

Different outcomes of phonemic verbal fluency in Parkinson's disease patients with subthalamic nucleus deep brain stimulation

Diferentes desfechos na tarefa de fluência verbal fonêmica em pacientes com doença de Parkinson submetidos à estimulação cerebral profunda

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ABSTRACT

Subthalamic nucleus deep brain stimulation (STN-DBS) is a surgical technique to treat motor symptoms in patients with Parkinson's disease (PD). Studies have shown that STN-DBS may cause a decline in verbal fluency performance. We aimed to verify the effects of STN-DBS on the performance of phonemic verbal fluency in Brazilian PD patients. Sixteen participants were evaluated on the Unified Parkinson's Disease Rating Scale - Part III and for phonemic fluency ("FAS" version) in the conditions of on- and off-stimulation. We identified two different patterns of phonemic verbal fluency outcomes. The results indicate that there may be no expected pattern of effect of bilateral STN-DBS in the phonemic fluency, and patients may present with different outcomes for some reason not well understood.

Keywords: Parkinson disease; deep brain stimulation; language; cognition.

RESUMO

A estimulação cerebral profunda do núcleo subtalâmico (ECP-NST) é uma técnica cirúrgica para tratar sintomas motores na doença de Parkinson (DP). Estudos têm mostrado que ECP-NST pode causar um declínio no desempenho de fluência verbal. O objetivo do estudo foi verificar os efeitos da ECP-NST sobre o desempenho da fluência verbal fonêmica em indivíduos brasileiros com DP. Dezesesseis participantes foram avaliados quanto ao desempenho motor (UPDRS-III) e à fluência verbal fonêmica (versão "FAS") nas condições de estimulação ligada e desligada. Identificamos dois padrões diferentes de resultados de fluência verbal fonêmica. Os resultados indicam que pode não haver um padrão esperado de efeito de ECP-NST bilateral na fluência fonêmica, e os pacientes podem apresentar desfechos diferentes de acordo com alguma razão não bem compreendida.

Palavras-chave: doença de Parkinson; estimulação encefálica profunda; linguagem; cognição.

Subthalamic nucleus deep brain stimulation (STN-DBS) is a procedure used to treat patients with Parkinson's disease (PD) when pharmacological treatment is no longer efficient¹. It has been proven that DBS suppresses motor symptoms and reduces the total dose of the antiparkinsonian drugs^{2,3}.

Among the adverse effects of STN-DBS in patients with PD, the postoperative decline in verbal fluency is well documented^{4,5,6,7,8,9,10,11}. However, there are fewer studies about the effect of the stimulation per se, comparing on- and

off-stimulation conditions^{12,13,14}. Longitudinal studies verified a worsening of verbal fluency in the first months after surgery, but an improvement in the later studied months⁹. These authors suggest that this effect of the DBS on the verbal fluency may be due to the micro-lesions caused by the implantation procedure of the electrodes in the STN.

The verbal fluency test evaluates the capacity to search and retrieve data stored in long-term memory within a certain category and demonstrates the capacities of

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organization, self-regulation and operational memory. This instrument offers three main variations: phonemic fluency, semantic fluency, and action or verb fluency^{15,16}. Each type of verbal fluency task may offer specific information regarding cognition, given that each one requires access to specific lexical and/or semantic representations according to the criteria used. The verbal fluency tasks activate overlapping areas of the frontal brain regions, but different word retrieval criteria likely activate additional distinct regions¹⁶. Executive dysfunction is the predominant profile of cognitive impairment in patients with PD, and phonemic fluency may be a good type of verbal fluency task to evaluate this population because the executive deficit is associated with frontal-lobe dysfunction¹⁷. Furthermore, PD may be a good neural model to study the principles of subcortical lexical processing, and studies in different cultural settings may enrich the theoretical framework about this issue as well.

It is important to understand the effects of STN-DBS on the patient's language to adequately manage the treatments (speech therapy, cognitive training, pharmacological treatments, adjustment of the stimulator) and to improve quality of life. Thus, this study aimed to verify the effects of STN-DBS on the performance of phonemic verbal fluency in Brazilian PD patients.

METHODS

Participants

Brazilian patients with PD who had undergone bilateral STN-DBS were selected from the Movement Disorder Clinic at *Hospital de Clínicas de Porto Alegre*. Exclusion criteria were: a poor response to the procedure, presence of another neurological condition (e.g., stroke, dementia), and not being a native speaker of Brazilian Portuguese. The study was approved by the local ethics committee (No. 10.0508) and all participants gave written informed consent.

Instruments and procedures

Clinical and demographic data were obtained from the patient's records to describe the sample. The assessment team consisted of one movement disorder neurologist, and three speech and language therapists.

Cognitive screening was carried out using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) at the start as a baseline, using the adapted version for Brazilian population^{18,19}.

Motor function was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III (maximum score of 108 points).

Verbal fluency was assessed by the FAS test for phonemic verbal fluency²⁰. The participants were asked to say as many words as possible that started with the letters

"F", "A" and "S" during one minute for each letter. Proper names, numbers, the same word with different suffix or different verb conjugations were excluded. The final score was the sum of all correct words.

The UPDRS-III and the phonemic verbal fluency assessments were performed on the same day with patients on their usual antiparkinsonian medication, in the following conditions: 1) on-stimulation: the patients were evaluated with the DBS turned on and adjusted for the best symptom control by each patient (baseline); 2) off-stimulation: the DBS was turned off and the assessments were carried out after 60 minutes or until the patient could not tolerate the symptoms. At the end of the off-stimulation evaluation, the DBS was turned on again.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 21.0) with a significance level of 5% ($p \leq 0.05$). Continuous variables were reported as the mean and standard deviation. Categorical variables were described by the absolute and relative frequencies.

To compare the phonemic fluency and UPDRS-III performances between on- and off-stimulation conditions we used the Wilcoxon signed ranking test. We calculated the delta value to verify the change in the phonemic verbal fluency (on-stimulation total score minus off-stimulation total score). The participants were split into two groups, according to the percentile of delta values: "improvement in on-stimulation", and "worsening in on-stimulation". The variables of: age in years, education in years, MMSE, MoCA, years after diagnosis, months after surgery, UPDRS-III in on- and off-stimulation, voltage, frequency, and pulse of DBS, were compared between the groups "improvement with on-stimulation", and "worsening with on-stimulation" using the Mann-Whitney U test or the Chi-square test. Correlations were verified with the Spearman's correlation test.

RESULTS

Sixteen Brazilian PD patients were included in the study. Three participants did not tolerate the motor symptoms during the off-stimulation condition and were not able to complete the evaluation at that time. Table 1 shows the descriptive data of the participants.

We compared the performance of the phonemic verbal fluency between on- and off stimulation conditions and it showed no statistical difference ($p = 0.168$). On the other hand, the scores on the UPDRS were significantly worse in the off-stimulation period ($p < 0.000$).

When we observed the performance of patients individually, we realized that they presented diverse patterns of

outcomes after the DBS had been turned *off* (Figure A). Some participants seemed to improve, others worsened and others showed no difference, which made us realize that we could divide the participants into different groups according to their performance and evaluate these on their different outcomes. To do this, we calculated the delta value of phonemic fluency and, based on the percentiles of the delta values, we split the participants into two groups, which were named: “improvement with DBS *on*” ($n = 5$), and “worsening with DBS *on*” ($n = 8$) (Figure B).

We compared the demographic (sex, age, education), cognitive (MMSE, MoCA, delta of phonemic verbal fluency) and clinical variables (years after diagnosis; months after surgery; delta of UPDRS-III; voltage, frequency, and pulse of DBS) between the groups “improvement with on-stimulation” and “worsening with on-stimulation” and there was no statistical difference for any variable, except for phonemic verbal fluency (Table 2). As expected, the delta of phonemic fluency was statistically different between groups.

Furthermore, we tested the correlation between the delta of phonemic verbal fluency and all the studied variables in the full sample. There was no correlation between phonemic verbal fluency and any variable (age: $r = 0.42$, $p = 0.15$; education: $r = -0.05$, $p = 0.87$; MMSE: $r = -0.17$, $p = 0.62$; MoCA: $r = -0.35$, $p = 0.26$; years after diagnosis: $r = 0.04$, $p = 0.91$; months after surgery: $r = -0.05$, $p = 0.88$; voltage R: $r = -0.21$, $p = 0.50$;

voltage L: $r = -0.19$, $p = 0.54$; frequency R: $r = 0.06$, $p = 0.85$; frequency L: $r = 0.06$, $p = 0.085$; pulse R: $r = -0.40$, $p = 0.19$; pulse L: $r = -0.11$, $p = 0.73$; delta of UPDRS-III: $r = -0.07$, $p = 0.82$).

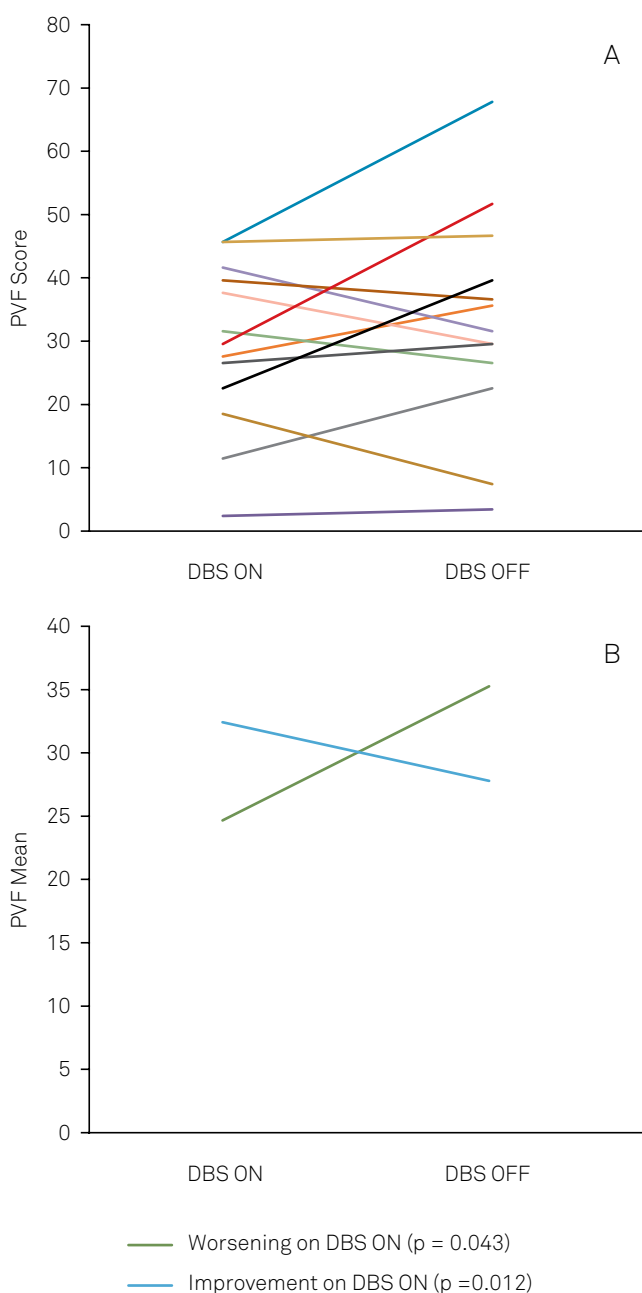
DISCUSSION

This study verified the effect of STN-DBS on the performance of phonemic verbal fluency in a sample of Brazilian PD patients, testing the phonemic fluency in on- and off-stimulation conditions. The phonemic verbal fluency did not differ between on and off conditions, however when participants

Table 1. Descriptive data of participants ($n = 16$).

Variable	M (SD) or N (%)
Gender – male	12 (75%)
Education	12.06 (4.20)
Years after diagnosis	12.31 (4.03)
Months after surgery	23.88 (13.38)
MMSE	24.29 (5.18)
MoCa	19.27 (5.75)
UPDRS-III	
On-stimulation	24.19 (11.07)
Off-stimulation	37.77 (15.37)
Voltage (v)	
Left	29.75 (5.5.6)
Right	27.75 (8.89)
Frequency (Hz)	
Left	156.25 (29.92)
Right	156.25 (29.92)
Pulse width (ls)	
Left	84.38 (19.65)
Right	90.00 (18.97)
Phonemic verbal fluency	
On-stimulation	28.00 (12.03)
Off-stimulation	26.75 (13.94)
Delta of phonemic verbal fluency	1.25 (8.41)

M: mean; SD: standard deviation; N: number; MMSE: Mini-Mental State Examination; MoCa: Montreal Cognitive Assessment; UPDRS: Unified Parkinson's Disease Rating Scale.



A: Individual performance. B: Group performance.

Figure. Performance on phonemic verbal fluency (PVF) in the on- and off-stimulation conditions.

Table 2. Descriptive data and comparisons between groups “improvement with DBS on” and “worsening with DBS on”.

Variable	Improvement with DBS on (n = 5)	Worsening with DBS on (n = 8)	p
Gender – male	1 (20%)	2 (25%)	1.00
Age	63.00 (11.31)	57.38 (12.88)	0.52
Education	12.00 (5.10)	12.38 (4.37)	1.00
Years after diagnosis	12.20 (4.38)	12.25 (4.59)	1.00
Months after surgery	25.20 (17.18)	24.38 (13.46)	1.00
MMSE	23.80 (5.26)	23.67 (6.38)	1.00
MoCA	17.40 (6.84)	19.43 (5.91)	0.64
Voltage (v)			
Left	28.20 (5.93)	28.75 (5.37)	1.00
Right	27.20 (5.07)	29.12 (6.71)	0.62
Frequency (Hz)			
Left	152.00 (31.14)	148.12 (30.23)	0.72
Right	152.00 (31.14)	148.12 (30.23)	0.72
Pulse width (ls)			
Left	78.00 (16.43)	78.75 (15.53)	1.00
Right	84.00 (13.41)	86.25 (19.23)	1.00
Delta of UPDRS	13.80 (6.56)	15.12 (7.68)	0.62
Delta of phonemic VF	7.40 (3.36)	-10.62 (8.86)	0.002*

M: mean; SD: standard deviation; DBS: deep brain stimulation; VF: verbal fluency; MMSE: Mini-Mental State Examination; MoCa: Montreal Cognitive Assessment; UPDRS: Unified Parkinson's Disease Rating Scale. *p ≤ 0.05, Chi-square or Mann-Whitney U test.

where individually observed we found two different outcomes in effect: in one group the phonemic verbal fluency improved when DBS was on, while in the other group it worsened.

The improvement of motor patterns in the presence of DBS stimulation is already a consensus^{1,21}. Also, the majority of previous studies pointed to a negative effect of STN-DBS on verbal fluency when they studied postsurgical patients²². Some of the studies on pre- and post-DBS have found a decline in phonemic fluency^{5,7,10}, others a decline in semantic fluency⁶ and still others in both verbal fluency tasks^{4,8,9}.

However, the studies comparing verbal fluency performance between pre- and postsurgical periods may reflect the surgery consequences more than the stimulation per se. The comparison between on- and off- conditions of DBS may be more indicative of the effect of the stimulation. Some previous studies using this approach found no differences in phonemic verbal fluency^{12,13,14,23}, corroborating our analysis with the full sample, in which we did not find any effect of DBS on the phonemic fluency, despite finding a positive effect of the stimulation on the motor function.

The results that showed a decline in verbal fluency post-surgery and those that found an absence of effect of stimulation in the on-condition point to the hypothesis that verbal fluency deficits may not be caused by the electrical stimulation but rather by the surgery or the evolution of PD. In our study, we found that the neurostimulation increased the verbal fluency performance in one group of PD patients while it was impaired in another, which contradicts the previous hypothesis. Furthermore, any of the demographic, clinical, cognitive variables and parameters of STN-DBS may be able to explain the different outcomes. The data of a previous study suggested that the stimulation effect may depend on the locus and volume of activated tissue²⁴, which was not investigated in our study and may be a hypothesis for our findings.

Our results should be interpreted with consideration of some limitations, such as the small sample size and the fact that three participants did not perform the task in the off-stimulation period. Despite this, our study indicates that there may be no unique pattern from the effect of bilateral STN stimulation on phonemic verbal fluency, and patients may present with different outcomes according to some reason that is not well understood. It is necessary to understand what leads to different outcomes to improve patient management and understand which subcortical pathways are involved in lexical access. Future studies should analyze the different outcomes of verbal fluency in STN stimulation in bigger samples, using diverse tasks, i.e. semantic and verb fluency, and to verify the association with the lead and localization of the electrodes.

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