Running title: Unilateral subthalamotomy: cognition and behaviour

Unilateral subthalamotomy in Parkinson´s disease: cognitive, psychiatric and neuroimaging changes

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Abstract

Unilateral subthalamotomy is an effective treatment for the cardinal motor features of Parkinson´s disease (PD). However, non-motor changes possibly associated with right or left subthalamotomy remain unknown. Our aim was to assess cognitive, psychiatric and neuroimaging changes after treatment with unilateral subthalamotomy. Fourteen medicated patients with PD were evaluated before and after (mean 6 months after operation) unilateral subthalamotomy (5 right, 9 left). In addition to motor assessments, cognitive (global cognition and executive functions), psychiatric (apathy, depression, anxiety, mania, hypo- and hyperdopaminergic behaviours, impulsivity), quality of life evaluations and volume of lesions were obtained. After surgery, significant improvement of motor signs was observed. Unilateral subthalamotomy improved general cognitive status, but left subthalamotomy reduced semantic verbal fluency compared to the pre-operative state. Depression and quality of life were improved with both right and left subthalamotomy. However, hyper-emotionality was present after surgery and right subthalamotomy increased impulsivity and disinhibition (on NeuroPsychiatric Inventory and Ardouin Scale for Behaviour in PD), a result linked to larger lesion volumes. We conclude that unilateral subthalamotomy is effective for treating the cardinal motor features of PD and improves mood. Right subthalamotomy is associated with greater risk of impulsivity and disinhibition, while left subthalamotomy induces further impairment of semantic verbal fluency.

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established treatment for Parkinson's disease (PD), whereas ablative surgery, i.e. subthalamatomy, is limited to special medical and economic circumstances. PD laterality is a critical aspect for surgery as implantation of DBS electrodes or surgical lesioning is guided by the most affected body side, determining if surgery is performed uni- or bilaterally. If the patient's motor signs are predominant on one hemibody, DBS or lesions are completed unilaterally (Alvarez et al., 2009; Krack, Fraix, Mendes, Benabid, & Pollak, 2002). A host of controlled studies and meta-analyses (Combs et al., 2015; Wang et al., 2016) have established that STN-DBS does not induce any significant decline in global cognition, but verbal fluency, some tests of executive function and inhibitory control show impairment with STN stimulation (Jahanshahi, 2013; Jahanshahi et al., 2000; Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Obeso, Wilkinson, Rodríguez-Oroz, Obeso, & Jahanshahi, 2013; Witt et al., 2008). In terms of behaviour and mood, after STN-DBS, some authors report improvement in apathy (Campbell et al., 2012) and depression (Witt et al., 2008); while others have documented worsening of depression and apathy (Lhommee et al., 2012; Thobois et al., 2013) in association with medication reduction.

Unilateral subthalamotomy has also been successfully used to treat the motor features of PD (Alvarez et al., 2005, 2009; Patel et al., 2003). Although unilateral and bilateral subthalamotomy for PD are by and large efficacious and safe (Alvarez et al., 2005, 2009), the cognitive and neuropsychiatric effects of subthalamotomy have only been examined in three studies. McCarter et al. (2000) evaluated cognitive functioning before and 12 months after subthalamotomy in 12 PD patients with a variety of surgical procedures, including 3 with right subthalamotomy, 2 with left subthalamotomy, 4 with right subthalamotomy + left STN-DBS and 4 with bilateral subthalamotomy. They reported no significant change after subthalamotomy on the cognitive tests used, but it was noted that left subthalamotomy was associated with worse cognitive outcome. However, the mixed group of patients with subthalamotomy and DBS leaves the results up to verification. A similar result of no change in cognition was obtained in 6 patients who had right and 7 who had left subthalamotomy (Patel et al., 2003). In the third study (Bickel et al., 2010), on 10 PD patients who had bilateral subthalamotomy, there was no significant change in cognition but a parallel motor and neuropsychiatric (depression and apathy) improvement was reported 24 months after surgery, whereas disinhibition and euphoria increased post-operatively.

Thus, the available evidence regarding the cognitive and psychiatric effects of subthalamotomy is inconsistent and potential laterality effects are not well-defined. Clarifying laterality effects is important since the two most consistent side effects of surgery (particularly after DBS) such as verbal fluency and disinhibition have clear hemispheric effects and may mainly present as side-effects of left or right subthalamotomy respectively.

In this study, our aim was to assess whether unilateral left and right subthalamotomy in PD may impact cognition, mood and behaviour differently. With this aim, we used an extensive battery of measures of cognition, mood and behaviour combined with imaging morphometric measures after subthalamotomy.

Methods

Patients

Fourteen (12 males) consecutive patients with PD who were candidates for unilateral subthalamotomy were enrolled in the study from October 2009 to December 2014 in the Centro Internacional de Restauración Neurológica (CIREN) in La Habana (Cuba). The patients were diagnosed with PD according to UK Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992) (see Table 1). Following previous surgical protocols (Alvarez et al., 2001, 2009), unilateral subthalamotomy was indicated based on predominant asymmetric hemibody motor features (mainly tremor and bradykinesia). Patients receive ablation of the STN contralateral to hemibody motor signs performed in a single surgery session. The STN sensorimotor region was localized using microrecording and stimulation while neurologists explore the motor signs while the patient is awake. Finally, when the target is located, a thermolytic lesion was placed accordingly. Nine patients received left and 5 right subthalamotomy. Neuropsychological assessment (by IO and EC) was completed before surgery and repeated approximately 6 months after surgery. For comparison purposes on some neuropsychological scores, healthy control data is shown in Figure 1 from previous studies (Obeso et al., 2012; Obeso et al., 2011). All patients were under levodopa treatment during assessments (except for the UPDRS-III OFF evaluation, see below).

Table 1. *Demographic and clinical information for individual operated patients. Mean and standard deviations (in brackets) are given for each variable.*

	Age (years)	**Sex**	**Education (years)**	**Lesion side**	**Duration of illness (years)**	**UPDRS (R/L side) pre – post**		**UPDRS pre – post**		**LEDD (mg) pre - post**		**MMSE pre - post**	
1	**48**	**M**	**12**	**right**	**10**	**18/21**	**17/11**	**57**	**9**	**1750**	**689**	**27**	**29**
2	**53**	**M**	**12**	**right**	**8**	**2/17**	**2/10**	**35**	**21**	**1138**	**1012**	**28**	**28**
3	**50**	**M**	**12**	**left**	**10**	**14/11**	**14/7**	**36**	**28**	**1500**	**1250**	**27**	**28**
4	**46**	**M**	**12**	**left**	**9**	**17/14**	**11/14**	**44**	**24**	**1100**	**600**	**30**	**30**
5	**49**	**F**	**9**	**left**	**18**	**21/16**	**9/16**	**60**	**28**	**945**	**350**	**27**	**28**
6	**64**	**M**	**17**	**left**	**9**	**10/8**	**4/8**	**44**	**32**	**1225**	**1225**	**30**	**30**
7	**53**	**F**	**9**	**left**	**10**	**11/5**	**4/4**	**45**	**18**	**500**	**500**	**27**	**28**
8	**57**	**M**	**9**	**left**	**16**	**16/10**	**7/10**	**42**	**22**	**1350**	**725**	**29**	**29**
9	**62**	**M**	**9**	**right**	**12**	**14/19**	**12/10**	**44**	**24**	**1110**	**600**	**28**	**28**
10	**63**	**M**	**12**	**left**	**10**	**17/2**	**7/2**	**36**	**18**	**1225**	**725**	**29**	**29**
11	**65**	**M**	**9**	**left**	**8**	**14/11**	**8/10**	**45**	**24**	**1075**	**1075**	**27**	**28**
12	**43**	**M**	**12**	**left**	**7**	**17/14**	**9/14**	**34**	**21**	**1350**	**725**	**27**	**29**
13	**63**	**M**	**12**	**right**	**7**	**17/21**	**16/13**	**39**	**22**	**600**	**350**	**29**	**28**
14	**57**	**M**	**12**	**right**	**11**	**8/10**	**8/6**	**26**	**24**	**1110**	**820**	**30**	**30**
	55,21 (7,3)	**2F 12M**	**11,28 (2,1)**	**9 left 5 right**	**10,35 (3,1)**	**14.0/ 12.8**	**9.1/ 9.6**	**42 (8,90)**	**23 (5,46)**	**1141.28 (322.3)**	**760.42 (289.0)**	**28.40 (1.1)**	**28.71 (.8)**

Study exclusion criteria were presence of focal neurological deficits, cognitive impairment (Mini-Mental State Examination, MMSE<26), major neuropsychiatric problems refractory to medical treatment or other health condition that was a contra-indication to surgery. Ethical approval was obtained from the CIREN scientific committee and the Cuban National Ethical Committee. All participants provided informed consent.

Assessments

Change in motor signs was evaluated using the Unified Parkinson´s Disease Rating Scale (UPDRS-III, motor), rated by a neurologist prior and after surgery. Patients were assessed both in the ON and OFF medication states (with OFF state defined as overnight medication withdrawal).

The neuropsychological assessment focused on global tests of cognition and also on executive function. The MMSE and the Mattis Dementia Rating Scale-2 (MDRS-2) were used for assessment of global cognition and screening for dementia. The Frontal Assessment Battery (FAB) was used to assess executive function. Other executive function measures as the Stroop test and Hayling test were included: (i) the Stroop test from the Delis-Kaplan Executive Function System (DKEFS) battery was used, consisting of 4 subtests: word reading, color naming, inhibition and inhibition/switching (for details see (Obeso et al., 2011)). (ii) The Hayling sentence completion test (Burgess & Shallice, 1997) in Spanish was included as previously used (Obeso et al., 2011). The test has two sections: Section A: response initiation: patients are instructed to provide an appropriate word to complete a sentence from which the last word is missing (‘the captain wanted to stay with the sinking…’ for which the word ‘ship’ would be an appropriate response). Section B: response suppression: participants were required to provide a word unrelated to the context of the sentence (‘Most cats see very well at …’ for which ‘night’ is the high-frequency word that has to be suppressed and ‘table would be a correct and unrelated response. Response time and errors were measured separately for each section. For section B, errors are also recorded and distinguished into Type A (connected to the meaning of the sentence) and Type B (somewhat related to the meaning of the sentence). Other tests of cognition included the following: (i) verbal fluency: semantic (animals, boys names) and phonemic (words starting with letters “F”, “A” and “S”): patients were given one minute per word condition to say as many words as possible excluding proper nouns and numbers; (ii) Paired associate learning, where a list of 10 word pairs (5 easy and 5 difficult pairs: easy pairs were matched in category while difficult ones were unrelated) were read aloud to the patient three times. After each presentation of the complete list, the examiner presented the initial word of each pair and patients were required to produce the associated word. The total words correct for easy and hard pairs were recorded. (iii) The arithmetic (mathematical calculations), digit span (recall of sequence of numbers presented) and letter-number sequencing (reordering of numbers and letters in correct numerical or alphabetic order) of the WAIS-III to derive the working memory index (WMI).

Behavioural and psychiatric problems were evaluated using a series of validated patient self-rating scales or interviews with patients or their relatives. The patient self-rating scales included the Hospital Anxiety and Depression scale (HADS; (Zigmond & Snaith, 1983)), Beck Depression Inventory (BDI; (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)), the Starkstein Apathy Scale (Starkstein et al., 1992), the Internal State Scale (Bauer, Vojta, Kinosian, Altshuler, & Glick, 2000), the Barratt impulsivity scale (BIS-III) (Patton, Stanford, & Barratt, 1995), and the 39-Item Parkinson's Disease Questionnaire (PDQ-39; (Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995)). For all the scales, the greater the score, the greater presence of pathological behaviour or mood. On the PDQ-39 higher scores indicate worse quality of life. The neuropsychologist obtained further information by means of the NeuroPsychiatric Inventory (NPI; (Cummings et al., 1994)), which is a semi-structured interview with a family member. On the NPI, presence/absence of the following behaviours are assessed: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, sleep disturbance, and changes in appetite/ eating behaviour. For any of the behaviours considered to be present in the past month, further frequency and severity ratings were obtained and the emotional distress experienced by the relative was also rated. The Ardouin Scale of Behaviour in Parkinson's Disease (Lhommee et al., 2012) was used for interviewing the patient about their experience of hypo and hyper-dopaminergic behaviours. This includes 21 items assessing the patient’s general mental state (hypo-dopaminergic behaviours: apathy, depressive mood, hypomanic mood, anxiety, irritability, hyperemotivity and psychotic symptomatology), non-motor fluctuations and hyperdopaminergic behaviours (nocturnal hyperactivity, diurnal somnolence, excessive eating behaviour, creativity, hobbyism, punding, risk-seeking behaviour, compulsive shopping, pathological gambling, hypersexuality, compulsive dopaminergic medication use and overall functioning in an appetitive mode). Each item was rated for frequency and intensity of occurrence of each symptom.

MRI acquisition and processing

Post-operatively, 3 patients could not perform the MRI due to intolerance of the MRI procedure. Thus, analyses were performed on 11 of 14 patients. MRI examinations (1.5T MR scanner, Siemens) were used for analysis of the lesion placement (axial and coronal T2-weighted fast spin-echo; TR/TE = 6000 ms/99 ms, flip angle = 150º, slice thickness = 2mm). The boundaries of lesions were traced manually by an imaging specialist (R.RR), blinded to patient information, and their volumes determined by STASSIS 3.0 software (in-house software). The total volume of each lesion (V_{lesion}) is computed by summing all the intra-lesional voxels in each slice and multiplying this by the in-plane resolution and slice thickness. The digitized Shaltenbrand &Wharen (SW) atlas was matched to the T2-weighted images using STASSIS through rigid (translation and rotation) and non-rigid (scaling) transformations, guided by homologous landmarks visible in both the atlas and MR images. We also considered the red nucleus, substantia nigra, mamillo-thalamic tract and anterior (AC) and posterior commissures (PC). Next, the nuclei were translated and co-registered such that their boundaries best encapsulated the subthalamic region, as marked by multi-unit activity recording during surgery. The volumes of the subthalamic lesion ($Vstn$) were then measured in normalized units by computing the voxels that were common to the lesion and the STN: $V_{stn}=[V_{lesion}\ \Pi\ STN]/V_{lesion}$. Thus $Vstn$ indicates the fraction of the ablative lesion effectively targeting the STN.

In order to capture the spatial variability of lesions among individual STNs in the form of spatial probability anatomic maps (SPAMs), data volumes were automatically mapped into the MNI stereotaxic space. Probabilistic data can be threshold to compose a Maximum Probability Map (MPM). A low conservative threshold of 0.3 was used for visualization purpose, indicating that each voxel in the surface-based MPM is common to at least the 30% of lesions.

The manually-drawn right and left hemisphere volumes were compared using a 2-sample t-test to compare the effect of surgery side. Neuropsychiatric scores were normalized as a ratio of change with respect to baseline values [(final score−baseline score)/baseline score]. We performed multiple regression analyses to identify total and normalized volume correlations with neuropsychiatric scales (NPI: disinhibition, hypersexuality, excessive eating; depression (HADS) and apathy (Starkstein apathy rating scale). Age and disease duration were entered into the design matrix as nuisance variables. Statistical calculations were performed using Statistica 7.0 for Windows (StatSoft, Inc).

Data analysis

We analysed the data using non-parametric Wilcoxon matched pairs test for comparison of scores before and after surgery. For global cognitive measures (MMSE, DRS), mean and standard deviations from composite z scores were used. Spearman rank correlation coefficients were computed between clinical and demographic variables and cognitive measures and neuropsychiatric scales and MRI measures of lesion volume. Post hoc comparisons were type I error-corrected (Benjamini & Hochberg, 1995).

Results

Effect of unilateral subthalamotomy on cardinal motor features

Unilateral subthalamotomy resulted in significant improvement of the motor signs of PD (Table 1, z=-3.29, p = .001) with a 44% reduction in total UPDRS III scores. In addition, significant levodopa dose reductions (Table 1, z=-2.93, p = .003) were seen with 32% reduction at 6 months follow-up. No patient experienced any major complications associated with the procedure.

Effect of unilateral subthalamotomy on cognition

Global aspects of cognition did not show major change after surgery, as indicated by a lack of significant change on the MMSE and MDRS-2 from pre to post-operative assessment (see *Table S1*).

Phonemic and semantic word generation showed laterality effects. A 2-way ANOVA on total number of words generated on the semantic fluency test with Time (pre vs post surgery) and Lesion side (right vs left subthalamotomy) as the within subject and between groups factors respectively, revealed a significant Lesion side effect ($F_{(1,12)}$= 5.97, p = .03) and a significant Time x Lesion side interaction ($F_{(1,12)}$= 6.80, p = .02). Post-hoc tests revealed a baseline pre-surgical difference in semantic fluency performance, with patients with left subthalamotomy (17.22±3.1) generating significantly more words that those who subsequently had right subthalamotomy (13.20±2.4, p=.03). Following surgery, patients with left subthalamotomy showed significant decline in semantic fluency performance compared to before surgery (Figure 1A, p=.01). A 2-way ANOVA on the number of words generated on the phonemic fluency test with Time (pre vs post surgery) and Lesion side (right vs left subthalamotomy) showed no significant main effect of Time, Lesion side or interactions (Fs<1). Learning values were unaffected by surgery (see *Table S2*).

In the executive domain, no significant changes on the FAB test (p>0.05, see *table S3*) were seen. A 2-way ANOVA on the Stroop mean total completion time with Task (colour, naming, inhibition, inhibition-switching), Time (pre vs post surgery) and Lesion side (right vs left) as the factors was completed. As expected, the main effect of Task ($F_{(3,12)}$= 29.43, p < .001), was significant, explained by different task difficulty levels. No other main or interactions on the Stroop were significant. No significant changes were seen in errors (corrected and uncorrected) from before to after surgery (see *Table S4*).

On the Hayling test, surgery produced a significant overall improvement in type B errors after left subthalamotomy (z=-2.02, *p*= .04) but not after right subthalamotomy (z=-1.62, *p*= .10) (see Figure 1B; *Table S5*). Finally, no significant change was observed for the WAIS-III working memory index from pre to post surgery (p> .05) in either the patients with left or right subthalamotomy (*Table S7*).

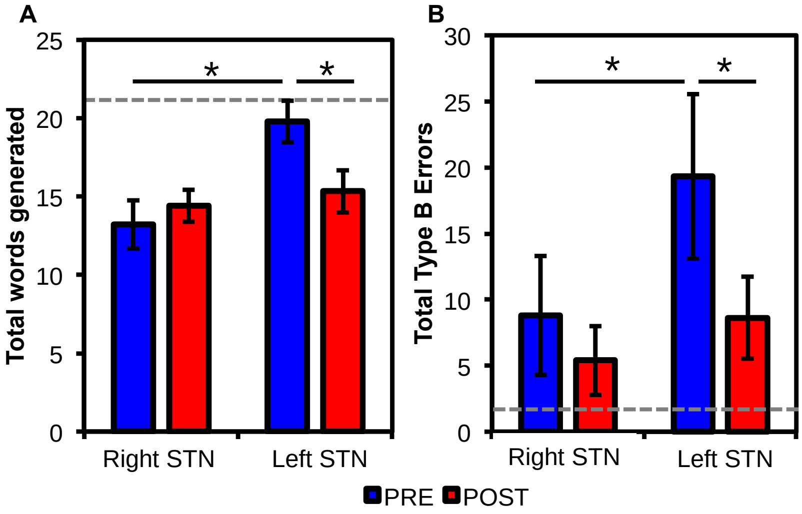

Figure 1. *Cognitive changes before and after surgery for (A) total words generated on the semantic fluency test and (B) the Total B type errors on the Hayling test. Grey dotted lines represent average of healthy control data obtained from previous studies (A, Obeso et al., 2012; B, Obeso et al., 2011). The error bars represent standard error of the mean. Asterisks indicate significant differences between means.*

Effect of subthalamotomy on mood and behaviour

a) Patient self-rating scales: A positive effect on general well-being following surgery was indicated by improvement of HADS and BDI depression scores and PDQ-39 (see Table 2). No significant changes were found from before to after subthalamotomy in measures of anxiety

(HADS), apathy (Starkstein Apathy Scale), impulsivity (BIS-III), or mania (Internal State Scale) (see Table 2).

Table 2. *Mean scores (SD in brackets) on the self-rated measures of mood and quality of life. The statistics shown are non-parametric Wilcoxon or Mann-Whitney tests for within-group (pre vs post surgery) and between-groups (left and right subthalamotomy) comparisons. p values are reported. HADS: Hospital Anxiety and Depression Scale*

	Right subthalamotomy			**Left subthalamotomy**			
	Pre	Post	Within-group	Pre	Post	Within-group	Between-groups
HADS Depression	9.20 (3.4)	6.00 (2.4)	z=-1.22 p=.22	9.78 (3.0)	5.89 (3.0)	z=-2.31 p=.02	pre > .05 post>.05
HADS Anxiety	9.80 (1.9)	6.60 (1.9)	z=-1.76 p=.07	10.33 (4.0)	7.44 (4.1)	z=-1.60 p=.10	pre > .05 post>.05
Beck Depression Inventory	16.80 (7.7)	6.80 (3.3)	z=-2.02 p=.04	15.22 (8.4)	13.00 (10.5)	z=-0.41 p=.67	pre > .05 post>.05
Starkstein Apathy scale	14.60 (4.4)	15.60 (5.9)	z=0.81 p=.41	14.67 (6.2)	13.56 (9.4)	z=-0.83 p=.40	pre > .05 post>.05
Mania (Internal State Scale)	1.80 (1.7)	3.80 (2.3)	z=-1.08 p=.27	6.00 (3.1)	5.00 (2.9)	z=-1.34 p=.18	pre =.01 post>.05
Barratt Impulsivity Scale	62.80 (9.3)	59.00 (4.5)	z=-0.94 p=.34	64.56 (9.1)	62.33 (17.1)	z=-0.59 p=.95	pre > .05 post>.05
PDQ-39	69.80 (30.4)	33.60 (14.9)	z=-2.02 p=.04	98.67 (24.7)	57.33 (24.6)	z=-2.66 p=.008	pre > .05 post=.04

b) Relative interviews: NPI scores showed reduction in some psychiatric symptoms such as depression and irritability in both right and left subthalamotomy groups (see Table 3). However, disinhibition was the only significant change after right subthalamotomy (Table 3, p =.003) which was not present after left subthalamotomy (p<.05). In addition, after surgery, increased euphoria (p =.049), aberrant motor behaviour (p =.01) and sleep disorders (p =.01) were higher for the right compared to the left subthalamotomy group.

Table 3. *Results on the Neuropsychiatric Inventory (NPI) showing frequency x severity for each symptom separately for the right and left subthalamotomy groups. Within-group comparisons indicate differences before and after surgery for each lesion group. Between-groups refer to comparisons between right and left subthalamotomy before surgery and also after surgery.*

	Right subthalamotomy			**Left subthlamotomy**			
	Pre	Post	Within-group	Pre	Post	Within-group	Between-groups
NPI	**9.00 (3.61)**	**13.20 (4.32)**	z=-2.03 p=.04	5.33 (2.87)	7.33 (4.50)	z=-.17 p=.85	pre p>.05 post p>.05
Delusions	0.0	0.0	z=0.00 p=1.0	0.0	0.0	z=0.00 p=1.0	pre p>.05 post p>.05
Hallucinations	0.0	0.0	z=0.00 p=1.0	0.0	0.11 (0.33)	z=-1.00 p=.31	pre p>.05 post p>.05
Agitation	0.0	1.80 (4.02)	z=-1.00 p=.31	1.33 (4.00)	2.44 (5.46)	z=-.53 p=.59	pre p>.05 post p>.05
Depression	4.20 (4.44)	0.60 (0.55)	z=-1.10 p=.26	4.78 (4.99)	3.44 (3.78)	z=-1.07 p=.28	pre p>.05 post p>.05
Anxiety	2.40 (1.67)	3.20 (4.09)	z=-.27 p=.78	2.11 (2.57)	4.78 (3.70)	z=-1.52 p=.12	pre p>.05 post p>.05
Euphoria	0.0	2.00 (2.83)	z=-1.34 p=.18	0.0	0.0	z=0.00 p=1.0	pre p>.05 post p=.049
Apathy	4.20 (3.49)	2.00 (2.83)	z=-1.28 p=.19	4.00 (3.67)	4.89 (4.54)	z=-.28 p=.77	pre p>.05 post p>.05
Disinhibition	1.20 (2.68)	8.80 (3.03)	z=-2.06 p=.03	0.0	0.11 (0.33)	z=-1.00 p=.31	pre p>.05 post p>.001
Irritability	5.80 (6.50)	3.00 (4.24)	z=-1.09 p=.27	5.67 (6.50)	2.44 (3.24)	z=-1.19 p=.23	pre p>.05 post p>.05
Aberrant Motor	1.20 (2.68)	3.80 (3.90)	z=-1.60 p=.10	0.0	0.0	z=0.00 p=1.0	pre p>.05 post p=.01
Sleep Disorder	2.60 (3.97)	5.80 (4.02)	z=-1.21 p=.22	2.11 (4.20)	1.11 (1.54)	z=-.81 p=.41	pre p>.05 post p=.01
Appetite	2.40 (5.37)	4.80 (4.09)	z=-.67 p=.49	0.44 (1.33)	3.00 (5.70)	z=-1.60 p=.10	pre p>.05 post p>.05

c) Patient interviews: The Ardouin Scale of Behaviour in Parkinson's disease was analysed separately for hypodopaminergic and hyperdopaminergic behaviours with percentages of patients for whom the symptom was present. No significant difference in terms of the effects of right or left subthalamotomy was observed (non-significant McNemar contingency table for percentages of symptom). Due to sample size limitations, a joint analysis was therefore applied across left and right subthalamotomy patient groups for hypo- and hyperdopaminergic behaviours. For the hypodopaminergic behaviours, a general trend towards decreased prevalence from before to after surgery was seen numerically (Figure 2A). There was a significant increase for hyperemotive states after surgery compared to before (McNemar test *p* = .018), suggesting greater emotional lability after subthalamotomy. The score for hyperdopaminergic behaviours showed non-significant increase after surgery compared to pre-operatively, specifically for eating behaviours (McNemar test *p* = .07), but significant increase in nocturnal hyperactivity (McNemar test *p* = .03) and hypersexual behaviours (McNemar test *p* = .03; Figure 2B).

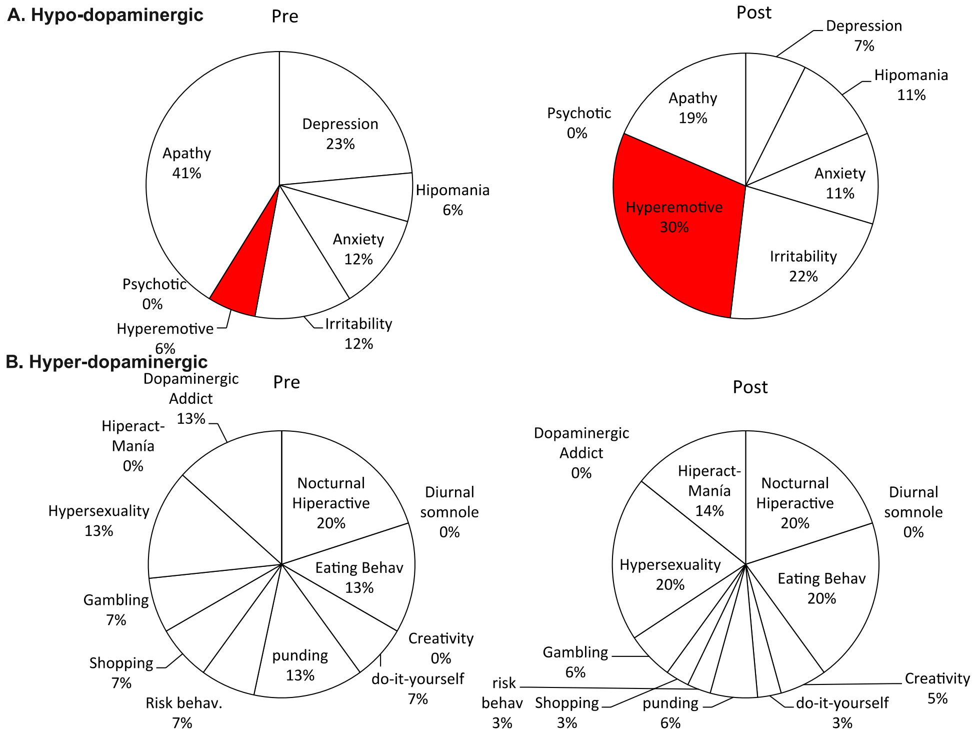

Figure 2. *Results on the Ardouin Scale of Behaviour in Parkinson's Disease. A: hypodopaminergic behaviours. B: Hyperdopaminergic behaviours. Red triangles show significant change from before to after surgery.*

Correlational analysis

Levodopa equivalent dose (LEDD) change scores after surgery were negatively and significantly related to the total impulsivity scores on the BIS-III (r=-.58, p=.02), suggesting larger reductions in LEDD after surgery was associated with lower impulsivity. Hyperemotive behaviours showed a significant and negative correlation with apathy (r=-.61, p=.01), indicating that higher emotional reactivity was associated with lower apathy.

Correlation with STN morphometric parameters

Figure 3 represents the lesion locations in the dorsolateral STN in the 11 patients (warm colours refer to common ablative spot across patients). A multiple regression analysis showed that mean lesion volume significantly predicted changes in apathy and impulsivity following unilateral subthalamotomy. Although no significant change was seen after surgery on overall impulsivity scores, STN lesion size (irrespective of laterality) was a significant predictor for impulsivity change (Vstn: partial r=0.69; p=0.006). Thus, larger STN lesions were associated with increased impulsivity. We completed partial regressions for right and left subthalamotomies. These showed striking positive correlations between impulsivity (BIS-III) and right STN lesion size (r=0.85; p=0.026), but no effect of left STN lesions (r=0.27; p=0.110). Similarly, Vstn after right subthalamotomy was also predictive of improved apathy scores (measured by Starkstein scale; partial r=-0.69; p=0.027), i.e. larger lesions were associated with more improvement in apathy. We could not find any significant right-left subthalamotomy differences in the lesion volume and extension of nuclei ablation (*Table S8).* This result was expected as all surgical procedures follow the same methodology (Alvarez et al., 2009). Thus, the targeted hemisphere was not included as a confounding variable in the regression analysis.

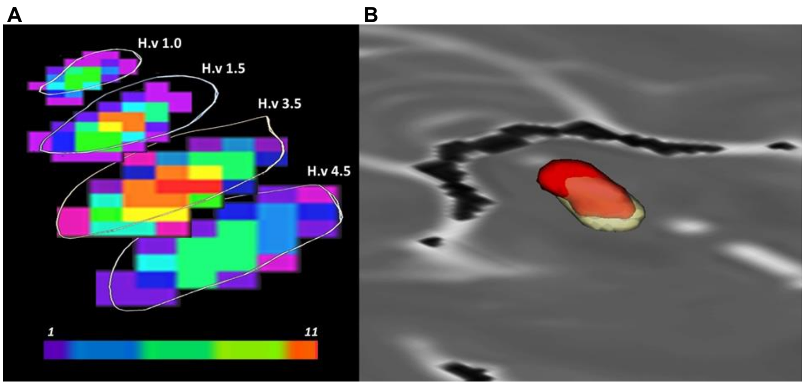

Figure 3. *(A) Spatial probability anatomic maps (SPAMs) of lesions fitted in serial axial section of the SW atlas. Color scale represents the number of overlapping lesions; (B) Maximum probability map (MPM) of lesions (red volume) positioned with respect to the three dimensional atlas of the subthalamic nucleus (yellow volume).*

Discussion

In this study, the use of detailed assessment of cognition, mood and behaviour and neuroimaging measurement of lesion volume provided evidence on the impact of unilateral subthalamotomy in PD. As expected, we observed significant improvement in the cardinal motor features of PD and also in depression, quality of life and no changes in global aspects of cognition. Importantly, a laterality effect was present, showing differences in the effects of left and right subthalamotomy on cognition, mood and behaviour and in the morphometric results. Patients with right subthalamotomy more often experienced disinhibited behaviours and this correlated with STN lesion volumes. In contrast, semantic verbal fluency became worse after left subthalamotomy. Admittedly, the number of patients here studied is not very large and the outcome must be taken with caution. Performing such a comprehensive evaluation in a high number of patients treated with subthalamotomy is indeed very difficult and beyond our resources. Nevertheless, our results provide insight into the general impact of lesioning the STN and suggest a laterality effect for cognitive and behavioural functions of the right and left STN.

In line with previous reports (Bickel et al., 2010; McCarter et al., 2000; Patel et al., 2003), unilateral subthalamotomy did not alter global aspects of cognitive function. Here, we report a change in semantic verbal fluency after left subthalamotomy compared to before the operation. In a previous study, the side of onset of motor signs on the right hemi-body predicted greater reduction of semantic verbal fluency in a large cohort of un-operated PD patients (Obeso, Casabona, Bringas, Alvarez, & Jahanshahi, 2012), which combined with the current results, indicates greater vulnerability of the language dominant left hemisphere to the effects of dopamine depletion in PD and to subthalamotomy to produce deterioration in semantic verbal fluency. Our results should be considered with caution as baseline differences between the patient groups were present (better semantic verbal fluency performance for patients with right hemibody motor signs before surgery compared to those with left hemibody motor signs) and potentially the larger effects in the left subthalamotomy group may be partly explained by sample size or individual differences between groups. Similar results for semantic verbal fluency have been described with unilateral STN-DBS (Schulz et al., 2012). Overall, most of the available data consistently indicate that bilateral STN-DBS disrupts semantic fluency (Combs et al., 2015; Tripoliti et al., 2008; Wu, Han, Sun, Hu, & Wang, 2014) associated to fronto-striatal circuits changes after STN-DBS (Houvenaghel et al., 2015). As lesioning provides more direct evidence for structure-function relationships, our results establish for the first time that therapeutic lesioning of the left STN is causally linked to changes in semantic verbal fluency after surgery in PD.

Right/left asymmetry of dopaminergic loss in the striatum impacts to different degrees cognition, mood and behaviour in PD (Lambert et al., 2012; Ventura et al., 2012). Previous studies with unilateral STN-DBS have shown that left STN-DBS impairs verbal fluency compared to right-sided DBS (Schulz et al., 2012). This decline in verbal fluency with STN-DBS is associated with increased premotor cortical activity (Narayana et al., 2009) and has been proposed to be due to microlesioning effects of the electrode trajectory when passing through the left frontal hemisphere (Le Goff et al., 2015). The current results show that lesioning the left STN is also associated with decline in semantic verbal fluency, which also suggests a role of the STN itself in mediating the decline in verbal fluency with STN-DBS. Such an STN role in verbal fluency is reflected by Anzak et al.’s (Anzak et al., 2011) finding that increased gamma band activity recorded from the *left* STN contacts significantly correlated with the average number of correct words generated in the semantic fluency task, indicating modulation of STN activity during performance of task.

We found improvement in psychiatric manifestations such as depressed mood after unilateral subthalamotomy, probably partly related to the satisfaction with the reduction of parkinsonism and better quality of life following surgery. However, a manifest disinhibition (reported both by patients and families) in those patients receiving right subthalamotomy was found and this was linked to the volume size of right subthalamotomies. PD itself alters behavioural (Obeso et al., 2011) and neural systems involved in control of behavioural inhibition (Alegre et al., 2013), with evidence for a 'causal' role of the right STN in motor inhibition on the stop signal task provided in a previous study of unilateral subthalamotomy (Obeso et al., 2014).

The extent to which the lesions were confined to the motor or limbic/cognitive sections of the STN was analysed in an attempt to define the association of the lesion volume with the observed cognitive, mood and behavioural effects. However, as no accepted spatial model for the anatomo-physiological correlates of the three subdivisions of the STN is available (Buot et al., 2013), we cannot rule out the possibility that in some cases the subthalamotomies extended to the non-motor associative or limbic regions of the STN, thus potentially influencing cognitive or limbic function, as it is now recognized that the cortico-subthalamic-striatal-pallidal circuits may not be as segregated as previously described (Draganski et al., 2008).

Thus, the current results show that unilateral subthalamotomy produces distinct effects on cognition, mood and behaviour, improving executive function and depression; while semantic verbal fluency, disinhibition, euphoria and hyper-emotionality became worse after surgery. Aspects of functioning that are improved following unilateral subthalamotomy are likely to reflect distant effects through 'release of frontal function' from abnormal functional connectivity with the STN. By contrast, aspects of cognition and behaviour that became worse after surgery are likely to represent disruption of functions partly mediated by the STN itself.

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