RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 5, pages: 341–347
DOI: 10.5603/PJNNS.a2019.0045

ISSN 0028–3843

Evaluating reflexive saccades and UDPRS as markers of Deep Brain Stimulation and Best Medical Treatment improvements in Parkinson's disease patients: a prospective controlled study

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ABSTRACT

Introduction. To date, there has been no clear evidence regarding the evaluation of saccades as a monitoring tool of motor impairment in Parkinson's disease (PD) Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) patients. The aim of this study was to evaluate the long-term impact of STN-DBS and pharmacological treatment on reflexive saccades' (RS) parameters and UPDRS alterations.

Material and methods. The DBS group consisted of 20 PD patients who underwent bilateral STN-DBS. The Postoperative (POP) group consisted of 14 post-DBS patients. The Best Medical Therapy (BMT) group consisted of 20 patients on pharmacotherapy only. RS parameters and the UPDRS scale were measured during three visits in four phases of treatment (i.e. BMT-ON/OFF, DBS--ON/OFF).

Results. The significant UPDRS III and UPDRS. Total improvements were observed in all three study groups ($p < 0.05$), but RS latency improvement was stated only in the DBS group in the DBS-ON phase ($p < 0.05$). A significant correlation between RS latency increase and UPDRS III score worsening was found in all study groups, with the most evident effect in the UPDRS III ON phase ($p < 0.05$).

Conclusion. RS parameters correlated with UPDRS III outcomes during the postoperative period in DBS-STN patients. Therefore, saccadic evaluation may be a good biomarker of the patient's response to surgical and/or pharmacological treatment.

Key words: Parkinson's disease, BMT, DBS, reflexive saccades, marker

(*Neurol Neurochir Pol 2019; 53 (5): 341–347*)

Introduction

Deep brain stimulation (DBS) has become the standard surgical procedure in Parkinson's disease (PD) patients, particularly in advanced stages of the disease and with complications after levodopa therapy. The subthalamic nucleus (STN) is the most often chosen localisation because of the impact on most of the motor symptoms, particularly tremor, bradykinesia and rigidity [1–3] as well as because of the possibility of decreasing the daily levodopa dose [4].

STN is a part of the saccadic system, the impairment of which influences other structures implicated in the generation of saccades, provoking alterations of saccadic movements [5–7]. PD patients present abnormalities in random saccades, reflexive saccades as well as antisaccades or smooth pursuit movements [8–10]. STN-DBS has also been shown to have

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an observable impact on saccades' parameters such as latency, velocity, amplitude, gain or accuracy [11–17]. Levodopa or dopamine agonist treatment has also been shown to have a possible influence on saccadic movements, but changes in ON-Levodopa state are not clear [18–23], which makes the existing evidence more conflicting. Nevertheless, reflexive saccades' (RS) evaluation is a simple method of assessing the possible influence of DBS or pharmacotherapy on the saccadic system, which can be due to alteration or alleviation of the balance between direct and indirect dopamine pathways [24, 25].

All randomised studies comparing the quality of life of PD patients after STN-DBS implantation to the group of PD patients treated with best medical therapy (BMT) in advanced [26–28] or early PD [29] have revealed clinically meaningful improvements of PDQ-39 score and UPDRS-II, UPDRS-III Stim ON evaluation in DBS patients as compared to the BMT-group in a 6-month [26, 27], 12-month [28], or 24-month [29] re-assessment. None of the randomised trials [26–29] has compared the mean change in UPDRS-III score between the BMT-group and DBS patients in a full OFF phase (BMT-OFF/ /DBS-OFF) after DBS implantation — all of the studies have evaluated the BMT-OFF/DBS-ON phase only.

The aim of this study was to evaluate the impact of bilateral STN-DBS and pharmacological treatment on changes in reflexive saccades' (RS) parameters and the UPDRS scale [30] in four phases of treatment (BMT-ON/OFF, DBS-ON/ OFF) and to estimate the possible usefulness of eye movement (EM) measurements as a biomarker of PD patients' response to surgical and pharmacological treatment.

Material and methods

Study concept

Patients enrolled to this study were clinically diagnosed as having idiopathic Parkinson's disease and fulfilled the UK Parkinson's Disease Society (UKPDS) Brain Bank criteria [31]. All of the study patients also met the CAPSIT-PD criteria [32] in order to have the qualification criteria for bilateral STN DBS implantation.

The patients were divided into three groups:

1) The BMT (Best Medical Therapy) group: 20 patients (mean age 56.7 years, 11 females, nine males) treated only with pharmacotherapy through the whole time of observation.
2) The DBS (Deep Brain Stimulation) group: 20 patients (mean age 51.1 years, eight females, 12 males) who underwent surgical procedure and pharmacotherapy.
3) The POP (Postoperative) group: 15 patients (mean age 51.4 years, seven females, eight males) who had been operated upon a median time of 30 months before the study began. This group was created in order to estimate any possible long-term motor effect of DBS.

The patients were examined during three visits (V1, V2, V3) made at intervals of 7-11 months. The UPDRS scale and reflexive saccades were evaluated twice during each visit in the BMT-group and preoperative assessment in the DBS-group (BMT-ON and BMT-OFF phase), and four times (Total-ON, DBS-ON/BMT-OFF, DBS-OFF/BMT-ON, Total-OFF) during postoperative evaluations (V2, V3) in the DBS group, and during all visits (V1, V2, V3) in the POP group.

The characteristics of the patients are set out in Table 1. All of the patients signed informed consents. This study was approved by the Ethics Committee of the Medical University of Warsaw. The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki.

UPDRS examination and saccadic assessment

The motor evaluation of the patients was performed by a neurologist experienced in movement disorders, using the UPDRS scale and saccadometry. The assessment was conducted in different phases of treatment: BMT-ON/DBS-ON when patients were on/off antiparkinsonian drugs and (in postoperative evaluation) with both stimulators switched on/off.

Saccadometry was evaluated using a head-mounted saccadometer (Ober Consulting, Poznan, Poland), which analyses binocular infra-red reflections from each eye. The saccadic step task paradigm was used with 20 calibration saccades followed by 50 random horizontal points projected in a random fore-period of 0.5–1.5s, which were always preceded by fixation central points. The parameters analysed were: saccadic latency [ms], saccades' amplitude [deg], and peak of velocity of saccades [deg/s]. The data was analysed using LatencyMeter software, version 6.9.

Surgical procedure

All of the patients who underwent surgery qualified for bilateral subthalamic nucleus deep brain stimulation

Table 1. Study population characteristics

	BMT group	DBS group	POP group
Gender	11 F, 9 M	8 F, 12 M	7 F, 8 M
Mean age	56.7 ± 15.4 years	51.1 ± 15.3 years	51.4 ± 8.7 years
Mean age at onset	46.3 ± 15.1 years	39.7 ± 13.3 years	40.9 ± 8.3 years
Mean symptoms' duration time	10.4 ± 4.9 years	11.3 ± 3.9 years	10.5 ± 3.5 years
Mean LEDD	1,254.0 ± 511.6 mg	1,379.5 ± 510.0 mg	1,273.2 ± 464.3 mg
Mean time of dyskinesia	1.8 ± 2.6 hours / day	4.9 ± 2.9 hours / day	5.9 ± 2.6 hours / day
Mean OFF time	2.7 ± 1.3 hours / day	4.6 ± 3.2 hours / day	4.4 ± 1.8 hours / day

(STN-DBS). The procedure was performed using microrecording and macrostimulation (Leadpoint®, Medtronic) and permanent electrodes (3389-28, Medtronic, Minneapolis, MN, USA) which were connected to internal pulse generators (Activa SC, Medtronic).

Data analysis and statistical assessment

The linear mixed model analysis was implemented by the use of LME4 (version 1.1) with intercepts for subjects included as random effects. Pairwise interactions between each fixed factor were included in the model. Tukey contrasts (from lsmeans package, version 2.25) were used to compare results between timepoints and treatments [33]. All calculations were performed in statistical computing software R (version 3.3) [34]. P values < 0.05 were considered significant.

Results

The mixed model analysis of RS showed a significant inter-phase latency difference ($p < 0.05$) with a visible relation in inter-visit changes in BMT-ON and DBS-ON phases ($p = 0.1$). The pharmacotherapy (levodopa and other dopaminergic treatment) did not significantly influence the saccades latency ($p > 0.05$). On the other hand, bilateral STN-DBS ON significantly improved RS latency (regardless of pharmacotherapy phase) in both (short-term and long-term) postoperative groups ($p < 0.05$). There was also statistically significant amplitude reduction in the first postoperative (ΔV2-V1) Total-OFF evaluation in DBS group ($p < 0.05$), not observed in other groups and other inter-visit assessments. The same results were also found in saccades' peak velocity: no statistically significant inter-phase or inter-visit changes in RS peak velocity, other than a definite reduction in peak velocity of saccades in the first postoperative (ΔV2-V1) examination of the DBS group in Total-OFF phase ($p < 0.05$) (Fig.1C–E).

The mixed model analysis of inter-phase UPDRS III score alterations was statistically significant ($p < 0.05$), as was the analysis of UPDRS III score alterations among visits in all three groups of patients ($p < 0.05$). The inter-phase analysis showed a significant improvement in UPDRS III score in Total-ON phase (compared to Total-OFF phase) in all three study groups ($p < 0.05$) (Fig. 1A). The improvement was observed in consecutive visits in all study groups ($p < 0.05$), with a more visible impact of the STN-DBS procedure. The mean inter-phase change was more evident in both postoperative groups in phases with stimulators switched ON (DBS and POP group) ($p < 0.05$) than in BMT-ON only phase (with stimulators switched off).

The analysis of inter-phase UPDRS TOTAL score was also statistically significant ($p < 0.05$) as were UPDRS TOTAL score changes among visits in the BMT, DBS and POP groups ($p < 0.05$). The improvement of UPDRS TOTAL score was observed in all three groups of patients, with the most evident effect of STN-DBS procedure in the short-term postoperative DBS group ($p < 0.05$), but was not observed in long-term postoperative assessment (POP-group, $p > 0.05$). The mean inter-phase alterations in the UPDRS TOTAL score were observed in phases with stimulators switched ON (DBS and POP group) rather than in phases with BMT-only ON ($p < 0.05$) (Fig. 1B).

The mixed model analyses between inter-phase and inter-visit UPDRS III and saccades' latency, amplitude and peak velocity in the DBS, BMT and POP groups were performed to compare the possible usefulness of both methods of assessment

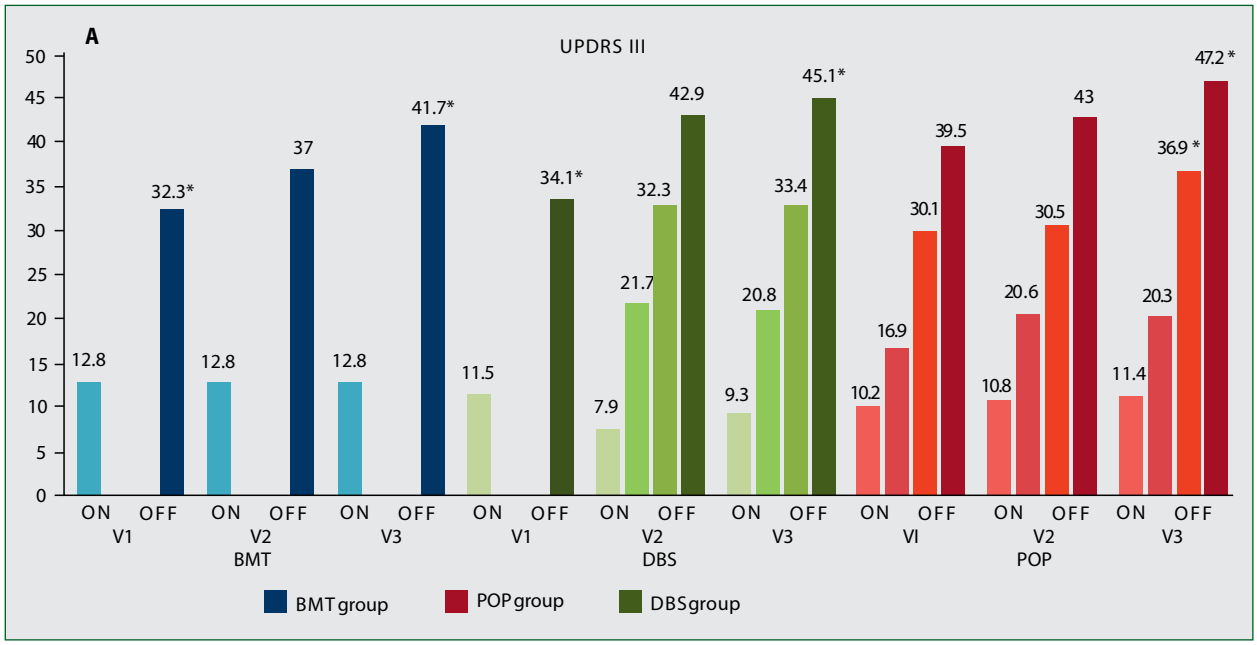

Figure 1. A. UPDRS III

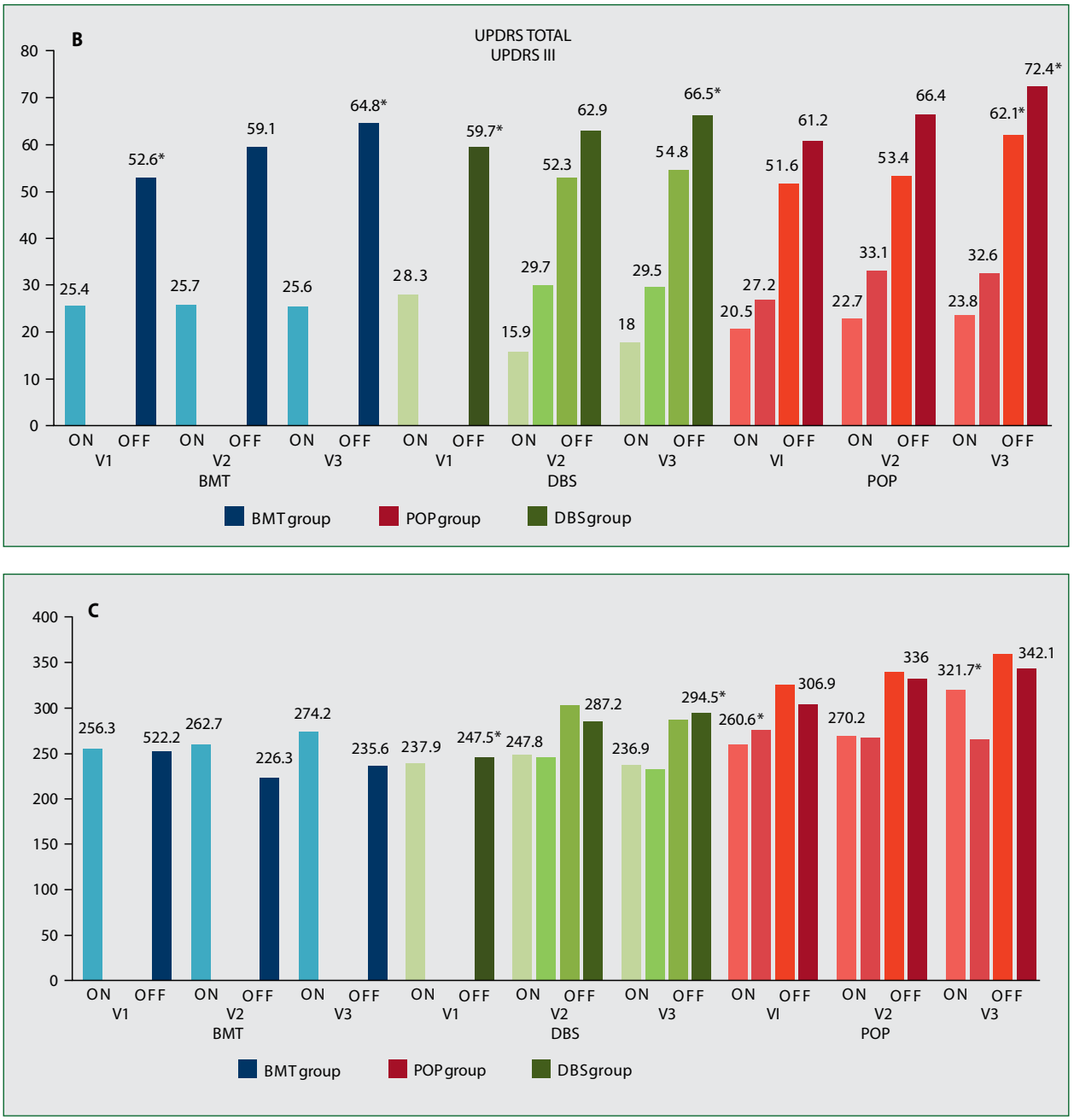

Figure 1. B. UPDRS TOTAL, **C.** mean RS latency

in operative and non-operative PD patients. The analyses revealed a statistically significant correlation between RS latency increase and UPDRS III score worsening in all study groups, with the most evident effect in the UPDRS III ON phase ($p < 0.05$). Such a clear correlation between UPDRS III and RS amplitude and / or RS peak velocity was not demonstrated ($p > 0.05$).

Inter-visit PDQ-39 and AIMS evaluations in all study groups were also carried out to compare the influence of surgical procedure and pharmacotherapy on the patients' quality of life and the level of dyskinesia intensity. The analyses showed a significant improvement of quality of life and a decrease of AIMS in the short-term postoperative DBS group ($p < 0.05$), which was not observed either in the BMT or the POP group ΔV3-V1 assessment ($p > 0.05$).

Discussion

The motor improvement of PD patients after STN-DBS has been previously proven in randomised trials [26–29], but to date there has been no clear evidence on UPDRS and RS application as biomarkers of STN-DBS treatment.

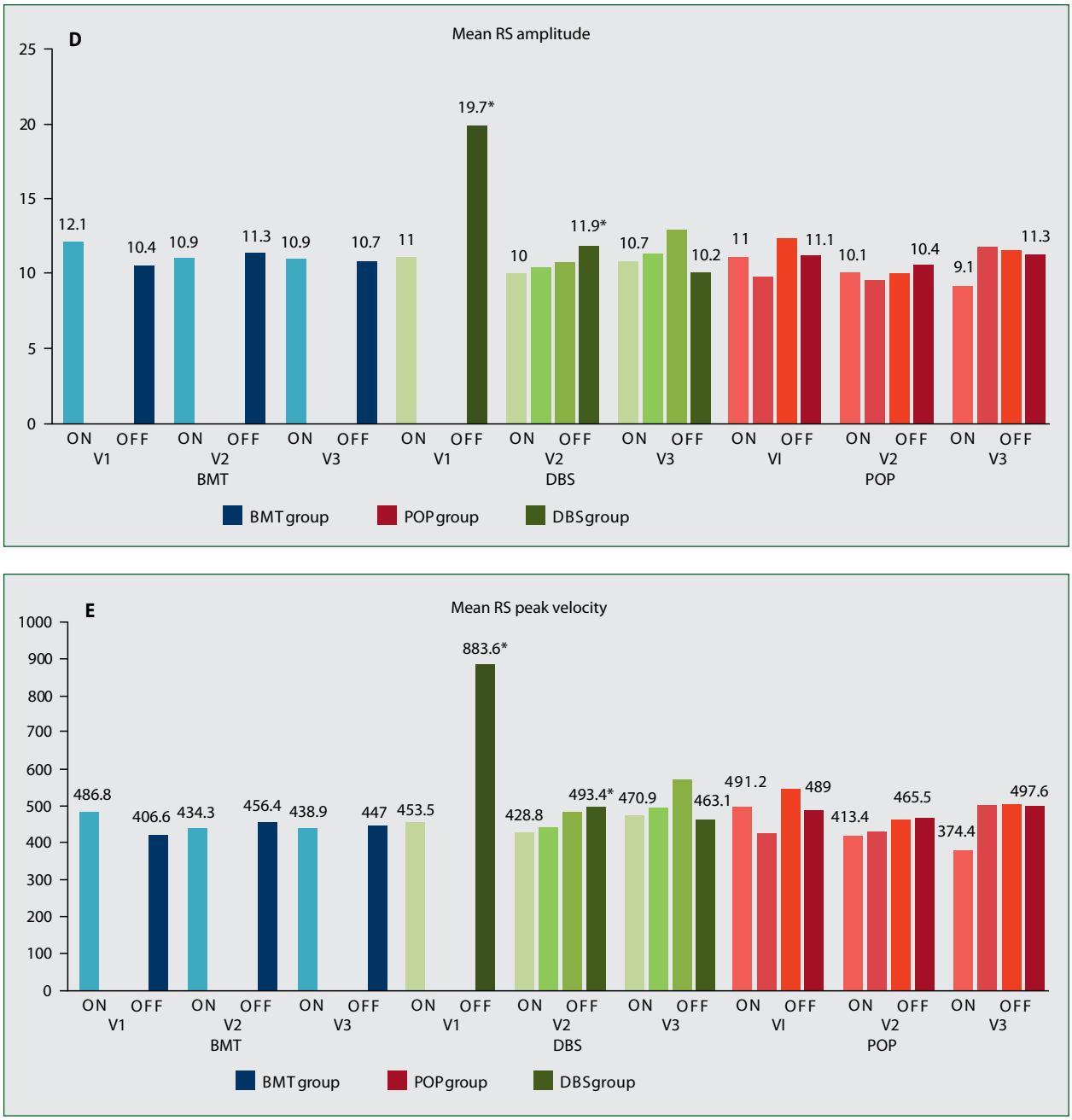

Figure 1. D. mean RS amplitude, **E.** mean RS peak velocity in BMT, DBS and POP group (V1, V2, V3). Consecutive phases: Total-ON, DBS-ON/BMT-OFF, DBS-OFF/BMT-ON, Total-OFF * $p < 0.05$

In all previous randomised studies, the authors proved a great improvement in UPDRS III DBS-ON BMT-OFF evaluation in patients after STN-DBS surgery, and a significant impact of STN-DBS procedure on quality of life in STN-DBS patients [26–29], but none of them compared total OFF phase in the DBS group in consecutive examinations.

In contrast, our study completed this comparison in all four treatment phases in order to establish the full impact of STN-DBS on UPDRS-III and saccadic alterations in BMT/STN-DBS PD patients.

Saccadometry was first described as a possibly useful clinical tool for the quantification of the motor effects of STN-DBS in PD in 2009 by Temel et al. [17], but there were also some other prior studies on monkeys and humans which showed a potential use of this method as a parametric tool in the assessment of motor changes in PD treatment [8, 11, 15, 16, 18–23]. Because of the fact that STN is a part of the saccadic system, various methods of treatment which influence its stimulation can result in alterations of saccadic movements. Therefore we assessed reflexive saccades' parameters in DBS

ON/OFF and BMT ON/OFF in order to estimate the possible correlation between motor improvement in UPDRS III scale and reflexive saccades' variations. Our results are consistent with previous studies, and show a greater improvement in RS latency in the DBS-ON phase (compared to the OFF-phase) rather than in the BMT-ON phase (compared to the BMT--OFF), which may also be an indicator of a more significant effect of STN-DBS, rather than pharmacotherapy, on saccadic system alterations. The other clinical problem of using saccadic movements' assessment as a parametric evaluation of motor deficits in PD patients under various methods of treatment is a lack of information concerning the rate of progression of saccadic alterations in PD. The only assessment has been performed by Antoniades et al. [13] who examined nine PD patients during four visits in order to observe the variations of saccades, which were anomalous: first postoperative assessment in OFF-phase revealed deterioration which was later improved in the following assessment [13], possibly due to astroglial neuroinflammatory reaction to stimulation confirmed in recent animal studies [35–37].

Conclusions

The definite improvement of RS latency with significant correlations to UPDRS III and UPDRS TOTAL score improvement in DBS-ON phase in both DBS (short and long term postoperative) groups with a co-existent non-significant improvement in RS latency (but with preserved significant UPDRS III and UPDRS TOTAL improvement) in the BMT group in the ON phase may suggest that BMT interferes mostly with the dopaminergic system, while STN-DBS may affect other systems as well.

Our results show that the application of RS measurement as a parametric tool (apart from UPDRS III assessment, which is a subjective scale) may be a good prognostic indicator of STN-DBS and pharmacological treatment effect on PD patients' motor outcome and quality of life. The limitations of our study, i.e. the study group sizes and the restricted duration of the study, may necessitate a prolonged assessment on larger populations in order to confirm the quality of these results.

Conflict of interests: *All of the authors declare no conflict of interest.*
Funding: *This publication was prepared without any external source of funding.*

Abbreviations:

PD — Parkinson's disease
RS — reflexive saccades
DBS — deep brain stimulation
STN-DBS — subthalamic nucleus deep brain stimulation
BMT-group — Best Medical Treatment group
POP-group — Postoperative group
UPDRS — Unified Parkinson's Disease Rating Scale
LEDD — Levodopa equivalent daily dose

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