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## Deep Brain Stimulation Improves Parkinson's Disease-Associated Pain by Decreasing Spinal Nociception

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participants provided written consent for their participation in the study and consent to publish and for the video.

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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

## Deep Brain Stimulation Improves Parkinson's Disease-Associated Pain by Decreasing Spinal Nociception

Pain is a frequent non-motor symptom in patients with Parkinson's disease (PD) with increased pain sensitivity and high impact on quality of life.<sup>1,2</sup> Both dopaminergic treatment and deep brain stimulation (DBS) of the subthalamic nucleus (STN) diminish clinical pain and experimental pain sensitivity.<sup>3,4</sup> Dopamine has been assumed to exert its pain-relieving effects at cortical and spinal levels,<sup>4,5</sup> whereas only cortical effects were described for DBS thus far.<sup>6</sup>

The nociceptive flexion reflex (NFR) threshold, reflecting spinal nociception, was assessed during medication *on* (MED-*on*) by the Paintracker ([www.dolosys.com](http://www.dolosys.com)): (1) once with the DBS switched ON (DBS-ON); (2) twice with the device switched OFF (DBS-OFF); and (3) once with the device switched ON again (DBS-ON). Automatic threshold determination lasted 5 minutes (30 stimuli with 10-second inter-stimulus interval). The Paintracker assesses the NFR threshold by using 6.085 times the standard deviation of the noise signal as cutoff within the predefined time frame from 90 to 150 ms for the RIII response (nociceptive reflex).<sup>1</sup> NFR thresholds were determined by logistic regression including the last 11 stimuli.<sup>7</sup> The protocol has been approved by the Institutional Review Board (BASEC ID: 2017:00502). The patients gave their written consent.

The assessment was performed in two female PD patients (48 and 61 years) suffering from an akinetic-rigid subtype for

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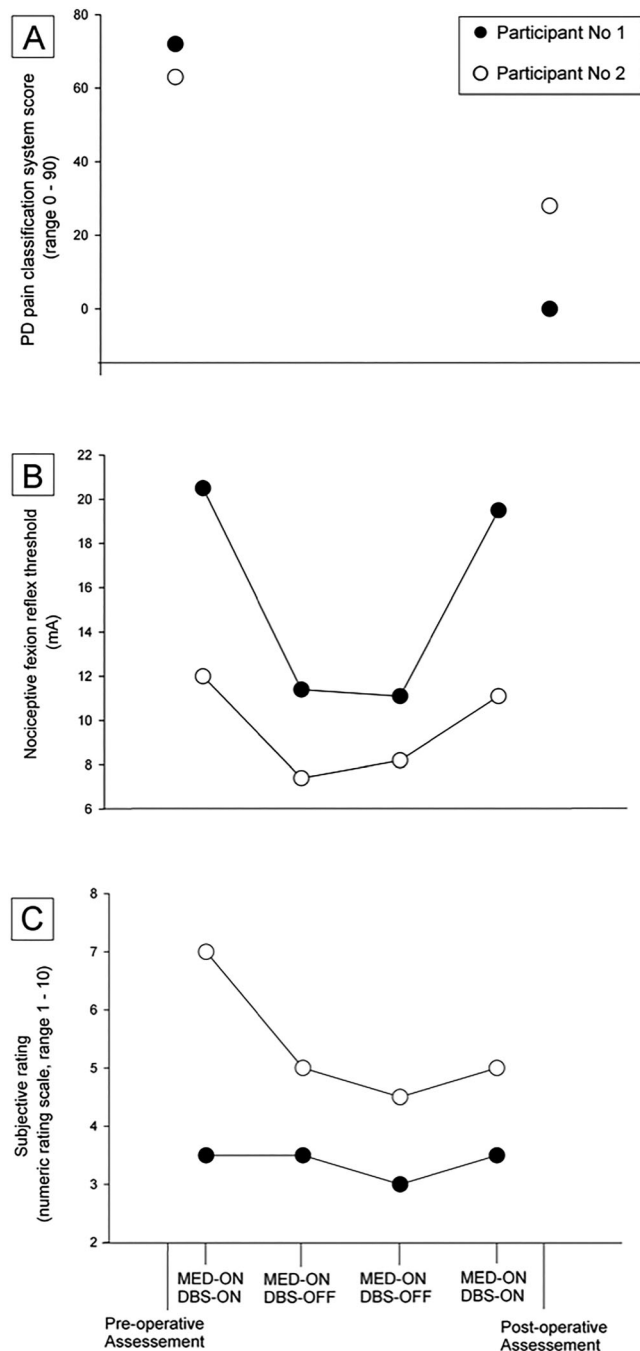
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4 and 12 years. The PD pain classification system score of their PD-associated nociceptive pain was 72/90 and 63/90 before DBS and 0 and 28/90 after DBS implantation (first patient, 1 month after DBS; second patient, 2 years after DBS) (Fig. 1).<sup>2</sup>

In an MED-*on* and DBS-ON setting, the NFR threshold was 20.5/12 mA (first/second patient) and in the MED-*on*/DBS-OFF setting 11.4/7.4 mA and 11.1/8.2 mA, respectively. After switching DBS-ON again, a threshold of 19.5/11.1 mA



**FIG. 1.** (A) Displays the pre- to postoperative pain assessment in two Parkinson's disease patients. Nociceptive flexion reflex thresholds (B) and psychophysical pain ratings (C) are shown in a medication *on* and stimulation ON setting (MED-*on*/DBS-ON) and in a medication *on* and stimulation OFF setting (MED-*on*/DBS-OFF).

was measured. This corresponds to a mean NFR threshold increase of 44% and 32%, respectively. The stimuli were rated with an average of 3.5/6 on a numeric rating scale (NRS; 1–10) with DBS-ON and 3.25/4.75 with DBS-OFF. With DBS-ON and medication-*off*, the second patient had a NFR threshold of 7 mA with a corresponding pain report of 6/10 (second patient only).

Here, we present the first observation of DBS effects on spinal nociception in two PD patients with DBS-responsive PD-associated nociceptive pain. Therefore, besides the effects on the somatosensory cortex, the modulation of pain in DBS-responsive patients extends to the spinal level.<sup>6</sup> Because the patients were assessed in the MED-*on* and dopamine exerts its effects also at the spinal level,<sup>4</sup> we hypothesize additive effects on descending inhibitory control. The amount of NFR threshold increase (DBS-ON compared to DBS-OFF) may serve as indicator for DBS programming to treat PD-associated nociceptive pain.

We overcame the problem of increased muscle tone because of inactivating DBS by assessing the NFR directly after turning the DBS OFF and by using a new device allowing for comfortable stimulation. Verbal pain reports in both conditions and results obtained in DBS-ON condition both, before, and following the DBS-OFF condition, underline the validity of our observations. ●

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## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Morbus Fabry and Parkinson's Disease—More Evidence for a Possible Genetic Link

Although investigation of the potential role of lysosomal storage disorders in Parkinson's disease (PD) has been ongoing since reports highlighted that Gaucher disease can be accompanied by parkinsonism,<sup>1</sup> for Fabry disease (FD), an X-linked recessive multisystem disorder caused by *Galactosidase* gene (*GLA*) mutations, the potential relationship to PD has not been studied until more recently<sup>2</sup> and literature cited therein. Here, we report the frequency of *GLA* variants in 252 PD patients retrospectively selected from our database (mean age, 68.6 years; range, 33–93 years; 59.9% male). With the systematic sequence strategy applied, we found a mean  $\alpha$ -galactosidase-A (GAL)-activity of  $3.4 \mu\text{M/h} \pm 1.44 \mu\text{M/h}$  (cutoff,  $<2.8 \mu\text{M/h}$ ) and mean Lyso-globotriaosylsphingosine (Lyso-Gb3) levels of  $3.6 \text{ ng/mL} \pm 1.30 \text{ ng/mL}$  (cutoff,  $>3.5 \text{ ng/mL}$ ). By bidirectional Sanger

sequencing of all seven exons and flanking 5'untranslated region with at least 20 base pairs of flanking intronic sequences, we detected a total of 96 *GLA* variants in 57 individuals. None of these variants were classified as pathogenic/likely pathogenic for FD according to the American College of Medical Genetics and Genomics, inasmuch as most variants were intronic or in non-coding part of the gene.<sup>3</sup> Most had similar mean allele frequencies (MAF), as reported in major genetic databases gnomAD.<sup>4</sup> Nevertheless, two variants predicted to alter the *GLA* protein were detected in four patients (p.Asp182Asn and p.Asp313Tyr, both of uncertain significance). Of these, p.Asp313Tyr (MAF, 0.85%; MAF in general world population [GWP], 0.30%;  $P = 0.094$ ; MAF in European Non-Finnish Population [ENFP], 0.45%;  $P = 0.209$ ) drew our attention (Table 1). All three patients displayed clinical FD features predominantly involving the central nervous system and heart (Table 1), showing a lower mean GAL-activity of  $2.3 \mu\text{M/h} \pm 0.19 \mu\text{M/h}$  than cutoff ( $P = 0.001$ ) and normal mean Lyso-Gb3 level of  $3.0 \text{ ng/mL} \pm 0.33 \text{ ng/mL}$  ( $P = 0.197$ ). Because p.Asp313Tyr formerly was considered to result in a "pseudodeficient allele" with a pH-dependent enzyme activity, it failed to be classified as clinically relevant or pathogenic for FD. In recent literature, however, this opinion has shifted, as p.Asp313Tyr may cause predominantly FD nervous system manifestations associated with a milder phenotype and later disease onset—a hypothesis that our data support.<sup>5,6</sup> We performed a meta-analysis with a similarly-sized previous study,<sup>7</sup> which screened 236 PD patients in a multistep approach, including *GLA* next generation sequencing in females and all males with abnormal GAL levels, thereby identifying four women with a p.Asp313Tyr variant. By merging the data, MAF of the *GLA* p.Asp313Tyr variant in PD patients clearly reached statistical significance ( $P = 0.006$  compared to MAF of the GWP/alone  $P = 0.021$ ; and  $P = 0.038$  to ENFP/alone  $P = 0.068$ ).<sup>7</sup>

In closing, ours is the first biochemically and genetically systematic study of FD in patients with PD. The limited sample size and the lack of a control group make it challenging to draw firm conclusions; nevertheless, we believe our study is meaningful because it highlights anew the possible link between the *GLA* p.Asp313Tyr variant and PD. Further studies involving larger cohorts are required because the possible pathogenic role might influence monitoring of p.Asp313Tyr variant carriers and decisions involving potential enzyme replacement therapy. ●

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### Data Availability Statement

Data are available from the corresponding author upon individual request.

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