

Shifting from constant-voltage to constant-current in Parkinson's disease patients with chronic stimulation

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Abstract The study aimed to evaluate safety and efficacy of shifting stimulation settings from constant-voltage (CV) to constant-current (CC) programming in patients with Parkinson's disease (PD) and chronic subthalamic nucleus deep brain stimulation (STN DBS). Twenty PD patients with chronic STN DBS set in CV programming were shifted to CC and followed for 3 months; the other stimulation settings and the medication regimen remained unchanged. Side effects, motor, non-motor, executive functions, and impedance were assessed at baseline and during follow-up. No adverse events were observed at time of shifting or during CC stimulation. Motor and non-motor measures remained unchanged at follow-up despite impedance decreased. Compared to baseline, inhibition processes improved at follow-up. The shifting strategy was well tolerated and the clinical outcome was maintained with no need to adjust stimulation settings or medications notwithstanding a decrease of impedance. Improvement

of inhibition processes is a finding which needed further investigation.

Keywords Deep brain stimulation · Constant current · Parkinson's disease · Subthalamic nucleus · Executive functions

Abbreviations

CC	Constant current
CV	Constant voltage
DBS	Deep brain stimulation
NMSS-PD	Non-motor symptom scale for PD
PD	Parkinson's disease
PDQ-8	Parkinson's disease questionnaire short form
STN	Subthalamic nucleus
UPDRS	Unified Parkinson's disease rating scale

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Introduction

Deep brain stimulation (DBS) is an established treatment for Parkinson's disease (PD) based on the delivery of an electrical current to a specific brain target. The amount of stimulation depends on current intensity and determines the clinical outcomes [1]. Traditionally, DBS devices have been designed based on constant-voltage (CV) stimulation, which leads to fluctuations of current delivered if impedance changes [2]. It has indeed been reported that impedance varies over time, particularly in the immediate postoperative period, but also later on, as reported in patients with STN implants [3]. The resulting changes of stimulation may account for some of the observed side effects or the need to further adjust voltage after a successful programming [4].

Recently, some internal pulse generators have been designed to allow choosing between CV and constant-current (CC) delivery. CC devices dynamically adjust voltage depending on impedance variations [5]. We aimed to evaluate safety and efficacy of switching to CC stimulation PD patients with chronic STN implants set in CV mode without changing medication or the other stimulation parameters.

Materials and methods

We designed a prospective study on the safety and outcome of shifting PD patients with chronic STN DBS implants from CV to CC settings. We compared motor and non-motor features before and after the switch.

We selected patients with idiopathic PD and chronic bilateral STN DBS driven by an Activa® (Medtronic Inc., Minneapolis, USA) pulse generator set in CV mode. All had excellent response to DBS, stable stimulation settings, and medication doses. Inclusion and exclusion criteria are listed in the supplementary material. The study was approved by the local review board and carried out according to the Declaration of Helsinki.

After baseline assessment, the patients were shifted from CV to CC stimulation. Current intensity under CV stimulation was recorded as measured by the N'Vision programmer model

8840 (Medtronic Inc., Minneapolis, USA). This value was then used to set the CC stimulation mode and the patients were prospectively followed for 3 months. The remaining stimulation settings (e.g., active contacts, frequency, pulse width) and dopaminergic medication remained unchanged throughout the study. Impedance was measured for each active contact at baseline, soon after switch and after 3 months of CC stimulation. Clinical assessments were carried out at baseline and follow-up using validated clinical scales for motor, non-motor, and quality of life measures (see details in the [supplementary material](#)). Cognitive evaluation was performed using a compound battery for executive functions, assessing working memory, set shifting, inhibition, and flexibility (see [supplementary material](#)). A list of possible adverse events related to STN DBS was checked during the entire observation period. Evaluations were carried out by raters blinded to the study aims.

Data were expressed as group means $\pm$ SD. Baseline and follow-up measurements were compared using Wilcoxon signed-rank test and the significance level was set at .05. Friedman test with a significance level set at .05 was used for impedance comparison; post hoc analysis was conducted using Wilcoxon signed-rank test with a Bonferroni correction resulting in a significance level of .017. Statistical analysis was carried out with statistical package for the social sciences (SPSS) release 22.0.

Table 1 Motor, non-motor, quality of life, and cognitive features after 3 months of CC stimulation

	Baseline (CV) <i>n</i> = 20	Follow-up (CC) <i>n</i> = 20	<i>p</i> value
UPDRS motor score	11.8 ($\pm$ 2.6)	11.6 ($\pm$ 2.6)	.432
NMSS-PD	11.1 ($\pm$ 2.5)	12.1 ($\pm$ 2.7)	.383
PDQ8	5.7 ($\pm$ 3.7)	5.6 ($\pm$ 3.5)	.831
Stroop test—time	26.8 ($\pm$ 13.4)	23.1 ($\pm$ 8.2)	.079
Stroop test—errors	1.6 ($\pm$ 1.9)	1.9 ($\pm$ 2.4)	.831
Trial making test A	46.3 ($\pm$ 20)	46.8 ($\pm$ 23.7)	.906
Trial making test B-A	140.7 ($\pm$ 96.4)	125.1 ($\pm$ 97.5)	.093
Working memory—correct items	10.4 ($\pm$ 4.7)	11.5 ($\pm$ 3.6)	.408
Working memory—errors	8.7 ($\pm$ 10.6)	5.9 ($\pm$ 8.6)	.115
Working memory—reaction times	830.3 ($\pm$ 252.4)	764.5 ($\pm$ 232.3)	.149
Flexibility—correct items	77.1 ($\pm$ 22.5)	68.9 ($\pm$ 28.1)	.205
Flexibility—reaction times	1608.5 ($\pm$ 662)	1892.1 ($\pm$ 1792)	.619
Divided attention—correct items	37.4 ($\pm$ 5.1)	38.6 ($\pm$ 1.8)	.626
Divided attention—reaction times	590 ($\pm$ 110.8)	574 ($\pm$ 64.8)	.999
Go/no-Go—correct items	22 ($\pm$ 3.4)	23.9 ($\pm$ 0.2)	.041
Go/no-Go—errors	3.6 ($\pm$ 4.5)	1 ($\pm$ 2.5)	.011
Go/no-Go—reaction times	667.1 ($\pm$ 129)	670 ($\pm$ 183.2)	.068

Variables are expressed as mean ($\pm$ SD). Comparisons are made by Wilcoxon signed-rank test. Boldface indicate statistically significant difference ($p < .05$); italics indicate statistical trend ($.05 < p < .09$)

NMSS-PD Non-motor symptoms scale for PD, *PDQ8* Parkinson disease questionnaire, *UPDRS* Unified Parkinson disease rating scale

Results

Twenty PD patients were included in the study; they had an average duration of STN stimulation set in CV mode of 3.5 (± 2.4) years. Their demographic and clinical characteristics are listed in Supplementary Table 1.

No adverse events were reported at time of change in setting or during the entire period of CC stimulation. At follow-up, there were no significant differences in motor, non-motor, and quality of life measures, as shown by the UPDRS motor, NMSS-PD, and PDQ-8 scores (Table 1).

Cognitive assessment after 3 months showed an increased number of correct items and a decreased number of errors in the go/no-go test (Table 1). The other tests showed no variation compared to baseline (Table 1).

Significant differences in impedance were observed during the observation period ($p = .001$): post hoc analysis showed that impedance decreased from 1132 Ω (baseline, CV) to 1033 Ω (after shift to CC; $p = .001$) and to 1059 Ω (after 3 months of CC; $p = .008$). There was no difference comparing the two impedance values under CC stimulation (Supplementary Fig. 1).

Discussion

This is a within subjects prospective study investigating the safety and efficacy of shifting PD patients with STN implants from CV to CC stimulation. The results show that CC stimulation is well tolerated and is as efficacious as CV when this switching procedure is implemented. Under such circumstances, there is no need to adjust frequency, pulse width, the active contact or antiparkinsonian medication. In earlier studies, CC stimulation was tested in newly implanted PD patients [6] or in PD patients undergoing impulse generator replacement [7]. We add the observation in patients with chronic and stable treatment regimens and propose a practical strategy for shifting to CC.

The STN is a small nucleus with different functional subdivisions [8] and the associative portion is strategically involved in executive functions, particularly in inhibitory processing [9]. Executive dysfunctions, particularly of inhibitory processing, have been reported in PD patients with STN stimulation under CV modality [10]. Switching to CC was also safe regarding cognitive functions: inhibition, as measured by the go/no-go test, improved and other executive tests did not vary after the shift. Four patients with impaired go/no-go test performed normal after switch to CC, an effect possibly mediated by the reciprocal connections between the STN and the prefrontal cortex [11]. This finding have to be taken cautiously as the study design cannot rule out a learning effect bias. However, we administered parallel versions of go/no-go test and this task showed low test-retest effect in others studies [12].

The motor and non-motor effects of STN stimulation were stable after the shift to CC without any need to change settings or medication requirements. This stability of clinical outcome, while impedance decreased from 1132 to 1059 Ω during the observation period, suggests that CC programming may compensate for possible impedance variations after implant. In keeping, findings in non-human primates showed that CC stimulation is associated to less variations in the amount of current delivered [13]. A possible advantage of CC programming is that decrease of impedance may prolong battery life while unaffected clinical outcome. Controlled studies with longer follow-up need to confirm these observations also with an aim to define updated treatment algorithms for large-scale implementation.

Author contributions Paolo Amami: Analysis and interpretation; manuscript writing

Marcello Mascia: Acquisition of data

Angelo Franzini: Acquisition of data

Felipe Saba: Acquisition of data

Alberto Albanese: Critical revision of the manuscript for important intellectual content; study supervision

Compliance with ethical standards

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