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Research Report

Kinematic Effects of Combined Subthalamic and Dorsolateral Nigral Deep Brain Stimulation in Parkinson's Disease

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Abstract.

Background: Additional stimulation of the substantia nigra (SNr) has been proposed to target axial symptoms and gait impairment in patients with Parkinson's disease (PD).

Objective: This study aimed to characterize effects of combined deep brain stimulation (DBS) of the subthalamic nucleus (STN) and SNr on gait performance in PD and to map stimulation sites within the SNr.

Methods: In a double-blinded crossover design, 10 patients with PD and gait impairment underwent clinical examination and kinematic assessment with STN DBS, combined STN+SNr DBS and OFF DBS 30 minutes after reprogramming. To confirm stimulation within the SNr, electrodes, active contacts, and stimulation volumes were modeled in a common space and overlap with atlases of SNr was computed.

Results: Overlap of stimulation volumes with dorsolateral SNr was confirmed for all patients. UPDRS III, scoring of freezing during turning and transitioning, stride length, stride velocity, and range of motion of shank, knee, arm, and trunk as well as peak velocities during turning and transitions and turn duration were improved with STN DBS compared to OFF. On cohort level, no further improvement was observed with combined STN+SNr DBS but additive improvement of spatiotemporal gait parameters was observed in individual subjects.

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Conclusions: Combined high frequency DBS of the STN and dorsolateral SNr did not consistently result in additional short-term kinematic or clinical benefit compared to STN DBS. Stimulation intervals, frequency, and patient selection for target symptoms as well as target region within the SNr need further refinement in future trials.

Keywords: Deep brain stimulation (DBS), Parkinson's disease, gait analysis, substantia nigra

INTRODUCTION

Subthalamic deep brain stimulation (DBS) is an established and efficacious treatment for motor symptoms of Parkinson's disease (PD) [1]. Axial motor symptoms and especially gait abnormalities such as freezing of gait are not well treated with DBS and, if present, may be considered exclusion criteria during patient selection. Nevertheless, gait disability is a frequent symptom of advanced stages of PD with great variance in phenomenology, which may present as hypokinetic gait patterns with short, shuffling steps and reduced arm swing, irregular gait patterns due to dyskinesia, impaired gait initiation and distinct phenomena such as freezing of gait, defined as "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [2, 3]. Many PD patients develop gait disturbances during the course of the disease years after initiation of STN-DBS leading to clinically relevant disability [4, 5]. Since STN-DBS only exceptionally has been shown effective to alleviate freezing of gait [6], new experimental DBS targets such as the pedunculopontine nucleus [7–10] and the substantia nigra (SNr) [9, 10] have been explored to address gait impairment.

While DBS of only the SNr was insufficient to control both axial and segmental symptoms [11, 12], studies using combined stimulation of STN and SNr for intervals from 30 min to 4 months have reported heterogeneous improvements of gait performance [13–17] or during freezing assessments [18, 19]. Latest technical advances with sensing devices have pushed the field of closed loop DBS paradigms, thereby expanding the potential for dynamically addressing specific symptoms [20–22]. In this setting, monitoring gait performance with sensors presents a promising approach for integrating information on motor performance with the DBS device. To explore the therapeutic potential of combined STN+SNr DBS, this study aims to characterize acute clinical effects on gait performance and to identify objective gait parameters for personalized programming in a cohort in which lead placement allowed simultaneous stimulation of STN and SNr via different monopolar contacts of the same lead targeting the STN and the SNr. Despite the intention to modulate distinct networks, this approach, however, limits contact selection within SNr volume and programming parameter space.

METHODS

Study cohort

Study design was a single center double-blinded, prospective, pseudorandomized crossover study.

Patients who had previously undergone bilateral implantation of subthalamic DBS electrodes with 8 cylindrical contacts (Boston Scientific Vercise Model DB-2201-30DC, stimulator Boston Scientific Vercise DB1110-C) were screened for the study ($n = 14$). In this cohort, the center of the most ventral of the 8 contacts had been positioned within the SNr 1 mm ventrally from the border to the STN as identified by intraoperative microelectrode recordings to optimally cover the extent of the STN and potentially allow SNr stimulation. Electrode placement was confirmed by postoperative CT imaging. Ten patients with gait impairment (UPDRS III gait item ≥ 1 OFF medication pre-OP) were included for the study (all male, age 53.1 ± 4.5 years, average time with DBS 10.1 ± 6.7 months, see Table 1 for more details). Two patients could not complete assessments due to severe gait instability with DBS switched OFF at the time of the study and two were not included which had a tremor-dominant phenotype with no gait pathology (UPDRS III gait item = 0 with DBS and MED OFF)).

Study protocol

The study protocol was approved by the local institutional review board (EA2/016/16) and all patients signed an informed consent.

Motor assessments were performed > 12 h after last intake of dopaminergic medication (= MED OFF). STN stimulation parameters were defined during standard clinical assessment (STN-DBS) and had been stable for at least two weeks. Prior to assess-

Table 1
Clinical characteristics and stimulation parameters

Patient	Sex	Age	Disease duration [y]	Time with DBS [mo]	LEDD [mg]	UPDRS III STN	UPDRS III STN+SNr	UPDRS III OFF	DBS Settings									
									STN LEFT		STN RIGHT		SNr LEFT		SNr RIGHT		Frequency Hz	Pulse width µs
									Contact	Amplitude mA	Contact	Amplitude mA	Contact	Amplitude mA	Contact	Amplitude mA		
Patient 1	M	57	4	3	300	16	24	29	4-	2.6	12-	1.4	1-	1.5	9-	0.9	130	60
Patient 2	M	58	12	3	150	25	25	35	4-, 6-	4.7	14-	3.5	1-	1.5	9-	1.5	119	60
Patient 3	M	51	14	12	–	6	6	23	3-	3.2	11-	3.6	1-	1.5	9-	1.5	130	60
Patient 4	M	45	8	2	475	24	25	48	4-	0.8	12-	1.6	1-	1.5	9-	1.5	130	60
Patient 5	M	57	19	12	850	23	23	33	4-	3.5	12-	2.5	1-	1.5	9-	1.1	180	60 R/ 30L
Patient 6	M	63	9	16	400	12	11	28	2-, 3-	4	10-, 11-	4	1-	1.5	9-	1.5	130	30
Patient 7	M	52	7	12	–	18	15	37	3-	2.2	11-	3	1-	1.4	9-	1.4	130	60
Patient 8	M	57	9	24	1325	41	41	53	4-	1	12-	2	1-	1.5	9-	1.5	130	60
Patient 9	M	51	14	23	750	31	31	36	4-	2	13-	2	1-	1.5	9-	1.5	130	60
Patient 10	M	51	16	4	451	17	16	26	3-	1.8	11-	1.7	1-	1.5	9-	1.5	130	60

Demographic and clinical characteristics of the cohort. The numbering of the active contacts of DBS electrodes (Boston Scientific Vercise ModelDB-2201-30DC) according to the preset nomenclature of the programming tablet: Contacts 1 to 8 correspond to the left hemisphere with contact 1 being the most ventral. Contact 9 to 16 correspond to the right hemisphere with contact 9 being the most ventral. Amplitudes are given in mA (milliampere), frequency in Hz (Hertz) and Pulse width in µs (microseconds). DBS, deep brain stimulation; LEDD, levodopa equivalent daily dose; M, male; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; UPDRS III, Unified Parkinson's Disease Rating Scale part III (motor).

ments, monopolar reviews were conducted for the most ventral contact (SNr) and side effects were determined up to the maximum stimulation intensity of 1.5 mA as suggested by Weiss et al. [18]. The same pulse-widths and frequency were set for the SNr-contacts as for STN-contacts. Both stimulation conditions were saved as programs to the IPG, the order of STN and STN+SNr DBS assessment was randomized using random number tables. Programs were activated by a person not involved in this study, while patient and examiner were blinded to stimulation condition. For each stimulation condition, wash-in time was 30 min after which clinical and gait assessments were conducted. After crossover evaluation of both STN and STN+SNr DBS, stimulation was deactivated and after a washout of 30 min, clinical and gait assessments were repeated OFF DBS.

Clinical and gait assessment

UPDRS III was rated for each stimulation condition by a rater blinded to the stimulation condition.

Performance during walking was assessed over a total distance of 20 m, covered in 2 walking bouts of 10 m. Patients walked at their self-selected, preferred comfortable gait speed. Transitioning and turning performance was recorded over the first iteration (with no additional task) of the sequence of maneuvers used in the freezing of gait assessment course (FOG-AC) [23] using the iTUG of Mobility Labs preset assessments [24]. Freezing was scored according to the rating instructions for the FOG-AC.

Gait performance was assessed with the Mobility Lab system (V1 hardware, APDM, Oregon, USA) using six sensors (Opals) worn at wrists, shanks, sternum and lower back. Data was sampled at 128 Hz and processed within Mobility Lab software V1.0.0.201503302135 [25] to determine trial validity, perform turn excision, and generate an export of stridewise timecoded values of gait parameters as well as averages per trial. Performance of the manufacturers' algorithms regarding delineation of gait parameters for patients with PD have been validated against clinical assessments and other motion analyses technologies in numerous studies (https://apdm.com/publications).

Spatial and temporal parameters extracted from Mobility Lab software export were: stride length, stride velocity (representing gait speed), stride time, cadence, swing and stance time, ranges of motion of knees, shanks, arms, and trunk as well as peak velocities of limb and trunk movements. From freezing assessments, duration, number of steps and peak velocities during turns, sit to stand and turn to sit-transitions were extracted.

Statistical analysis

Shapiro-Wilk-tests were performed for gait parameters and clinical scores on group level. Given the small number of subjects and as not all parameters were normally distributed, non-parametric Friedman-ANOVAs were used to investigate the effect of stimulation conditions (STN, STN+SNr, OFF) on gait performance and Wilcoxon-sign-rank-tests were used for post-hoc analyses. Results are reported as mean $\pm$ standard deviations. Outliers defined as observations differing more than 3 standard deviations from cohort averages were not included in analyses. An alpha level of 0.05 was considered significant. Statistical analyses were conducted with exploratory intent.

Electrode localization and stimulation volume overlap

Analyses were conducted consistent with previous publications from our group [26, 27]. In detail, spatial localization of DBS electrodes was performed using the open-access toolbox Lead-DBS (V2.1.0, RRID:SCR_002915) [28]. Linear coregistration of postoperative images to the preoperative MRI was performed using SPM (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in case of postoperative MRI ($n = 5$) or advanced normalization tools [29] in case of postoperative CT ($n = 5$). This step was followed by meticulous visual inspection, manual refinement (when needed) and brain shift correction of coregistered images. Later, preoperative MRIs were warped to the MNI template used within Lead-DBS (namely, ICBM2009n NLIN asymmetric ("MNI") standard space) [30]. All coregistration and normalization tools were implemented within lead-DBS. DBS electrode artefacts were detected and automatically reconstructed in the MNI template space using PaCER method (for postoperative CT) [31] or TRAC/CORE approach (for postoperative MRI) and manually refined if necessary.

Next, each patient's bilateral stimulation volume mask was spatially overlapped with three different publicly available atlases featuring the subthalamic nucleus and substantia nigra. These atlases are distributed with Lead-DBS in the MNI space. The reason

for including three atlases is to maximize unbiased inferences. This was mainly driven by the fact that each atlas can depict structures slightly differently from the other depending on the methodology. In addition, our focus on nigral stimulation effect call for a better understanding of the anatomical ingredient in this area which these atlases can provide. Precisely, the DISTAL atlas [32] provides a model of the SN stemming from high-quality histological data [33]. Additionally, a SN-segmentation provided by Avecillas-Chasin et al. [34] was used to validate findings. Lastly, in order to conform with the common neuroanatomical knowledge of the functional organization of SN, we further included the CIT168 atlas [35] that lend another parcellation scheme, namely SNc and SNr. For each atlas, bilateral structures (STN and SN or its subdivisions) were used as regions of interest to which the bilateral stimulation volume in STN-DBS or STN+SN-DBS were overlapped. The volume of overlap was then calculated in MNI ICBM 2009b Nonlinear Asymmetric space voxel resolution ($0.5 \times 0.5 \times 0.5$) as provided within lead-dbs. Volumes of overlap across the three atlases were then compared between stimulation conditions (STN vs. STN+SN).

RESULTS

Clinical scores

UPDRS III was significantly improved with stimulation ($p < 0.0001$) compared to OFF DBS (36.6 ± 9.5) but post-hoc comparison revealed no difference between STN-DBS (21.3 ± 9.4) and combined STN+SNr-DBS (21.7 ± 9.6; $p = 0.67$). Similarly, no difference in DBS effects were obtained when testing the gait item of UPDRS III (29) that was significantly improved from 2.1 ± 0.7 (DBS OFF) to 1.2 ± 0.9 (STN-DBS, $p = 0.004$) and 1.3 ± 0.9 with combined STN+SNr-DBS ($p = 0.03$ vs. OFF). Response of UPDRS III gait item to DBS was similar to improvement during levodopa challenge from 1.9 ± 1.0 to 1.0 ± 1.0 ($p = 0.008$) at preoperative evaluation for DBS. Absolute differences with levodopa (0.9 ± 0.7) were not different from those with STN-DBS vs. DBS OFF (0.9 ± 0.3, $p = 0.99$).

Mean simplified FOG-AC was 2.0 ± 1.5 with DBS OFF compared to 0.89 ± 1.0 with STN-DBS ($p = 0.031$). No further improvement was reached with combined STN+SNr-DBS (0.89 ± 1.0) compared to STN-DBS alone (see Fig. 1).

Kinematic assessment

Friedman-ANOVAS revealed an impact of DBS conditions on multiple kinematic parameters that are characteristically impaired in PD such as stride length, stride velocity, peak velocity. Statistical results and numeric values for all parameters are provided in Supplementary Tables 1 and 2. Post-hoc analysis revealed DBS-induced improvement in gait parameters that was similar for STN-DBS and combined STN+SNr-DBS compared to OFF (all $p < 0.05$) including stride length, stride velocity, ranges of motion of shanks, knees, arms and trunk in horizontal plane, peak velocity of shanks, turn duration and peak velocity as well as peak velocities during transitions and range of motion of trunk during sit-to-stand. For none of these parameters post-hoc testing revealed a significant difference for STN+SNr-DBS compared to STN-DBS. Stimulation-induced relative changes of parameters on cohort level are illustrated in Fig. 2.

Since this cohort presented heterogeneous with respect to gait disturbances at baseline, we also analyzed the data on an individual level. Here, three patients (Patients 1-3) showed additional quantitative change of a majority of gait parameters towards normative values with STN+SNr-DBS as compared to STN-DBS alone whereas one patient (case 9) displayed worsening with additional SNr-DBS compared to the improvement reached with STN-DBS. Two patients had no change in gait parameters with stimulation at all and the remaining 4 patients showed a consistent improvement irrespective of the stimulation condition. This variable improvement with stimulation conditions was neither related to clinical type of gait disorder, baseline gait performance as depicted in UPDRS items, baseline stride length and strive velocity, nor to stimulation amplitudes of nigral contacts or stimulation-induced side effects during monopolar testing. Of note, the three patients with further quantitative change of gait parameters with STN+SNr-DBS did not exhibit freezing of gait in our assessments. (Supplementary Table 3) Individual changes of gait parameters are further displayed in Supplementary Figure 1.

Electrode reconstruction and stimulation volumes

Electrode reconstructions in relation to atlas representations of STN and SNr are displayed in Fig. 3.

Mapping of the VTAs of the most ventral electrode contacts revealed spatial clustering in the dorsolateral

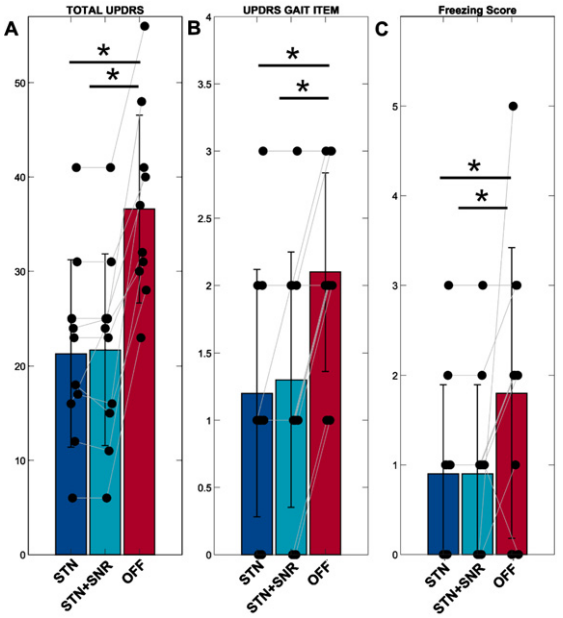

Fig. 1. Clinical scores corresponding to the stimulation conditions STN, combined STN+SNr-DBS and OFF DBS. A) Total UPDRS III – Scores. B) Gait item of UPDRS III. C) Freezing Scores assessed by the first level of the Freezing of Gait Assessment Course [23], meaning no additional tasks other than walking were performed during the sequence of maneuvers. * indicates $p < 0.05$.

area of the substantia nigra (Supplementary Figure 2), bordering the STN. The evaluation of VTAs for both stimulation conditions showed that in all patients VTAs of combined STN+SNr-DBS overlapped with each of the three atlas representations of the SNr. With the combined STN+SNr-DBS condition, stimulation volumes overlapped with 230.1 additional voxels of substantia nigra representation of DISTAL atlas compared to STN-DBS (241.8 ± 122.2 vs. 11 ± 17.5; $p = 0.002$). Correspondingly, in Avecillas atlas, an additional 255.3 nigral voxels (446 ± 347.6 vs. 190 ± 206.1; $p = 0.002$) and respectively 166.5 nigral voxels from CIT168 atlas (210.2 ± 148 vs. 43.7 ± 58.7 $p = 0.002$) overlapped with the VTA of STN+SNr-DBS compared to STN-DBS.

In a heatmap representing the number of VTAs of the cohort overlapping with each voxel, a maximum of 6 VTAs were overlapping in the right SN at $x = 10.5$, $y = -15.0$ and $z = -11.5$ and 5 volumes overlapping in the left SN at $x = -10.5$, $y = -15.5$ and $z = -12.0$.

Side effects

During test stimulation of the SNr contact, three patients (1, 5 and 7) experienced persistent paraesthesia with increasing stimulation amplitudes of the right electrode and one patient (7) upon increasing amplitudes on the left DBS contact. These side effects resulted in lower than 1.5 mA final stimulation amplitudes (see Table 1). Two patients (6 and 8) reported transient paraesthesia of short duration during test stimulation that did not persist at final stimulation amplitude of 1.5 mA. No further adverse effects were documented, particularly no acute subjective changes of mood [36] or alterations of affective state [37] were reported or visible to the examiner.

DISCUSSION

This cohort study investigated the effect of short-term combined DBS of the STN and the SNr on gait performance. We were able to robustly replicate previously well-described improvements of parkinsonian gait disturbances with STN-DBS [38]. Specifically, we showed improvement in objective kinematic parameters using gait analysis based on inertial sensors. Additional SNr-DBS did not further improve average kinematic performance on cohort level although electrode localization and stimulation volumes verified correct targeting of the STN and SNr in our patients.

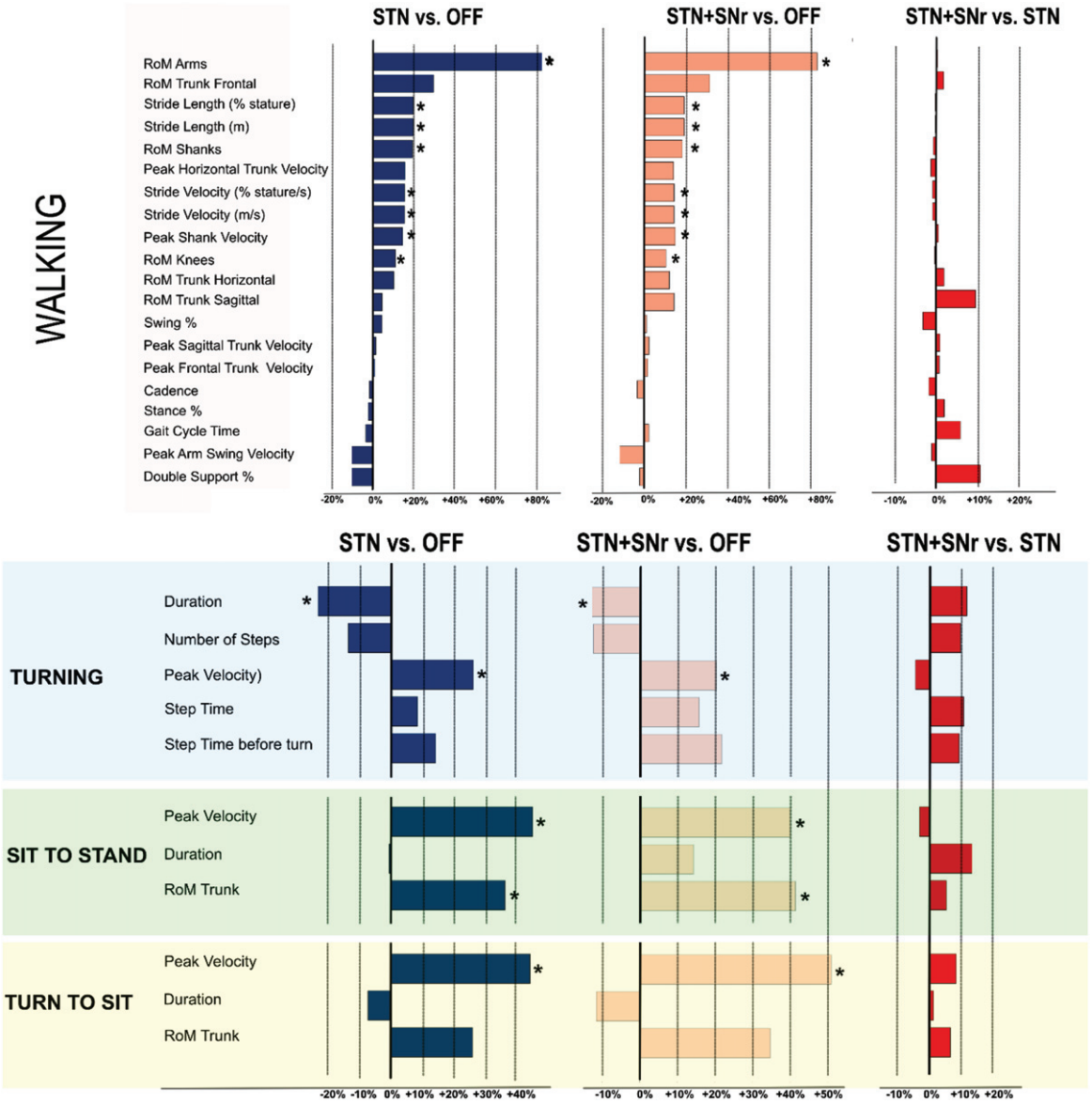

Fig. 2. Relative changes of spatiotemporal gait parameters between stimulation conditions STN vs. OFF (blue bars), STN+SNr vs. OFF (orange bars) and STN+SNr vs. STN (red bars). For each gait parameter, the relative quantitative change between stimulation conditions is expressed as percentage of baseline. Upper panel depicts parameters assessed during straight walking at self selected, comfortable pace. Lower panel depicts parameters of turning and transitioning while performing the first level of the Freezing of Gait Assessment Course [23] * indicates statistical significance ($p < 0.05$).

Target symptoms for nigral stimulation

To date, effects of combined stimulation of STN and SNr on gait disability have been reported in 5 cohorts with a total of 51 patients [13–15, 17, 18]. Across these studies, the interval for which combined DBS was applied before clinical or kinematic assessments varied from 30 min [18] up to 3 months [14]. The concomitant heterogeneity of (semi)quantitative gait assessment methods used in these studies further account for the inconclusive findings on SNr-DBS induced effects that include improvement in a freezing assessment score [18] or the freezing item of UPDRS [14], increased step length [15, 17] and a higher fraction of normal gait cycles [13]. Similar, we found improvement in standard kinematic parameters

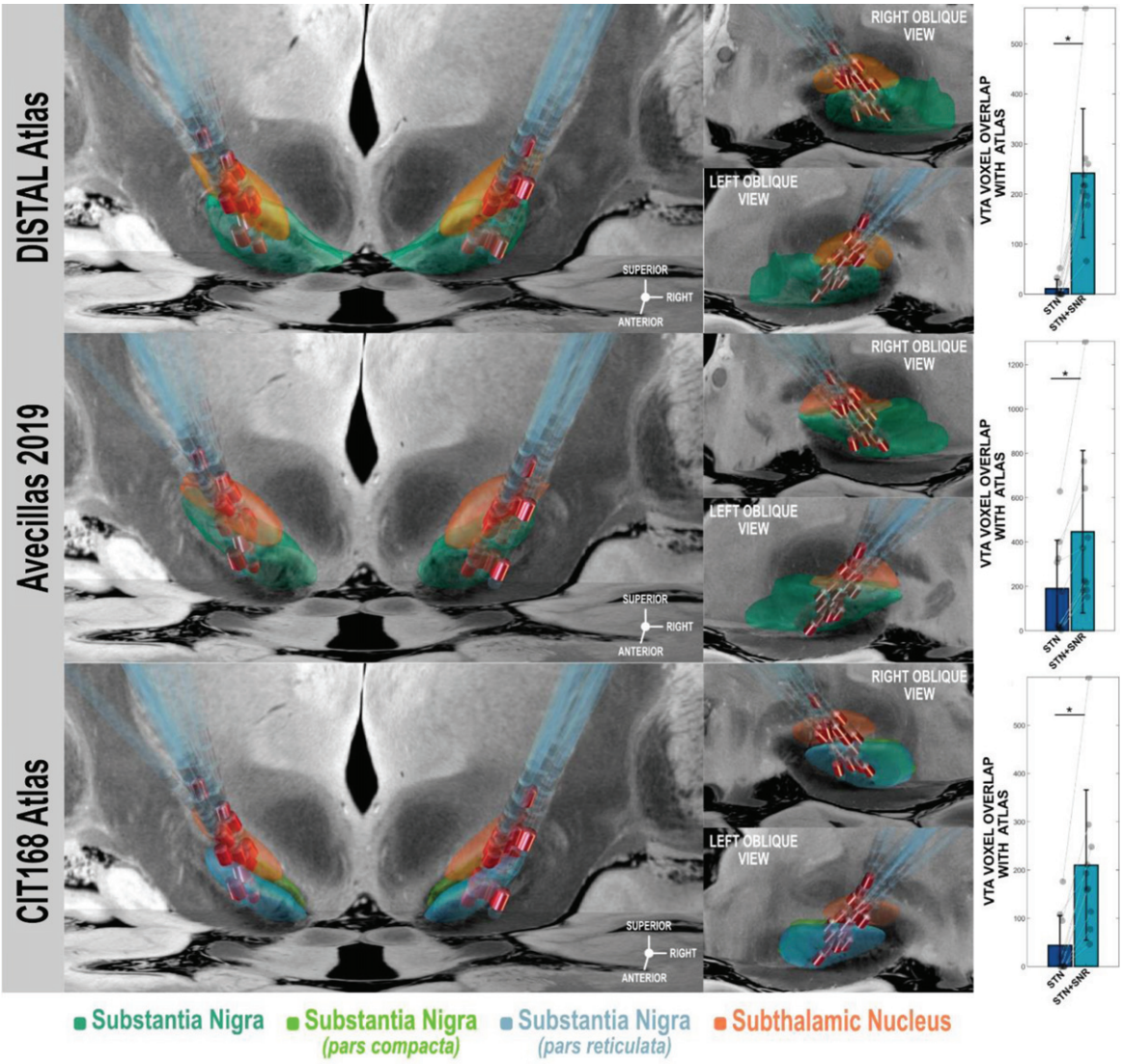

Fig. 3. Left Panel: 3D-visualization of DBS leads of the cohort in coronal view (left) and sagittal views on right and left STN (orange) and SN (turquoise) relative to target structures as represented by DISTAL Atlas [32], Avecillas atlas [34], and CIT168 atlas [35]. Contacts active in the STN+SNr-DBS condition are highlighted in red. Note the position of the most ventral active contacts within or in direct vicinity of the SNr atlas representations. Atlas structures and leads are superimposed on a slice of 7 Tesla MRI of ex vivo human brain at 200 micron resolution [61]. **Right Panel:** Bar charts showing numerical overlap of voxels of stimulation volumes for stimulation conditions STN and STN+SNr-DBS with corresponding atlas representation of substantia nigra of DISTAL Atlas [32], Avecillas atlas [34], and CIT168 atlas [35]. Voxel numbers account for both hemispheres. * indicates differences of overlapping voxels were significant ($p < 0.05$).

with STN-DBS in our cohort. Nevertheless, additional improvement was not achieved on cohort level related to combined STN+SNr stimulation beyond the effect of subthalamic stimulation alone. However, individual improvement was observed in three patients. Of note, gradual improvements of gait parameters were not reflected in the UPDRS III gait item, thus emphasizing the importance of quantitative gait assessment technologies for the evaluation of novel therapeutic approaches.

Gait disturbances in PD comprise a wide range of symptoms from persistent, hypokinetic gait features that can be attributed to basal ganglia dysfunction to episodic features like FoG or impaired gait initiation that are associated with cortical involvement of premotor and parietal areas and their projections.

Thus, target symptoms should be described accurately when evaluating therapeutic approaches. This has been done by Weiss et al. [18] who had defined a medication and stimulation refractory axial subscore of UPDRS III as inclusion criterium when showing SNr-DBS induced improvement of FoG. Horn and colleagues [15] report increased step length with STN+SNr-DBS compared to STN-DBS that was more pronounced during increased cognitive load under dual tasking. Wagner and colleagues report a reduction of step-time variability for STN+SNr-DBS compared to STN and OFF DBS [17] without specific gait-related inclusion criteria, similar to Villadóniga and colleagues [13] who report a significantly higher fraction of normal gait cycles as determined by deceleration, reversing and acceleration, yet the clinical significance of this finding remains speculative. Thus, gait related motor symptoms were variable across and within trials, which may explain the heterogeneity of results. In the same vein, one major limitation of our study is that patients were not preselected for the severity of gait disability or presence of freezing. For this study, we screened patients which had received DBS electrodes with 8 full ring contacts because their spatial extent allowed to place one contact in the SNr without compromising on STN hot spot targeting. Nevertheless, gait disturbances were present in all patients in the OFF medication/OFF stimulation condition according to UPDRS III. STN-DBS led to a significant modulation of gait parameters that was not equally improved by combined STN+SNr stimulation. However, STN+SNr stimulation effect was quite variable, which prompted an additional individual analysis in order to define potential predictive outcome variables. Yet, we did not find a relationship of clinical characteristics, specific baseline gait parameters or pattern and the individual improvement in gait parameters that was observed in three patients with STN-SNr-DBS (see Supplementary Table 3 for details).

Larger patient numbers and correlations with patient-reported outcomes will be needed to delineate the individual baseline profile of patients that would potentially benefit from additional SNr stimulation. Unlike for STN-DBS, where preoperative response of selected symptoms to levodopa may forecast their response to DBS [39, 40], this relation has only been reported for small cohorts [11] suggesting different patterns of modulation with levodopa and SNr-DBS. Potentially, relevant modulation of axial features due to SNr-DBS may have been masked with concurrent STN-DBS, yet clinically realistic scenarios would not involve SNr-DBS alone due to insufficient control of segmental symptoms.

Due to its paroxysmal and variable nature with different clinical phenotypes, standardized investigation of freezing of gait remains challenging in context of clinical studies. Assessment courses involving turning in narrow spaces [23] may increase probability of provoking freezing, yet may still be unable to determine clinically meaningful impact on patients' quality of life, especially when assessments are performed in laboratory or clinical environments rather than patients domestic environments. As our assessment was focused on unperturbed turning and transitioning performance, we did not include dual tasking or adding cognitive load to the freezing assessment. In the future, continuous monitoring of gait performance over longer intervals using wearables [41] may provide further insights on the impact of novel stimulation paradigms on motor performance in patients' domestic surroundings [42].

Stimulation parameters and intervals

While heterogeneity of kinematic effects of combined STN+SNr-DBS in previous studies stems from different scales, scores, kinematic parameters and sensor systems used to quantify effects, additional incongruence is introduced by the differences in time intervals over which combined stimulation was applied in these studies. The interval investigated in this cohort was 30 min after changing stimulation (STN, STN+SNr) in randomized order and 30 min after deactivation of DBS (OFF), following the protocol suggested by Weiss and colleagues [18, 43] who observed a consistent reduction in freezing both after 30 min and 3 weeks of combined DBS. For STN-DBS, temporal dynamics of washout-periods and onset of therapeutic effects have been mapped [44, 45] and confirm that intervals of 30 min would suffice for clinical effects to unfold following changes of STN-DBS. These dynamics have not been studied in the same manner for the SNr. Nevertheless, data from intraoperative recordings investigating firing rates of STN and SNr hint to an instant modulatory effect of lower frequency SNr DBS [46]. It is unknown whether plasticity within the SNr following chronic DBS may play an additional role which seems to be associated with severity of motor symptoms in PD [47].

Most previous studies have used standard stimulation frequencies from 120-130 Hz for the stimulation of SNr, except for Valldeoriola and colleagues, who

used 63 Hz, following reports of improvement of axial symptoms of PD with 60 Hz STN-DBS [48]. High-frequency stimulation applied to the STN has been shown to produce persistent synaptic inhibition of neuronal firing in the STN [46, 49] suppressing pathologically enhanced burst firing in the STN, that has been shown to encode pathological beta oscillations [50], a hallmark of PD pathophysiology. Synaptic inhibition resulting from the recruitment of striatal projections to the SNr, however, has been shown to depress at HFS in parallel with reoccurrence during ongoing stimulation [46]. Low frequency stimulation in the SNr may suppress this reoccurrence, as neuronal silencing has been suggested to be achieved at stimulation frequencies < 30 Hz in SNr [47] and thus frequencies, that are not yet subject to pronounced synaptic depression [51]. Furthermore, synaptic plasticity of inhibitory synaptic input to the SNr has been shown to directly relate to axial symptoms of PD [47]. Continuous suppression of SNr firing rates would result in a disinhibition of SNr projections and thus may modulate neural signaling in the MLR as previously suggested in animal studies with decerebrated cats [52]. Nevertheless, it remains speculative how continuous alteration of SNr activity would translate into dynamic kinematic changes of complex motor behaviors such as freezing of gait.

Due to the technical limitations of the IPGs used for this study, the same frequency had to be used for all active contacts. As lower frequencies than 100 Hz have demonstrated insufficient control of segmental symptoms of PD [48], the stimulation frequency of the SNr contact was determined by the STN contact in this cohort. Currently available generations of IPGs allow using multiple stimulation channels and different frequencies to address this issue in future cohorts.

Defining the sub-area of SNr for combined STN+SNr stimulation

The SNr is the largest nucleus in the midbrain and consists of functionally and anatomically distinct subdivisions [53, 54]. The dopaminergic neurons of the pars compacta (SNc) project to limbic, associative and motor striatum while GABAergic neurons of the pars reticulata constitute an output nucleus of the basal ganglia that is highly preserved across species [55], allowing inferences from animal studies that have attributed regulation of postural and dynamic motor behavior to stimulation of SNr [52]. Furthermore, microelectrode recordings within the SNr of patients with PD undergoing implantation of STN DBS have provided insight on local neuronal activity characterized by fast (80-100 Hz), regular firing [46, 51]. As recordings are obtained along the trajectory used for the implantation of the DBS lead, the neuronal population of the SNr recorded is located in the dorsolateral proportion of the SNr. Along this trajectory, this study as well as previous studies on combined stimulation have relied on the same implantation strategy, allowing combined DBS of SNr and STN via different contacts of the same DBS lead.

In addition to previous reports that relied on intraoperative electrophysiology to infer location of the lowermost contact in the SN from the characteristic high-frequency, regular spiking pattern [15, 17] and co-registration of pre- and postoperative imaging to confirm position of lowermost contact in relation to anatomical landmarks, our study is the first to describe the overlap of stimulation volumes with atlas representations of the SNr along with behavioral and kinematic effects. This allowed us to confirm stimulation of SNr for all patients, but further reveals that stimulation is restricted to the dorsolateral part of SNr with this surgical approach (Fig. 4).

In the STN, where subdivisions project to different networks [56], sweet spots for optimal outcome differ for motor symptoms and patient reported outcomes [57], with DBS of the sensorimotor STN being associated with clinically relevant reduction of motor symptoms as assessed by UPDRS III. In rodents, it has recently been shown that the SNr contains segregated subpopulations that differentially project to functionally distinct brain stem regions [58]. Of interest to the current study, brain stem regions that have been implicated in axial and gait symptoms such the pedunculopontine nucleus confine to spatially restricted populations of SNr neurons. Corresponding investigations in humans characterizing neuronal populations related to gait performance [59], may refine preselection of SNr subregions as DBS targets. Location of the nigral contacts did not reveal obvious spatial differences between responders, non-responders and the individual with deterioration of gait performance when mapped to a common atlas in our cohort. Thus, future trials must further elaborate on effects of neuromodulation of specific regions within the SNr on gait and balance. In contrast to the DBS leads with monopolar contacts used in

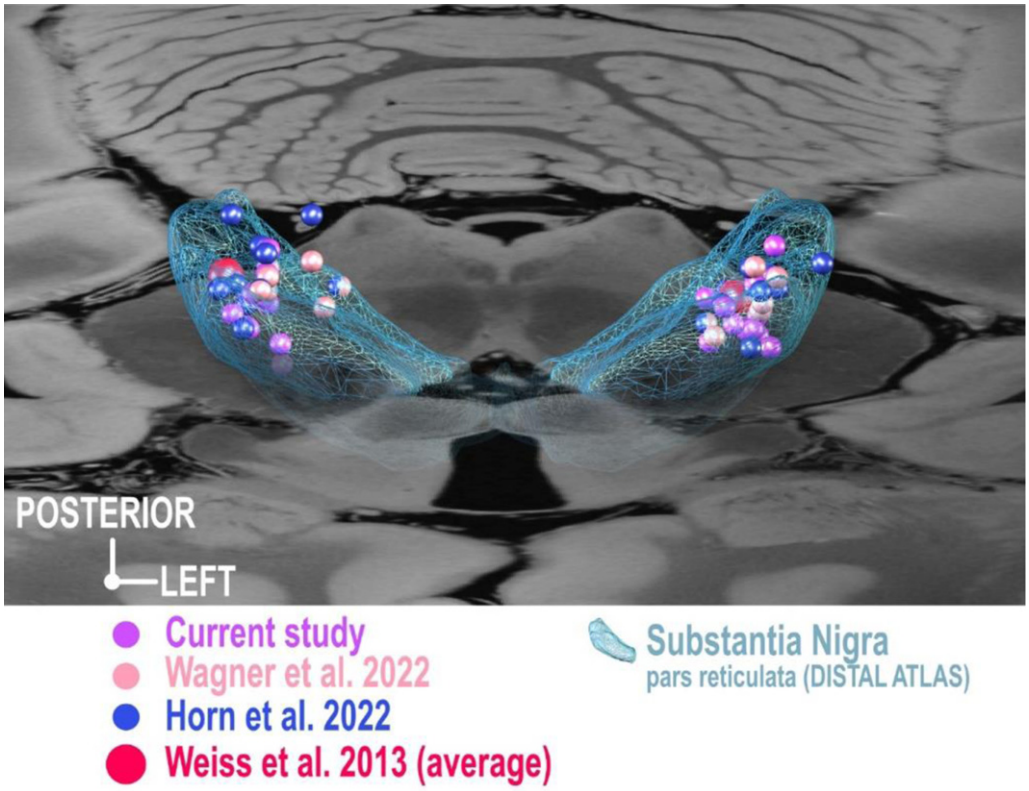

Fig. 4. 3D-visualization of previously published coordinates of electrodes targeting the substantia nigra from two studies [15, 17] as well as the cohort average of one study [18]. As coordinates for these studies were reported relative to AC-PC, an established conversion algorithm [62] was used to project coordinates into a common space (MNI) and relative to the substantia nigra atlas structure as defined by the DISTAL atlas [32] superimposed on a slice of 7 Tesla MRI of ex vivo human brain at 200 micron resolution [61]. Note that coordinates aggregate in the dorsolateral substantia nigra or even dorsal to the substantia nigra within the region of the subthalamic nucleus.

this study, modern electrode designs allowing current steering via segmented directional leads may be employed in future studies to selectively stimulate the SNr or smaller divisions of the structure. Lastly, it has to be considered that effects of combined stimulation from previous studies may also be a result of stimulation of additional STN neurons via current spread or due to position of the ventral contact within the STN or in the border zone, as pointed out by Horn and colleagues [15]. Particularly in cases where the active contact is not located within the SNr, spherical stimulation volumes from monopolar contacts will bear a greater risk of co-stimulating other anatomical structures than the target. This may be addressed in the future with the use of segmented electrodes with directional programming in combination with imaging, electrode localization and modelling of stimulation volumes [60]. Vice versa, we have shown that a substantial proportion of stimulation volumes intended for stimulation of the STN may overlap with the SNr.

Conclusion

No consistent additional benefit of combined STN+SNr-DBS was demonstrated in this cohort for the specific set of stimulation settings applied here. Objective, quantitative kinematic assessment should be used for monitoring of gait improvement instead of semiquantitative scores or subscores. Congruent with previous studies, stimulation volumes addressing the SNr were mapped to the dorsolateral part, demonstrating that DBS is restricted to this neuronal population if the same trajectory and electrode as for STN-DBS is used. Future trials on the potential role of the SNr as a target for neuromodulation should incorporate these findings in refinements of their study protocols.

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CONFLICT OF INTEREST

DK, BA, CM, and LAS report no conflicts of interests. GHS reports personal fees from Medtronic, Boston Scientific, and Abbott. AAK is on the advisory board of Boston Scientific and Medtronic, and has received honoraria unrelated to this manuscript from Boston Scientific, Medtronic, Abbott, Zambon, Stadapharm, Teva and Ipsen, companies manufacturing deep brain stimulation or pharmaceutical therapies.

DATA AVAILABILITY

The imaging data, electrode reconstructions and gait assessments are not publicly available due to federal and institutional data privacy regulations of patient data and the General Data Protection Regulation of the European Union. Patient consent for public sharing of their data was not obtained, but processed data can be made available from the corresponding author upon reasonable request in anonymized manner in the framework of a data sharing agreement.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JPD-230181.

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