specific enough of depression associated with PD. [55]

Furthermore, each patient can present variations of the neurodegeneration process. Canesi et al. reported that mood alterations in PD, considering both depressive symptoms and mood elevation, are related to the advanced stages of the disease as well as the presence of impulsive disorders, and dopaminergic therapy alone would not always be able to restore a normal mood condition. In addition, it has been described that the occurrence of psychiatric disorders is correlated with the mesocorticolimbic dopaminergic denervation more than the nigrostriatal denervation. [59-62]

Another aspect to consider, according to Thobois et al., is the Delayed Dopamine Withdrawal Syndrome (DAWS). It is due to the consistent postoperative reduction in dopamine and L-dopa medications. It is characterized by apathy, depression, and suicide attempts that have a significant percentage of regression after dopamine agonist administration[62].

All patients underwent the same degree of reduction in dopaminergic therapy, but the patients could have been affected in different ways according to disease duration or degrees of motor impairment.

The Student's t-test performed between preoperative and postoperative data turned out statistically significant for two psychological tests: HAM-A (*p*-value 0,0410) and BIS-11(*p*-value= 0,0483).

We did not find any statistical difference between patients who had a history of anxiety or mild/moderate depression and those who did not have a pre-existing psychiatric disorder.

However, in two cases, we assisted a significant mood improvement. Both patients had a longer disease duration with a history of mild depression. After DBS, they experimented improvement of their invalidated symptoms with significant better change of their quality of life and of their depression mood. This is in line with Combs et al. findings[18]; they stated a better chance of larger reductions of depressive symptoms correlated with the length of time an individual lives with Parkinson's disease prior to seeking DBS, hence with longer disease duration. This aspect is important to consider, because patients with high levels of depressive symptoms are routinely assessed as weaker candidates for surgical consideration. [63]

Some studies implied that an initial improvement in anxiety might be ascribable to the improvement in the motor domain, but it can be followed by a worsening subsequent to the several adjustments of stimulation parameters that the patients have to endure in the postoperative period (particularly an increase in voltage and intensity) or alteration of limbic circuits[64],whereas other studies did not find any significant correlation between DBS and anxiety. [18]

The worsening of impulsivity assessed by the BIS scale has been just reported. [57] [65]It is mandatory to underly, that albeit there was a statistically significant increase of impulsivity, it remained within the range limit for all the patients, compared to the general population. Furthermore, the intake of dopamine agonists in PD patients is a risk factor for the development of an impulsive disorder. [66]

In this scenario, it is important to underline that the increase in impulsive behaviors would lie in the functional characteristics in the STN itself. Indeed, it is involved in corticocortical motor networks, but also in cognitive and emotional pathways[10]. In particular, the ventromedial region actively draggers in the limbic circuits. It appears essential to allow the integration of all information related to the decision-making process for preventing premature, impulsive responses, especially in high-conflict situations. In other words, it is referred to a « hold your horses » signal allowing to delay the decision and gather additional information to choose the best option. [67]

Thus, the leads positioning within the NST can play a role in the mood disorders, induced by direct and indirect stimulation of the pathway enrolled in the mood control. York et al. [28] support the hypothesis that the dorsolateral subthalamus, responsible for motor control, is the most suitable site for electrode placement, since it guarantees the best outcome.

The *Suretune™ Medtronic®* software, that ensures a detailed and tridimensional evaluation of the leads' localization, showed dorsolateral location of all electrical contacts. Indeed, our patients experimented an improvement of motor symptoms with no significant changes of mood status. Therefore, two cases, distinguished by an important better change of their mood, characterized by a more lateral position of the contacts, confirming the key role of the lead location for the clinical outcomes.

In this contest, it is interesting evaluate the correlation between the neuropsychological alterations and the quantity of energy delivered in this highly organized structure.

To the best of our knowledge no previous studies evaluated this correlation, whereas few studies investigated only the relationship with motor outcomes[64]. In terms of stimulation settings, constant current (CC) and constant voltage (CV) to achieve equivalent motor efficacy have not shown any significant differences in non-motor outcomes, including cognition, mood, and quality of life. Dajal et al. in their review [68] analyzed the side effects emerging as a result in a change in the stimulation parameters delivered through a DBS contact. However, because of the natural anatomical variation between patients, as well as variations in surgical technique, targeting and precision, there is inevitably a confounding factor in the interpretation of stimulation adjustments between patients. Our TEED analysis showed no correlation with neuropsychological changes.

Given the complexity of the pathology and the limitations that underlie a correct neuropsychiatric evaluation, further studies with a more extensive series are needed. The future perspectives of DBS move towards ultra-tailored treatment by the BrainSense™ technology.

Limitations

A complete understanding of neuropsychological balance is difficult for several limitations. The assessments are based on tests outcomes that are not intended as diagnostic tools but as methods to assess the severity of the symptoms. Moreover, the hetero-evaluative scales are characterized by reduced objectivity, given that each answer is the result of a subjective evaluation of the doctor. The self-administered scales, on the other hand, may present the limit of a possible compromised understanding by the patients due to the educational level or the degree of cognitive impairment, especially in patients who have been suffering from the disease for a longer time. Furthermore, in some scales, such as the SAS, the Apathy Scale, and the BIS, for some items that explore well-being, the score is opposite to the others that instead explore negative symptoms, and it is meant for reducing the risk that the patient mechanically gives the same score to all items, however that can lead to confusion. Finally, the scale validity could be reduced by several factors, i.e., the poor educational background of the patient or a mood disorder related to any negative event that might occur in the follow-up year, albeit not having a causal correlation with the DBS, is mistakenly associated with it.

Conclusion

Our findings indicate that a tailored and multidisciplinary patient evaluation, alongside a correct target selection as well as the maximal accuracy in the postoperative treatment, ensure the best efficacy and safety without permanent neuropsychological disorders after Deep brain stimulation. Given the complexity of the pathology and the limitations that underlie a correct neuropsychiatric evaluation, further studies with a more extensive series are needed. The future perspectives of DBS move towards ultra-tailored treatment by the BrainSense™ technology.

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