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Anticipatory postural adjustments are modulated by substantia nigra stimulation in people with Parkinson's disease and freezing of gait

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ABSTRACT

Background: A precise understanding of the neuronal circuits involved in the control of anticipatory postural adjustments (APAs) for gait initiation is missing. Neurostimulation in Parkinson's disease (PD) provides a method of modulating APAs to gain insight into the underlying circuitry.
Objective: Our objective was to investigate if APA kinematics for step initiation could be modulated by high frequency stimulation of the subthalamic nucleus (STN) or substantia nigra pars reticulata (SNr) in people with PD and freezing of gait (FoG).
Methods: We studied 14 people with PD and FoG using neurostimulation of the STN and SNr areas after overnight withdrawal of dopaminergic medication on the instrumented stand and walk test. We tested patients in the following randomized conditions: 'off stimulation', 'STN' stimulation (only), and 'SNr' stimulation (only). Patients were blinded to the stimulation condition. The APAs were recorded with inertial sensors and processed offline. Moreover, we assessed clinical scores with respect to motor symptoms, non-motor symptoms, executive function, and FoG.
Results: SNr but not STN stimulation modulated the anterio-posterior size of APA. The SNr modulation of APA was associated with the stimulation effect on FoG (trend; $r = 0.580$, $P = 0.102$). The APA modulation was not correlated with any other cognitive or clinical measures.
Conclusion: Neuromodulation of the SNr but not of the STN modulated APAs in PD patients with FoG. The different effects of STN or SNr on the kinematic parameters of APA support the concept of segregate targets in order to address diverse kinematic components of PD gait.

1. Introduction

Postural instability and gait disturbances (PIGD) are hallmark features of Parkinson's disease (PD). As the disease progresses, PIGD increasingly leads to falls, comorbidities, and loss of self-dependence. A core component of human balance control is the ability to perform subtle anticipatory postural adjustments (APAs) in preparation for a subsequent voluntary movement, such as gait initiation. This preparatory phase involves shifting the centre of pressure in the lateral and posterior directions, in order to move the body centre of mass towards the stance leg and forward in the direction of movement progression [1,2]. Gait initiation is affected in PD patients [3] and APAs, as assessed with kinematic measurements, in particular are impaired. In early stage PD, the centre of pressure displacements in medio-lateral direction are reduced compared to healthy controls [4]. In later stages of the disease, APA amplitudes in both medio-lateral and anterior-posterior directions are reduced, and the APA duration increases [5–8]. Finally, start-hesitation during gait initiation is common in patients with freezing of gait (FoG), but the contribution of the size of APA to FoG is still unclear although a recent study discussed the reduced APA size as a

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compensatory strategy to avoid FoG [9]. In addition, it has been demonstrated that levodopa medication is effective in increasing APA size, although not completely restoring it to healthy controls range [10,11].

Currently, the brain circuitry involved in the pathophysiology of APAs is not well understood. It has been proposed that the supplementary motor area (SMA), primary motor cortex, as well as the brainstem, including the mesencephalic locomotor region, are involved in postural preparation for voluntary movement. However, our understanding of the brain circuitry involved in APAs and the relationship of temporal and spatial aspects of APAs and step initiation needs to be elucidated [1,12,13]. Deep brain stimulation (DBS) offers the opportunity to explore areas involved in the control of APAs in PD patients [14,15]. Specifically, whilst the subthalamic nucleus (STN) is integral part of the pallido-thalamo-cortical pathway and hyperdirect cortical connections to the SMA, the substantia nigra pars reticulata (SNr) has direct connections to the mesencephalic locomotor region (MLR) and the nigro-ponto-spinal pathway upon GABAergic efferents [15,16]. To this end, SNr stimulation might attenuate GABAergic over-inhibition of the locomotor brainstem centres [16]. Although STN or SNr do not exclusively modulate the locomotor network given their complex interconnection with other basal ganglia nuclei and outflows, there is clinical and kinematic evidence, that STN or SNr (mono stimulation) may indeed differentially modulate the spatial and temporal parameters of gait as well as the clinical outcomes [14,15,17]. Therefore, we hypothesized that STN stimulation would act predominantly by modulating the STN – thalamo – pallido – cortical circuit, whereas SNr stimulation would impact mainly the descending nigro-pontine pathway [14–16] and lead to distinct APA modulation in contrast to stimulation off condition. Here, we take advantage of PD patients with FoG and implanted DBS electrodes placed in both sites, the STN and the SNr area, to study the neuronal correlates of the APAs characteristics. The aim of the study is to measure distinct APA components and its modulation by STN or SNr DBS in order to explore the functional neuroanatomical representation of APAs in people with PD and FoG.

2. Material and methods

2.1. Participants

We included 14 patients with idiopathic PD (13 male, 1 female) and DBS therapy. Inclusion criteria were treatment with STN-DBS (lowermost contact of the quadripolar lead reaching the SNr; individual electrode coordinates given as Supplementary Table 1), age 18–85 years, > 5 years of disease duration, > 6 months since DBS implantation, and Mini Mental Status Examination (MMSE) > 22 points. We confirmed all patients as 'definite freezers' during the experimental sessions, i.e. FoG was observed in each individual patient. Twelve out of fourteen patients were identified as freezers when performing the Freezing of Gait Assessment Course [18]. In detail, seven patients showed start hesitation, 11 patients showed FoG when turning in place, and 11 patients showed FoG during the door task. In addition, two patients showed FoG during the straight walking part of the instrumented stand and walk test (ISAW).

Table 1 shows the patient characteristics. The participants had a mean age of 66.0 ± 10.4 years (all mean ± STD) and disease duration of 14.2 ± 4.9 years. The mean time since implantation of DBS electrodes was 41.0 ± 18.2 months. Clinical scores were 28.1 ± 1.6 points on the MMSE, 11.6 ± 8.1 on the Beck's Depression Inventory, and 14.7 ± 8.7 points (out of 24) on the New Freezing of Gait Questionnaire. The electrode contacts of the quadripolar lead reached both STN and the dorsal border zone of SNr (electrode 3389, Medtronic, Minneapolis, MN, USA) similar to work published elsewhere [14,15]. Detailed individual and mean electrode coordinates relative to the midcommisural point are given in the Supplementary Table 1. Individual stimulation parameters are given in Supplementary Table 2. We excluded patients with other neurological diseases than PD, uncontrolled psychiatric symptoms and other medical conditions that would have affected the data. All participants provided written consent before taking part in the study. The Ethics Committee of the University of Tuebingen (Nr. 354/2015BO1) approved the study.

2.2. Clinical assessments and experimental paradigm

We assessed the New Freezing of Gait Questionnaire, MMSE, and Becks Depression Inventory. In addition, we measured the set shifting capabilities with the Trail Making Test Part B the day before the gait testing. The experiment took place after an overnight withdrawal from dopaminergic medication (MedOff). The individual regular medications are summarized in Supplementary Table 3. Clinical and instrumented gait assessments were conducted in three stimulation conditions: stimulation off (StimOff), STN mono (STN), or SNr mono (SNr). No combined STN + SNr stimulation was intended in this pathophysiological study. Patients were blinded to the stimulation condition, stimulation conditions were randomized. To limit potential carry-over effects, the stimulation was active for at least 30 min prior to gait testing; except when discontinuation of stimulation caused remarkable Off-symptoms, then the StimOff condition was tested earlier. STN stimulation parameters were close to the individual chronic parameters. However, since the patients were in dopaminergic 'Off', we adjusted the parameters if better suppression of rigidity and bradykinesia was possible. We introduced SNr parameters by stepwise amplitude increase with 0.1 V increments until we found a clinical improvement of axial symptoms without inducing side effects. In general, we kept a distance of at least 0.5 V to the side effect threshold and aimed to keep SNr amplitudes symmetrical whenever effect and side effect profiles would allow.

Participants performed the ISAW: after 30 s of standing still and following a go signal presented by the experimenter, the patients initiated walking. Then they walked at usual speed over a distance of 7 m, turned 180° in place and went back. The experimenter accompanied the patients, but only intervened to prevent falls. Three inertial measurement units (Opal, APDM) were placed on the lumbar spine (L5) and bilaterally on the shins. Data were collected and analysed offline with a custom, semi-automatic algorithm in Matlab [9,19]. In addition, we collected the Freezing of Gait Assessment Course (FoG-AC) and UPDRS III motor scores in each stimulation condition. We videotaped the patients during the FoG-AC.

2.3. Spatial and temporal APA parameters

We analysed the APAs prior to gait initiation with a threshold-based algorithm as detailed elsewhere [9,19]. Briefly, after pre-processing the L5-trunk sensor acceleration data, medio-lateral (ML) APAs were defined as when the ML trunk acceleration exceeded 3SD of baseline postural sway. An APA started/ended when the signal exceeded 1SD of baseline postural sway prior to/after an APA. The following parameters were extracted: anterio-posterior (AP) and medio-lateral (ML) size of APA as maximal AP/ML acceleration (from average baseline postural sway over 5 s quiet stance) during APA [m/s^2], APA duration [s] and 1st step Latency [s] from APA onset to toe-off.

2.4. Statistical analysis

Normal distribution was first assessed using the Shapiro-Wilk Test. In case of normal distribution, we used a two-tailed dependent *t*-test to compare the STN vs. StimOff condition and the SNr vs. StimOff condition (otherwise Wilcoxon signed rank test). For correlation analysis we used Pearson's for normal distribution, otherwise we used Spearman's. We decided to use the direct STN vs StimOff and SNr vs. StimOff contrast, since we had the hypothesis that STN or SNr stimulation would differentially modulate locomotor integration and

Table 1
Patient characteristics.

ID	Age	Gender	Disease duration [years]	Disease duration at surgery [years]	Time with DBS [months]	LED [mg]	MMSE	NFoG-Q	FOG-AC in (MedOffStimOff)	UDPRSIII (MedOffStimOff)	UDPRSIII PIGD subscore (MedOffStimOff)	TMT-B
1	46	M	9	2	81	375	29	9	16	75	7	78
2	45	M	13	9	55	150	30	3	12	45	5	62
3	72	M	16	13	37	300	29	22	31	39	6	259
4	73	M	19	15	61	1073	27	24	n.a.	59	17	300+
5	68	M	26	22	48	100	24	24	n.a.	n.a.	n.a.	300+
6	63	M	15	14	22	607	29	8	30	51	5	117
7	76	M	14	10	45	740	29	24	36	44	14	300
8	68	M	10	7	36	656	28	4	7	64	13	300+
9	77	F	8	7	19	545	28	22	n.a.	n.a.	n.a.	n.a.
10	63	M	9	6	43	400	27	0	17	47	4	150
11	69	M	18	15	40	450	28	10	27	62	10	300+
12	64	M	11	11	11	650	30	19	22	56	9	63
13	80	M	18	15	27	885	27	19	24	43	10	255
14	60	M	12	7	49	300	29	18	n.a.	n.a.	n.a.	99

F = female, M = male; LED = levodopa equivalent dosage; MMSE = Mini Mental State Examination; TMT-B = Trail Making Test part B; MedOff = medication off (overnight withdrawal of dopaminergic medication); StimOff = Stimulation Off; Patient 9 could not fully cooperate on the Trail Making Test part B. Three patients did not wish to discontinue stimulation in MedOff.

eventually distinguish APA characteristics compared to StimOff as suggested from our previous work [17]. Specifically, we decided on pairwise comparison of STN or SNr against StimOff, since we had specific functional anatomic hypotheses for STN or SNr. We performed statistical analysis with IBM SPSS statistics, version 25 (IBM Deutschland GmbH, Ehningen, Germany).

3. Results

3.1. Anticipatory postural adjustments were modulated by SNr stimulation

APAs occurred in StimOff in 11 of 14 patients, in STN in 13 of 14 patients, and in SNr in 13 of 14 patients. SNr stimulation reduced AP APAs compared to StimOff, whereas STN stimulation did not change APAs compared to StimOff. In detail, AP size of APAs was smaller with SNr stimulation compared to StimOff (0.0242 ± 0.011 in SNr; 0.0319 ± 0.012 in StimOff (mean ± STD); $t\ (9) = -2.642$, $P = 0.027$) (Fig. 1). There was no difference in AP APA size when comparing STN (0.0302 ± 0.013 SD) with StimOff ($t\ (9) = -0.443$, $P = 0.668$). APAs in mediolateral direction did not differ between conditions, neither in SNr (Median 0.0315) vs. StimOff ($z = -0.255$, $P = 0.846$), nor in STN (Median 0.0308) vs. StimOff (Median 0.0235) ($z = -0.255$, $P = 0.846$).

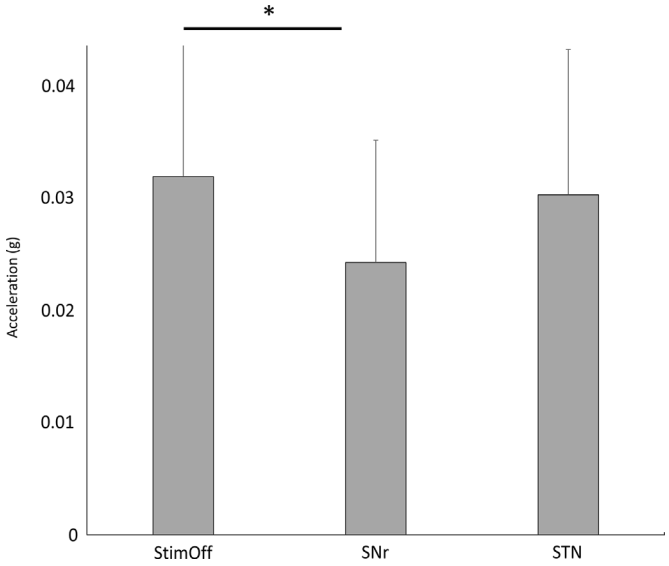

Fig. 1. Size of anterior APA with StimOff, STN, and SNr. SNr led to a significant decrease of anterio-posterior APA size compared to StimOff. X-axis: therapeutic condition. Y-axis: anterio-posterior APA acceleration (m/s^2). Significant difference is marked with asterisk ($P < 0.05$).

For temporal APA parameters APA duration did not differ between SNr and StimOff (SNr: Mdn = 0.7344; StimOff: Mdn = 0.6789, $z = -0.357$, $P = 0.770$), or between STN (Mdn = 0.6328) and StimOff condition ($z = -0.255$, $P = 0.846$). In addition, the first step latency did not differ between conditions: SNr (Mdn = 0.7773) vs. StimOff ($z = -0.296$, $P = 0.820$), and STN (Mdn = 0.7474) vs. StimOff (Mdn = 0.8151) ($z = -0.178$, $P = 0.910$).

3.2. Clinical outcome improved with both STN and SNr stimulation

DBS improved clinical motor symptoms, as expected. SNr stimulation (42.82 ± 10.29) improved the UPDRS III score compared to StimOff (53.18 ± 11.01) ($t\ (10) = 2.760$, $P = 0.02$) as did STN stimulation (33.27 ± 12.53) compared to StimOff (53.18 ± 11.01) ($t\ (10) = 4.840$, $P = 0.001$).

The UPDRS III PIGD subscore (items '27'-'31', i.e.: arising from chair, posture, gait postural stability, body bradykinesia and hypokinesia) improved with both stimulation conditions. SNr stimulation (Median 6.0) improved the PIGD subscore compared to StimOff ($z = -2.388$, $P = 0.016$) as well as STN stimulation (Median 5.5) compared to StimOff (Median 9.0) ($z = -2.689$, $P = 0.004$). The postural item 30 (postural stability) did not differ between SNr stimulation (Mdn = 1.00) and StimOff ($z = -1.000$, $P = 1.00$) or between STN stimulation (Median = 1.00) and StimOff (Median = 1.00) ($z = -1.732$, $P = 0.250$).

Stimulation modulated the occurrence of FoG gait as expressed with the FoG-AC. Both SNr stimulation (21.60 ± 11.09) and STN stimulation (18.44 ± 12.87) slightly reduced the FoG-AC score when compared to StimOff (23.20 ± 9.89), however neither observation reached statistical significance (SNr vs. StimOff: $t\ (9) = -0.952$, $P = 0.366$; trend for STN vs. StimOff: $t\ (8) = -1.937$, $P = 0.089$).

3.3. The reduction of antero-posterior APAs may associate with freezing of gait

We correlated the difference of APAs in AP direction with FOG-AC difference in StimOff versus SNr condition. Since the distribution of FOG-AC scores in SNr stimulation was skewed with one subject showing higher FOG-AC improvement compared to all other subjects (beyond

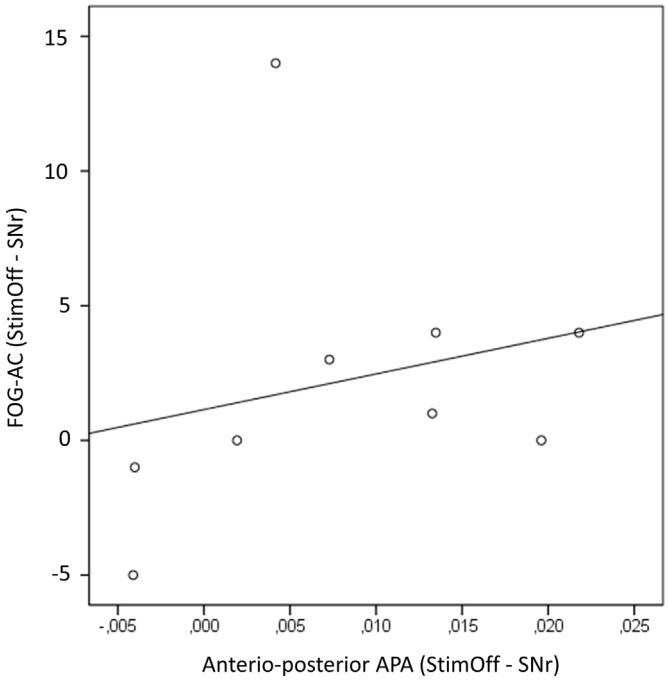

Fig. 2. Correlation plot between anterio-posterior APA change and FOG-AC change (StimOff – SNr, respectively) indicates a non-significant trend ($r = 0.580$, $P = 0.102$), i.e. the stronger the reduction of the AP size of APAs, the larger the FoG-AC reduction (improvement). X-axis: difference in anterio-posterior APA; y-axis: difference in Freezing of Gait Assessment Course.

mean + 2SD), we used a non-parametric Spearman correlation to test the association between the size of APAs and FOG-AC scores. We found a non-significant trend ($r = 0.580$, $P = 0.102$), i.e. the stronger the reduction of the AP size of APAs, the larger the FoG-AC reduction (improvement) (Fig. 2). In addition, no correlation was found with improvements in total UPDRS III ($r = 0.347$; $P = 0.327$) or UPDRS III PIGD subscores ($r = 0.069$; $P = 0.851$) and APA. Lastly, AP-APA differences did not correlate with the baseline characteristics of executive function in terms of TMT-B ($r = 0.088$; $P = 0.810$) nor with NFOG-Q ($r = -0.079$; $P = 0.828$).

4. Discussion

In this study, we compared the effect of neurostimulation at different subcortical targets on APAs in PD patients with FoG. We found a modulation of the anterio-posterior spatial APA component in SNr stimulation compared to StimOff. In contrast, we did not find an effect with STN stimulation.

4.1. Insights into network characteristics of APAs

When interpreting our findings in the light of the available literature, STN and SNr may play different roles in the neural integration and modulation of APAs - possibly due to their different positions and interactions in a global functional network of APA integration. The understanding of this functional network is by far incomplete. However, first insights on relevant network hubs emerge from this and related work. As such, the supplementary motor area, subthalamic nucleus, substantia nigra pars reticulata as well as the mesencephalic locomotor area – in particular the pedunculopontine nucleus – were suggested to contribute to the neuronal integration of APAs.

The supplemental motor area (SMA) may be involved in APA generation. One study found no effect on APAs when anodal tDCS (1 mA, 10 min) was supplied over the SMA [12]. However, two further studies with different cortical stimulation protocols supported an integrative role of the SMA. First, 1 Hz repetitive TMS supplied over the SMA reduced the APA duration of the first step [20]. In addition, application of a theta burst stimulation protocol (with presumably inhibitory net effect on SMA) led to a shortened APA phase duration [13]. In contrast, cerebellar stimulation did not modulate the preparatory APA phase, but rather the execution phase of step initiation [13].

Another network hub of interest is the STN, and it was argued that the STN would be meaningful to APAs owing to its connectivity to the SMA via the hyperdirect pathway. One study found that STN stimulation significantly increased APA amplitudes in both medio-lateral and anterio-posterior direction [21], in contrast to the stimulation off condition (both in medication off state). No correlation analyses of APAs with clinical outcome were performed and the sample population was not predominantly composed of people with PD and FoG. Therefore it cannot be concluded whether such 'increase' of the APA size would also reflect an 'improvement' (as might be assumed in analogy to the levodopa effect [10,22]). Another study confirmed that STN stimulation increased both the lateral and posterior displacement of the centre of pressure during gait initiation [23]. The recordings were performed in the MedOff condition and contrasted stimulation off and stimulation on conditions (both unilateral and bilateral DBS on). More recently, the stimulation effect of DBS on/off was challenged in a cohort of PD patients with either STN-DBS or GPi-DBS six months post-surgery [10]. Interestingly, in this study the postoperative STN-DBS effects on APAs were compared to the preoperative levodopa effects. Strikingly, the patients had smaller, non-significant APA spatial component changes with DBS (both in STN and GPi group) compared to the levodopa effect. When putting into context our findings, one important difference to previous studies was, that our patients were years post-surgery. There may be different ways to interpret the seemingly lower or absent effect of STN stimulation to increase the spatial APA component compared to medication. Generally, STN stimulation is expected to be equally effective in improving PD symptoms and increasing the spatial components of APAS as L-Dopa. On the one hand, the STN may be effective on gait measures initiation to a certain degree. When increasing stimulation amplitudes, however, there may be a transition point towards worsening of gait and related measures, e.g. when it comes to excessive stimulation [24] or current spreading to thalamo-pallidal fibers bordering the STN in anterio-medial direction [25]. The available studies did not control for these possibilities, and this may also explain some variability across studies depending on the medical centres' implantation and programming routines.

Another consideration is that clinical benefit or APA improvement will not necessarily be reflected by larger APA components, which we discuss below. Consistent with this hypothesis, cueing led to reduced APA size in recent work, and smaller APAs might be compensatory in PD patients with FoG, as recently observed [9,26].

The importance of the mesencephalic locomotor region – in particular the pedunculopontine area – in the control of locomotion and the available, direct access to that locomotor region through SNr-DBS evoked particular interest in recent studies of modulation of gait, gait initiation and FoG therapy. A substantial amount of pathophysiological studies implicate the PPN to be involved in facilitation and inhibition of leg muscle tone [27]. The SNr has been shown to modulate PPN function – presumably via the monosynaptic GABAergic pathway [27–29]. In PD patients, stimulation of the SNr was shown to attenuate this over-inhibitory outflow by supporting synaptic inhibition as well as attenuation of SNr single cell activity [16]. When relating our findings of AP-APA modulation by SNr-DBS to previous findings, it is noteworthy, that similar effects on gait initiation have also been described with unilateral PPN-DBS revealing significant improvement of the backward shift of centre of pressure and peak velocity of APAS [30]. Further, recent work on functional connectivity showed decreased connectivity between PPN and the SMA, which was correlated with longer duration of APAs [31]. Similar evidence on disrupted PPN – network interaction was derived from intraoperative PPN recordings [32].

In view of these findings, we propose that APA modulation is linked to the descending MLR outflow to the spinal central pattern generator with considerable control of cortical and basal ganglia areas regulating the MLR output in a meaningful way. Fronto-striatal projections may be less important in the APA modulation, which may be reflected in our work by a lack of correlation between APA modulation and set shifting capabilities. While executive dysfunction is highly meaningful to FoG, the impact on APA modulation might be negligible. Since this notion is, however, only correlative in nature, future studies may directly study the influence of executive interventions in a controlled manner to gain further insight on frontal contributions to APA regulation.

4.2. Smaller anterio-posterior postural adjustments to facilitate gait initiation control?

Remarkably, APAs are smaller in PD patients with FoG compared to patients without FoG [9,33]. Interestingly, within the group of PD patients with FoG, APAs were larger in gait initiation trials with observed start hesitation as opposed to trials without FoG [9]. To this end, it was argued that PD freezers might encounter problems to control for larger APA size when coordinating the temporal sequence of postural adjustment, effective gait initiation and consecutive, rhythmic stepping behavior. To this end, it is speculated that smaller APAs might be easier to control and reflect compensatory adjustment in order to attenuate the susceptibility of PD gait freezers to gait initiation failure [9]. This assumption seems to receive support from our findings, given a positive (albeit non-significant) correlation between the reduction in anterio-posterior size of APA and reduction in FoG severity with SNr stimulation. However, this finding needs reevaluation in future larger studies. In addition, future neuromodulation studies should further assess the relationship between APAs and gait improvement (as was postulated for STN stimulation), or conversely, unintended worsening in gait function [24,25].

4.3. Methodological considerations

There are some limitations in clinical-pathophysiological studies like this one. Most important, we were not able to balance the total electric energy delivery when stimulating at the level of STN or SNr owing to different response and side effect thresholds of the two nuclei. However, recent work revealed different stimulus response curves of the two nuclei [16]. Therefore, equal electric energy delivery would not necessarily be the solution to this shortcoming. Therefore, we sought to use stimulation parameters that were closely in line with previous work that suggested clinical efficacy on FoG [14]. There was a waiting period of 30 min between stimulation conditions, which may have different clinical effects as suggested from previous studies including STN or SNr stimulation protocols [14,17,34].

As in previous work, we selected the patients from an existing cohort with implanted STN leads and evaluated whether the most caudal contact would reach the border zone of STN and SNr. This means, that a caudal contact would not necessarily exclusively stimulate the SNr. Field spread to bordering nuclei, including the ventromedial STN or even the substantia nigra pars compacta (in more medially placed leads) cannot be excluded in individual patients. However, the therapeutically indicated DBS implantation procedure is necessarily oriented to the dorsolateral STN area, which may limit a specific, caudal electrode placement with exclusive stimulation of SNr. This issue needs to be reevaluated, when more clinical data of SNr stimulation for FoG are available from an ongoing active multicentre trial on nigral stimulation for FoG (clinTrials.gov: NCT02588144).

Finally, we acknowledge that the findings were obtained in a selected cohort of PD patients with FoG and neurostimulation and, therefore, cannot be generalized to the general PD population.

In summary, this work provides several novel aspects. First, neuronal integration of APAs depends on nigral contributions in patients with Parkinson's disease and FoG (incorporating SNr into the functional APA network). Future studies may test if smaller AP APAs contribute to the compensation of FoG. Finally, future neurostimulation applications for resistant gait and balance impairment need to consider the subtle components of gait initiation.

Conflicts of interest

There is no conflict of interest specific to this work. Daniel Weiss (DW) and Alireza Gharabaghi (AG) receive research support, travel grants, and speaker's honoraria from Medtronic, Abbott, and Boston Scientific. DW is supported by research grants from the German Research Council (DFG; WE5375/1–3) and the Michael J Fox Foundation. AG is supported by research grants from the German Federal Ministry of Education and Research [BMBF 13GW0119B, IMONAS; 13GW0214B, INSPIRATION; 13GW0270B, INAUDITAS].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.06.023.

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