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STN-DBS does not change emotion recognition in advanced Parkinson's disease

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ABSTRACT

Deep brain stimulation of the subthalamic nuclei (STN-DBS) for the treatment of levodopa-induced motor complications in advanced Parkinson's disease (APD) has been associated with neuropsychiatric disorders. It has been suggested that a postoperative decline in visual emotion recognition is responsible for those adverse events, although there is also evidence that emotional processing deficits can be present before surgery.

The aim of the present study is to compare the ability to recognize emotions before and one year after surgery in APD. Methods: Consecutively operated APD patients were tested pre-operatively and one year after STN-DBS by the Comprehensive Affect Testing System (CATS), which evaluates visual recognition of 7 basic emotions (happiness, sadness, anger, fear, surprise, disgust and neutral) on facial expressions and 4 emotions on prosody (happiness, sadness, anger and fear).

Results: In a sample of 30 patients 6 had depression or apathy at baseline that significantly increased to 14 post-surgery. There were no significant changes in the tests of identity discrimination, discrimination of emotional faces, naming of emotional faces, recognition of emotional prosody, and naming of emotional prosody after STN-DBS. The results of emotion tests could not predict the development of the neuropsychiatric symptoms.

Discussion: This study does not support the hypothesis of an acquired change in emotion recognition, either in faces or in prosody, after STN-DBS in APD patients. Neuropsychiatric symptoms appearing after STN-DBS should not be attributed to new deficits in emotional recognition.

1. Introduction

Subthalamic nuclei deep brain stimulation (STN-DBS) has been established as an effective treatment of advanced Parkinson's disease with levodopa-induced motor complications (APD) refractory to best medical treatment. Yet, notwithstanding its unquestionable motor benefits, this intervention has been associated with undesirable neuropsychiatric side effects, which have been attributed to the interference of the STN-DBS upon cognitive and limbic neural circuits [1–4].

With few exceptions, most cognitive and neurobehavioural changes following STN-DBS are transient. However, some neuropsychiatric disturbances like apathy [5–7] and impairments in verbal fluency [6] can be persistent. Some authors have discussed whether decline in cognitive performance or emotion recognition may have a role in apathetic behavior [8]. The studies of patients shortly after STN-DBS or comparing neurostimulators on *versus* off, have postulated an acquired disruption of emotional faces recognition [9–12] or altered recognition of emotional prosody [13], potentially related to behavioral correlates.

To probe that hypothesis we performed a study of emotion recognition in APD undergoing STN-DBS, comparing within patient

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performance before and one year after surgery both in auditory and visual modalities, in order to identify persistent effects.

2. Methods

A prospective longitudinal observational study was designed. Consecutive APD patients submitted to STN-DBS, between 2008 and 2009 in a Movement Disorders Outpatient Clinic of a University Hospital, were invited to participate. Eligibility criteria for surgery were the following a) clinical diagnosis of Parkinson's disease longer than ten years, b) age below 70 years, c) motor fluctuations and/or dyskinesias refractory to best medical management, and d) a positive motor response to levodopa challenge test. Candidates were excluded for surgery if there was clinical evidence of dementia, major psychiatric disorders, postural instability and freezing of gait non-responsive to levodopa, and brain imaging with significant changes namely atrophy or concurrent brain disorders such as vascular ones. Neuropsychological and emotional testing, before surgery, took place under the regular levodopa-medication (in "on" condition).

APD patients underwent bilateral stereotactic surgery under local anesthesia. Lead implantation was accomplished using stereotactic guidance with magnetic resonance and computed tomography imaging. Initial STN targeting was based on standard coordinates for the subthalamic nucleus (12 mm lateral from the midsagittal plane, 2 mm behind the midcommissural point and 4 mm below the AC-PC line). Intraoperative microelectrode recording and macroelectrode stimulation were used to locate the optimal site for implanting the quadripolar DBS lead (model 3389, Medtronic®). A neurostimulator (Kinetra or Activa PC, Medtronic®) was implanted in an infraclavicular pocket under general anesthesia on the same day after lead implantation. Postoperatively, the stimulation parameters and antiparkinsonian medication were progressively adjusted, in order to achieve the best clinical and functional condition for patients in daily life.

Post-operative evaluations were performed in all patients one year after surgery, after clinical stabilization, with the neurostimulators "on" and under antiparkinsonian medication (stimulation "on", medication "on").

Neuropsychiatric adverse events were actively looked for, during hospital stay and as part of the regular follow-up consultation in Neurology and Psychiatry. They were clinically assessed with patients and their caregivers or families and treated accordingly.

Emotion recognition was evaluated with the Comprehensive Affect Testing System [14], adapted to the Portuguese population [15]. The battery evaluates recognition of 7 basic emotions on facial expressions (happiness, sadness, anger, fear, surprise, disgust and neutral), and 4 emotions on prosody (happiness, sadness, anger and fear). Patients were evaluated with the following subtests: a) discrimination of identity between pairs of non-familiar faces— patients have to decide whether two portraits of faces displaying neutral emotion represent the same or different individuals; b) discrimination of facial emotions – two portraits of the same individual are shown simultaneously. Patients have to indicate whether faces display the same or different emotions; c) naming of single facial emotions – a single face is shown. Patients have to match it with the emotion that best describes the expression; d) discrimination of prosody – two sentences with neutral content are heard in sequence, patients have to decide whether prosodic intonation is the same or different; e) naming of prosody – a single sentence with neutral content is heard, patient has to match it with the emotion that best describes the prosodic tone. The number of stimuli is 22 in each task, 16 in naming of facial emotions. Each stimulus is presented with the possible answers written in a multiple choice format. Answers have no time limits, correct responses are converted to a percentage of the total. The Portuguese adaptation of the tests retained only stimuli scoring more than 50% correct responses in the healthy population. Faces are from the original battery, the original sentences were translated to Portuguese and produced by a native actor, which led to the exclusion of 4 stimuli in the subtest of naming emotional prosody [15].

The neuropsychological battery performed pre-operatively and at follow up evaluation was comprised of the Mini Mental State Examination [16], Dementia Rating Scale [17], Digit Spans Forward and Backward [18], an abbreviated version of the Token test [19], Semantic and Phonemic (letters *p*, *m*, *r*) fluencies, Logical memory (immediate recall) from the Wechsler Memory Scale [18], the 12 item AB Raven Matrices series [20], proverb interpretation [19], and the Stroop color word test [21].

The study protocol was approved by the Institution Ethics Committee and a written informed content for the study was obtained from all patients.

Statistical Analysis: Within-subject comparisons were analyzed with paired-sample *T*-tests for parametric variables or Wilcoxon test for non-parametric ones. To analyze whether the presence of neuropsychiatric symptoms (yes/no) differed at the baseline and one year post-surgery, we performed a McNemar test. In order to assess whether the presence of neuropsychiatric symptoms was predicted by emotion recognition deficits, we performed logistic regressions analyses with measures of emotion recognition as independent variables, and demographic (age, gender) and DOPA dosage as covariates. In order to find the best fitting model, we performed two stepwise forward procedures, one for pre-surgery and one for post-surgery. Cronbach's alphas to assess internal consistency at baseline in the sub-tests of facial naming of emotions and prosody naming of emotions were calculated. Analysis was performed with SPPS 20.0 software [22].

3. Results

There were 30 patients, 12 females and 18 males, aged 62.7 ± 7.7 years, with 6.7 ± 4.6 years of formal education and mean disease duration of 15.85 ± 7.02 years at the pre-operative evaluation. A comparison between pre- and one year post-operative UPDRS motor scores is presented in Table 1.

Concerning the performance in emotion recognition tests, there were no significant score changes between the pre and post STN-DBS evaluations in the tests of identity discrimination, discrimination of emotional faces, naming of emotional faces, recognition of emotional prosody, or naming of emotional prosody (Table 2). And there was no significant difference comparing either positive emotions (happiness 70.09 ± 17.12 *vs* 70.09 ± 16.43, $t = 0$, $p = 1.00$) or negative emotions as a whole (mean sadness, anger, fear and disgust 49.51 ± 11.11 *vs* 46.71 ± 14.31, $t = 1.25$, $p = 0.22$).

Table 1
Motor features, neuropsychiatric symptoms, DOPA dosage, and agonist and antidepressant medication of patients pre-operative and one year after STN-DBS.

	Pre-op on medication	Post-op on stimulation and on medication	*P*
HY score	2.21 ± 0.25	2.07 ± 0.17	0.08*
UPDRS 3 score (21 patients)	16.09 ± 6.52	14.95 ± 8.68	0.56
Apathy/depression (number of patients)	6/30	14/30	0.04[a]*
L-DOPA (mg/day) (30 patients)	1148 ± 433.5	425 ± 209	0.00*
Antidepressant drugs (number of patients)	6/30	14/30	0.04[a]*

HY-Hohen Yahr Score; Paired-samples test/[a]McNemar, *significant difference $p < 0.05$.

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Table 2
CATS sub-tests of emotional recognition.

	Pre-operative (%)	One year after STN-DBS (%)	*P*
Discrimination of identity	87.18 ± 11.54	84.90 ± 11.41	0.33
Discrimination of emotional faces	93.29 ± 6.11	91.39 ± 9.61	0.38
Naming of emotional faces[a,c]	59.37 ± 16.70	57.37 ± 13.29	0.53
Discrimination of prosody	91.23 ± 13.03	92.21 ± 13.06	0.60
Naming of emotional prosody[b,c]	48.14 ± 17.44	48.2 ± 17.93	0.99

P-Paired-samples test, *sig difference $p < 0.05$. Both alpha values were calculated for a sample of 54 pre-operative PD patients.
[a] Cronbach's alpha = 0.70.
[b] Cronbach's alpha = 0.56.
[c] Correlation between naming of emotional faces and prosody one year after DBS $r = 0.61$, $p < 0.01$.

Furthermore, there were no significant within subject changes in any specific emotions, presented in faces or prosody, nor any trend towards choosing a particular emotion, when the numbers of answers in each emotion were compared.

Cognitive assessment revealed a significant decline in phonemic fluency, abstract reasoning (proverb interpretation and Raven AB Matrices) and the Dementia Rating Scale (in the total score, as well as in the domain of initiation/perseveration), but a significant improvement in immediate recall of episodic memory after STN-DNS (Table 3). Other cognitive measures (MMSE, clock drawing, Token Test and the Stroop test) did not change significantly.

There was a significant increase in patients with neuropsychiatric symptoms, namely clinical apathy and/or depression, that implied being under antidepressant medication at the one year assessment (Table 1).

In order to assess whether the presence of neuropsychiatric symptoms was predicted by emotion recognition deficits, we performed logistic regressions analyses. Neither demographic variables nor emotion recognition tests predicted the development of neuropsychiatric symptoms, i.e., no single variable or combination of variables predicted the presence of neuropsychiatric symptoms (all *p* values > 0.05). Results were similar in the pre-surgery phase and one year the post-surgery.

4. Discussion

This study did not reveal any significant decline in the recognition of emotional faces or emotional prosody in APD patients one year after STN-DBS, which contrasts with some previous studies that found impairments in naming of selective emotions in faces at different times after surgery. The main reasons for these opposite results are possibly methodological, concerning time of assessment, study design and testing conditions.

Some studies compared scores obtained with stimulators "on" *versus* "off" [10,23], thus introducing another variable that might influence the quality and success of response. Others compared pre-operative evaluations with variable follow-up periods post STN-DBS. These have disclosed impairments in the recognition of negative emotions in "on" condition 3 months post-operatively [9], or in naming fear at a mean follow-up of 7 months (range 1–48 months) [11], or in naming fear and sadness 3 months after treatment [12]. Recently, Péron described impairments in processing emotional prosody after STN-DBS [13], in a cross-sectional study comparing a group of patients pre-operatively with another sample of patients, tested 3–72 months after STN-DBS, which may introduce a sample effect, particularly since the first group differed from healthy controls at baseline. No significant differences were found after surgery when categorical judgments were considered, although there were differences when more complicated judgements of intensity of emotions were considered.

Strengths of the current study are: a) the longitudinal and within subject design, b) the control of time post-surgery that was equal in all cases and c) the chronic period of assessment after STN-DBS overcoming transient changes that might occur shortly after surgery. In addition, the results obtained were congruent between visual and auditory tests which suggest a long-term global stability of emotion networks after STN-DBS.

The choice of the CATS battery, not previously tested in Parkinson's patients to our knowledge, relied upon its expanded use and norms in several countries and original validation in different patient populations such as fronto-temporal dementia, Huntington's Disease, as well as unilateral stroke, and schizophrenia [14,15], allowing the possibility of replication in other populations.

The cognitive effects of STN-DBS in our patients were also in accordance with most previous studies on the subject, showing a pattern of predominantly executive decline (phonemic fluency, verbal and visual abstraction) at one year follow-up [6,24–27].

We also acknowledge limitations to this study namely a) the rather small number of patients included, although larger than in previous series; b) the lack of a control group to evaluate test retest reliability and its potential learning effects; c) the restricted number of stimuli used to assess emotions, which may have missed subtle changes following surgery; d) the low internal consistency of facial naming subtest, possibly related to the reduced number of items and its sensitivity to education [15]. This limited reliability makes inferences about visual processing of emotions less predictable within our test population. However, the exact same version of this sub-test was sensitive enough to detect differences between patients with schizophrenia and healthy controls (mean difference of 10%). This lends support to the idea that sufficient differences between pre- and post-operative assessments would have been detected. Furthermore, in the sub-task 'naming of emotional prosody', in which reliability was adequate, we found a similar absence of difference between assessments. Since one-year post-operative scores of visual and prosodic emotional naming showed a good correlation, it seems reasonable to assume that in general STN-DBS did not result in an emotional processing impairment.

The discussion about the neuropsychiatric consequences of STN-DBS has raised several potential explanations such as an acquired frontal-executive dysfunction, disruption of primary emotional networks and impairment of subjective emotional experience [5,28,29]. In this series a frontal/executive cognitive decline after STN-DBS was confirmed by several concurrent

Table 3
Changes in cognitive testing one year after STN-DBS.

	Pre-operative	One-year post-operative	*P*
MMSE	27.2 ± 2.4	27.4 ± 1.6	0.74
Memory recall	8.9 ± 2.8	11.3 ± 3.0	0.01*
Phonemic fluency	26.2 ± 9.6	19.4 ± 8.8	0.00*
Proverb interpretation	7.7 ± 1.6	6.4 ± 1.8	0.01*
Raven AB matrices	7.5 ± 2.6	6.3 ± 2.8	0.01*
DRS (Total)	133.27 ± 5.7	126.73 ± 5.92	0.02*
DRS (I/P)	35.06 ± 1.56	32.50 ± 3.40	0.02*
Digit span (Forward + Backward)/2	8.57 ± 1.59	8.19 ± 1.36	0.08
Token test (abbreviated)	15.41 ± 2.09	14.29 ± 3.73	0.22
Semantic fluency (food)	16.34 ± 5.09	14.91 ± 5.34	0.41
Stroop test (word)	62.60 ± 18.25	62.46 ± 19.07	0.96
Stroop test (color)	48.86 ± 13.67	46.53 ± 12.18	0.35
Stroop test (interference)	24.53 ± 11.20	23.40 ± 6.15	0.68

DRS – dementia rating scale; I/P-initiation/perseveration.
Paired-samples test.
*Significant difference $p < 0.05$.

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measures (fluency, abstract reasoning of proverbs and Raven Matrices, and the Dementia Rating Scale domain of initiation/perseveration).

Apathy and depression are probably the more frequently reported neuropsychiatric effects of surgery and were clinically confirmed in this series, although not measured by specific scales. Antidepressant medication was provided to patients with clinical depression. Apathy seems not so much to be due to the STN-DBS itself, as to the simultaneous withdrawal of all dopaminergic medication [7]. In all these patients prevention of acquired apathy was actually attempted by avoiding complete withdrawal of L-DOPA.

Most relevant for this study, was the lack of predictive value of the emotion tests for the development of neuropsychiatric symptoms [8].

Other behavioral disorders like depression, dopamine deregulation syndromes, and impulse control disorders do not seem to worsen or appear consistently after functional surgery [27,30].

Pre-existing baseline possible impairments in emotional recognition were certainly not improved by surgery, however we could not disclose any aggravation of the capacity of emotional recognition after STN-DBS in the visual or auditory modalities. Neuropsychiatric symptoms developing after STN-DBS should therefore not be attributed to acquired or new deficits in emotional recognition.

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