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Corresponding author:
Roberta Ferrucci;
Email: roberta.ferrucci@unimi.it

Fabiana Ruggiero and Francesca Mameli contributed equally.

Can total electrical energy (TEED) after subthalamic DBS alter verbal fluency in Parkinson's disease patients? A preliminary evidence

Fabiana Ruggiero[1], Francesca Mameli[1], Edoardo Nicolò Aiello[2], Eleonora Zirone[1], Filippo Cogiamanian[1], Linda Borellini[1], Elena Pirola[1], Antonella Ampollini[1], Barbara Poletti[2,3], Angelica De Sandi[1], Marco Prenassi[4], Sara Marceglia[4], Nicola Ticozzi[2,5], Vincenzo Silani[2,5], Marco Locatelli[1,5], Giordano D'Urso[6], Sergio Barbieri[1], Alberto Priori[7,8] and Roberta Ferrucci[1,3]

[1]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan 20122, Italy; [2]Department of Neurology and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano, Milan 20149, Italy; [3]Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, Milan 20122, Italy; [4]University of Trieste, Trieste 34127, Italy; [5]Department of Pathophysiology and Transplantation, "Dino Ferrari" Center, Università degli Studi di Milano, Milan 20122, Italy; [6]Section of Psychiatry, Department of Neuroscience, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Naples, Italy; [7]Department of Health Science, "Aldo Ravelli" Center for Neurotechnology and Experimental Brain Therapeutics, University of Milan, Milan 20122, Italy and [8]ASST-Santi Paolo Carlo University Hospital, Milan 20142, Italy

Abstract

Objective. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves motor outcomes in Parkinson's disease (PD) but may have adverse long-term effects on specific cognitive domains. The aim of this study was to investigate the association between total electrical energy (TEED) delivered by DBS and postoperative changes in verbal fluency.
Methods. Seventeen PD patients undergoing bilateral STN-DBS were assessed with the Alternate Verbal Fluency Battery (AVFB), which includes phonemic (PVF), semantic (SVF), and alternate verbal fluency (AVF) tests, before surgery (T0) and after 6 (T1) and 12 months (T2). Bilateral TEED and average TEEDM were recorded at T1 and T2. For each AVFB measurement, changes from T0 to T1 (Δ-01) and from T0 to T2 (Δ-02) were calculated.
Results. At T1, PVF (p = 0.007) and SVF scores (p = 0.003) decreased significantly. TEED measures at T1 and T2 were unrelated to Δ-01 and Δ-02 scores, respectively. However, an inverse, marginally significant association was detected between the TEEDM and Δ-01 scores for the AVF (p = 0.041, against an $\alpha_{adjusted}$ = 0.025).
Conclusions. In conclusion, the present reports provide preliminary evidence that TEED may not be responsible or only slightly responsible for the decline in VF performance after STN-DBS in PD.

Introduction

While deep brain stimulation (DBS) of the subthalamic nucleus (STN) does ameliorate motor outcomes in Parkinson's disease (PD), such a surgical treatment might entail detrimental, long-term effects on specific cognitive domains – *i.e.* language, memory, and executive functioning.[1]

Data on the neuropsychological outcome of STN-DBS usually do not show global cognitive deterioration,[2] with the exception of a specific sample composed of elderly patients, who are more at risk of decompensation,[3,4] and patients who suffered from preoperative cognitive difficulties.[5] Therefore, comparisons between preoperative and postoperative (3 to 12 months after surgery) assessments have shown less consistent effects on global cognition and other cognitive tasks, while postoperative declines in verbal fluency[6–8] have been reported.

To the aim of detecting post-DBS cognitive decline, verbal fluency (VF) tests have been thoroughly shown to be suitable.[9] However, little is known about the underpinnings of VF changes after STN-DBS, with both disease- and treatment-related causes having been postulated.[10]

Among treatment-related factors possibly accounting for post-STN-DBS changes in VF, the total electrical energy delivered (TEED)[11] to the STN has been to this day largely neglected. Indeed, to the best of the authors' knowledge, only one study[12] has recently approached this matter: here, an association between increased TEED to the left STN and a decrease in semantic

VF 3 months after surgery was reported. However, such an investigation[12] solely included phonemic and semantic VF tests, while not alternate, phonemic/semantic ones—which are nevertheless useful for detecting executive deficits in this population.[13,14] Additionally, Clément *et al.*[12] followed up patients only up to 3 months after surgery—thus limiting the generalizability of their findings to the early postoperative phases.

Given the above premises, the present study aimed at exploring the association between the TEED by DBS to the STN and postoperative changes in phonemic, semantic, and alternate VF (PVF, SVF, and AVF) at 6- and 12-month follow-ups in a cohort of PD patients.

Methods

Participants

Seventeen PD patients (mean ± SD; age: 57.7 ± 7; education: 13.6 ± 3.9; disease duration in years: 11.9 ± 3.5; 9 males) undergoing bilateral STN-DBS lead implantation surgery at the Center for Movement Disorders of Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, were recruited. Patients were assessed by a multidisciplinary panel of clinicians based on CAPSIT-PD guidelines,[2] and surgery was performed according to Levi *et al.*[3] No patient presented with dementia according to the DSM-V criteria for a major neurocognitive disorder due to PD, and all of them had an above cutoff, age- and education-adjusted score on the Montreal Cognitive Assessment (MoCA)[4] before surgery. Participants provided informed consent; this study was approved by the local institutional review board.

Materials

At baseline, motor-functional status was assessed by UPDRS-III-Motor part,[5] which was administered both right after the intake of the usual dose of L-dopa (*i.e.*, UPDRS-on) and after overnight withdrawal from this medication (*i.e.*, UPDRS-off). Additionally, patients were screened for overall cognitive impairment *via* the MoCA,[4] being also assessed for depressive levels *via* the Beck Depression Inventory-II (BDI-II)[6] and for health-related quality of life *via* the Parkinson's Disease Questionnaire-8 (PDQ-8).[7]

Patients were administered the Alternate Verbal Fluency Battery (AVFB)[8] before surgery (T0) and at 6- (T1) and 12-month (T2) distance. The AVFB includes PVF, SVF, and AVF tests, as well as a Composite Shifting Index (CSI) reflecting the "cost" of shifting from a single- to a double-cued VF task.[8] When tested, patients were on medication and the STN-DBS was on.

The TEED per second was estimated according to the guidelines by Koss *et al.*[11] separately for the right and left STN both at T1 and at T2. These two measures were then summed up to compute the bilateral TEED. Bilateral TEED measures at T1 ($TEED_{T1}$) and T2 ($TEED_{T2}$) were also averaged to obtain an overall estimate of the TEED across the year-long observation period ($TEED_M$).

Statistics

To the aim of the current analyses, raw AVFB scores were adjusted for demographic confounders according to current Italian norms.[4]

AVFB scores and TEED measures proved to distribute normally (*i.e.*, skewness and kurtosis values < |1| and |3|, respectively).[15] Hence, parametric tests were employed to test associations/predictions of interest involving such variables.

One-way, repeated-measures ANOVAs were run separately on PVF, SVF, AVF, and CSI scores to explore their trends across the three time points. Significant main effects were decomposed *via* Bonferroni-corrected, *post hoc* comparisons.

Two percentage indices of post-STN-DBS changes in AVFB scores were then computed as follows: (1) changes from T0 to T1 (Δ-01): [(T1 − T0)/T0]*100 and (2) changes from T0 to T2 (Δ-02): [(T2 − T0)/T0]*100. Finally, four sets of Pearson's correlations were run to test the association between change indices in PVF, SVF, AVF, and CSI scores and bilateral TEED measures. More specifically, the following associations have been tested for each AVFB measure: (1) Δ-01 scores *vs.* bilateral $TEED_{T1}$ values, (2) Δ-02 scores *vs.* bilateral $TEED_{T2}$ values, and (3) Δ-01 and Δ-02 scores *vs.* $TEED_M$ values. For this last correlational set, a Bonferroni-adjusted significance threshold of $\alpha = 0.025$ (*i.e.*, $k = 2$ comparisons) was addressed. Analyses were run *via* jamovi 2.3 (https://www.jamovi.org/).

Results

Table 1 summarizes the baseline demographic and clinical characteristics of the patient cohort. Postoperative hemorrhage occurred in 4 patients (23.3%), while transient neurological complications occurred in 6 (35.3%) and 1 patient had transient cardiovascular sequelae. Adjusted MoCA scores remained stable across the three time points ($F(2,32) = 0.92$; $p = 0.41$), with only one patient scoring defectively at T2.

A main effect of *Time* was detected with regard to PVF ($F(2,32) = 5.75$; $p = 0.007$; $\eta^2 = 03.$) and SVF scores ($F(2,32) = 6.93$; $p = 0.003$; $\eta^2 = 0.08$), with *post hoc* comparisons revealing that such an effect was carried out by a significant decline in PVF and SVF scores between performances at T0 and T1 only (PVF: $t(16) = 3.21$, $p = 0.016$; SVF: $t(16) = 4.13$; $p = 0.002$). At variance, no significance of *Time* yielded as to AVF ($F(2,32) = 0.71$; $p = 0.502$) and CSI scores ($F(2,32) = 2.09$; $p = 0.140$). Table 2 reports overtime trends in AVFB scores across the three time points.

Table 1. Patients' Baseline Features

N	17
Sex (male/female)	9/8
Age (years)	57.7 ± 7 (47–70)
Education (years)	13.6 ± 3.9 (8–18)
Onset side (left/right)	12/5
Disease duration (years)	11.9 ± 3.5 (5–19)
UPDRS	
On medication	16 ± 5.6 (4–29)
After overnight withdrawal	37.8 ± 9.3 (18–54)
LEDD	1099.4 ± 321.7 (632–1774)
MoCA (raw scores)	26.1 ± 2.1 (22–30)
Below cutoff (%)	0%
BDI-II	11.2 ± 7.2 (2–25)
PDQ–8	37.6 ± 13.6 (3.8–53.1)

Notes: Data are presented as mean and SD.
Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, L-dopa equivalent daily dose; MoCA, Montreal Cognitive Assessment; BDI-II, Beck Depression Inventory-II; PDQ-8, Parkinson's Disease Questionnaire-8.

Table 2. AVFB Scores and Changes Across the Three Time Points

	T0	T1	T2	Comparisons
PVF	38.8 ± 11.7 (24.2–58.8)	33.7 ± 12.4 (18.2–56)	35.8 ± 13.8 (18.2–59.8)	T0 > T1; T0 = T2; T1 = T2
Below-cutoff (*N*)	0	0	0	–
SVF	46.2 ± 8.4 (29.3–62.7)	39.7 ± 9.9 (25.7–56.7)	41.8 ± 10.6 (19.9–57.1)	T0 > T1; T0 = T2; T1 = T2
Below-cutoff (*N*)	0	3	1	–
AVF	33.1 ± 11.8 (12.2–57.1)	31.8 ± 12.8 (15–54.7)	31 ± 12.3 (10.5–48.6)	T0 = T1 = T2
Below-cutoff (*N*)	1	0	1	–
CSI	0.8 ± 0.2 (0.4–1.2)	0.8 ± 0.2 (0.5–1.2)	0.8 ± 0.2 (0.4–1)	T0 = T1 = T2
Below-cutoff (*N*)	0	0	0	–

Notes: Displayed AVFB scores were adjusted for demographic confounders according to Costa *et al.*[8].
Abbreviations: AVFB, Alternate Verbal Fluency Battery; PVF, Phonemic Verbal Fluency; SVF, Semantic Verbal Fluency; AVF, Alternate Verbal Fluency; CSI, Composite Shifting Index; T0, presurgery; T1, 6 months after surgery; T2, 12 months after surgery.

We found that TEED values at T1 did not significantly differ from those at T2 (70.2 ± 25.7 vs 73.7 ± 23.5; $t(16) = -0.99$; $p = 0.339$). No significant correlations yielded either between Δ-01 scores and $TEED_{T1}$ values or between Δ-02 scores and $TEED_{T2}$ values. As to the association between Δ-01/Δ-02 scores and $TEED_M$ (71.9 ± 23.5), at $\alpha_{adjusted} = 0.025$, only an inverse, marginally significant association ($p = 0.041$) was detected between Δ-01 scores and $TEED_M$ (Table 3).

Table 3. Pearson's Coefficients Among TEED Measures and AVFB Changes

		TEED		
		T1	T2	Mean[a]
PVF				
Δ–01	*r*	−0.02	–	0.13
	p	0.930	–	0.626
Δ–02	*r*	–	0.31	0.19
	p	–	0.227	0.461
SVF				
Δ–01	*r*	−0.40	–	−0.33
	p	0.108	–	0.200
Δ–02	*r*	–	−0.11	−0.21
	p	–	0.677	0.414
AVF				
Δ–01	*r*	−0.45	–	−0.50[b]
	p	0.067	–	0.041
Δ–02	*r*	–	0.13	0.07
	p	–	0.629	0.787
CSI				
Δ–01	*r*	−0.33	–	−0.47
	p	0.203	–	0.056
Δ–02	*r*	–	0.05	0.07
	p	–	0.845	0.793

Notes.
Abbreviations: AVFB, Alternate Verbal Fluency Battery; TEED, total electrical energy delivered; PVF = Phonemic Verbal Fluency; SVF, Semantic Verbal Fluency; AVF, Alternate Verbal Fluency; CSI, Composite Shifting Index; T1, 6 months before surgery; T2, 12 months before surgery; Δ-01, changes from T0 to T1; Δ-02, changes from T0 to T2.
[a]Computed as $(TEED_{T1} + TEED_{T2})/2$.
[b]Marginally significant association at $\alpha_{adjusted}$, 0.025.

Discussion

The present study provides preliminary evidence that TEED appears to be unrelated or only slightly responsible for the decline in VF performance after STN-DBS lead implantation in PD patients. In fact, the percentage changes were not related to bilateral TEED at either 6 or 12 months after surgery. Notably, a slight association was found even when the mean of the two TEED measurements and changes in AVF values at T1 were taken into account.

Overall, the current results contrast with those of Clément *et al.*[12] who found a significant association between higher TEED scores and lower SVF scores 3 months after surgery.

However, it should be noted that the marginal relationship found here between AVF changes at T1 and the $TEED_M$ had the same directional dependence as that found for the SVF by Clement *et al.*,[12] i.e., higher TEED values correspond to greater decline in VF performances. Taken together, these results suggest that TEED may be at least partially responsible for the regression of VF performances, at least in the first 6 months after surgery. In fact, it cannot be ruled out that by using a larger sample, the above-mentioned marginal association reported here could become significant.

In this context, it is also interesting to recognize that this trend only appeared when looking at the $TEED_M$ values. This may suggest that looking at TEED measures recorded at single time points could be misleading when examining their role in explaining postoperative cognitive changes.

Overall, the present report suggests that further investigations are needed in order to actually determine the association between the TEED and changes in neuropsychological functioning in PD patients. In fact, another recent study by Mameli *et al.*[16] demonstrated that TEED to the right STN was associated with a change in depressive symptoms after 12 months. Hence, taken together, these stances prompt a more systematic analysis on the role of direct current stimulation towards changes in a wide spectrum of both cognitive and behavioral functions[17] in this population.

In this respect, it would be advisable that future studies on the role of the TEED towards VF changes in PD patients after STN-DBS also account for the interplay between this measure and stimulation frequency. In fact, it has been previously shown[16] that VF can be significantly impaired when high-frequency (130 Hz) stimulation was delivered to the STN. The STN can be divided into three main areas according to their functional specialization, with the dorsolateral STN involved in motor functions, ventromedial STN in limbic functions, and the ventrolateral STN with associative functions. While the primary target of STN-DBS is the dorsolateral STN, increasing evidence points to the fact that the stimulation can propagate and affects untargeted ventromedial and ventrolateral area.[16] Therefore, it is possible that the propagation of high-frequency current can produce cognitive side effects that stimulate the ventrolateral STN.

In addition, the present report also adds to the literature on VF declines after STN-DBS by suggesting that such involutional trends —which were herewith detected as to PVF and SVF tests only— occurred 6 months but not 12 months after surgery. In fact, they suggest that the decline in VF performances after surgery may be particularly evident in the early to mid-operative period, tending to reach a plateau in the following months and up to a year. Interestingly, such a stance appears to be supported by a previous study on the topic by Daniele *et al.*,[18] who found a worsening of PVF performances in comparison to the preoperative assessment only at a 3-month distance, when the DBS was off, while not after 6 or 12 months, when the stimulation was on.

Some limitations of the present study need to be considered. The first, and most relevant, is the restricted sample size, which prevents the current findings from being fully generalizable and likely played a role in the lack of an overtly significant association between VF changes and TEED measures. Additionally, medium-term follow-up was herewith addressed, and this investigation is flawed by a lack of randomization. Finally, we concentrated on the most relevant data according to cognitive DBS literature, and therefore, we focused solely on verbal fluency, neglecting at this time other cognitive domains that may be affected by DBS. All these issues should be taken into consideration when planning future studies.

Conclusions

In conclusion, the present reports provide preliminary evidence that TEED may not be responsible or only slightly responsible for the decline in VF performance after STN-DBS in PD. However, future research is needed to determine whether TEED plays a role in postoperative VF changes in this population, perhaps by evaluating its interaction with other treatment-related variables.

Data availability statement. Datasets related to the present study cannot be made publicly available because of sensitive information but can be made available upon reasonable request from interested researcher to the corresponding author.

Author contribution. Conceptualization: F.R., F.M., A.P., M.L., S.B. and R.F.; Methodology: F.R., F.M., E.Z., A.D. and R.F.; Formal analysis: E.N.A., S.M. and M.P.; Investigation: E.Z., F.C., L.B., E.P. and A.A.; Data curation: S.M. and M.P; Writing - original draft preparation: E.N.A, R.F.; Writing - review and editing, F.R., F.M., E.Z., E.N.A., B.P., N.T., V.S. S.M., M.P., G.D. and R.F.; Supervision: A.P., M.L. and S.B.; Funding acquisition: A.P., M.L., N.T., V.S. and S.B. All authors have read and agreed to the published version of the manuscript.

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Competing interest. The authors declare that there are no conflicts of interest relevant to this work.

Ethics. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (protocol code 883_2022 and date 13 September 2022). All subjects provided informed consent.

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