BRAIN
ORIGINAL ARTICLE

Subthalamic and nigral neurons are differentially modulated during parkinsonian gait

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The parkinsonian gait disorder and freezing of gait are therapeutically demanding symptoms with considerable impact on quality of life. The aim of this study was to assess the role of subthalamic and nigral neurons in the parkinsonian gait control using intraoperative microelectrode recordings of basal ganglia neurons during a supine stepping task. Twelve male patients (56 ± 7 years) suffering from moderate idiopathic Parkinson's disease (disease duration 10 ± 3 years, Hoehn and Yahr stage 2), undergoing awake neurosurgery for deep brain stimulation, participated in the study. After 10 s resting, stepping at self-paced speed for 35 s was followed by short intervals of stepping in response to random 'start' and 'stop' cues. Single- and multi-unit activity was analysed offline in relation to different aspects of the stepping task (attentional 'start' and 'stop' cues, heel strikes, stepping irregularities) in terms of firing frequency, firing pattern and oscillatory activity.

Subthalamic nucleus and substantia nigra neurons responded to different aspects of the stepping task. Of the subthalamic nucleus neurons, 24% exhibited movement-related activity modulation as an increase of the firing rate, suggesting a predominant role of the subthalamic nucleus in motor aspects of the task, while 8% of subthalamic nucleus neurons showed a modulation in response to the attentional cues. In contrast, responsive substantia nigra neurons showed activity changes exclusively associated with attentional aspects of the stepping task (15%). The firing pattern of subthalamic nucleus neurons revealed gait-related firing regularization and a drop of beta oscillations during the stepping performance. During freezing episodes instead, there was a rise of beta oscillatory activity.

This study shows for the first time specific, task-related subthalamic nucleus and substantia nigra single-unit activity changes during gait-like movements in humans with differential roles in motor and attentional control of gait. The emergence of perturbed firing patterns in the subthalamic nucleus indicates a disrupted information transfer within the gait network, resulting in freezing of gait.

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Received July 22, 2022. Revised December 01, 2022. Accepted December 22, 2022. Advance access publication February 2, 2023

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Keywords: Parkinson's disease; freezing of gait; microelectrode recordings; subthalamic nucleus; substantia nigra

Introduction

The parkinsonian gait disorder and freezing of gait (FoG) represent a main therapeutic challenge, with considerable impact on quality of life and high risk of hospitalization.[1] Pathophysiologically, it has been proposed that these symptoms are due to a network-level disorder,[2] with aberrant neuronal activity within the subthalamic nucleus (STN) and the substantia nigra (SN) as key elements in a final common pathway.[3] The subcortico-cortical gait network is proposed to be based on a spinal central pattern generator controlled by descending tracts of supraspinal centres such as the primary motor cortex and supplementary motor area, dorsolateral prefrontal motor cortex projecting via basal ganglia (BG), subthalamic locomotor area and mesencephalic locomotor region (MLR).[4] In particular, the dense interactions between the STN, SN and the MLR as the subcortical sites of the gait network represent a key factor in the adaptation of gait.[3,5] The importance of the STN in this critical final pathway has been emphasized recently by human intraoperative STN data.[6] The STN was there interpreted to act as a 'hand brake' that is engaged or disengaged by conflict-mediated cortical activity.[6] The strategic localization of the STN within the network underlines that the STN is an important, vulnerable 'key hub' within the distributed gait network, which is able to destabilize and shift the gait network over a critical threshold resulting in FoG.

In the treatment of the parkinsonian gait disorder, the effects of deep brain stimulation (DBS) have been assessed extensively. The effect of STN-DBS on gait and FoG is variable,[7] with gait improvement in only about a third of Parkinson's disease patients, lasting for 3–5 years.[8] Recent efforts have been made to stimulate simultaneously the STN and the SN (STN+SN DBS)[9]; however, the role of SN in the control of gait, FoG and in the mediation of beneficial DBS effects is not well understood.

The routine procedure of implantation of therapeutically indicated DBS electrodes offers the opportunity for direct, single-cell recordings from the STN and SN during the surgical placement of the stimulating electrodes in Parkinson's disease patients. To date, there are data on the contribution of subthalamic single units to general motor control in animal and human models[10-13]; however STN single-cell activity has not been specifically investigated during gait-like tasks in humans. The goal of the study was to characterize single neurons with gait-related activity changes within the final common pathway of the gait network, the STN and the SN.

Materials and methods

This study was conducted in agreement with the declaration of Helsinki (1967) and was approved by the local ethics committee (PV5281). All patients gave their informed consent to participate.

Participants

Twelve Parkinson's disease patients (all male, 56.5 ± 6.6 years, Montreal Cognitive Assessment score of 27.8 ± 2.0)[14] suffering from moderate idiopathic Parkinson's disease (disease duration: 9.5 ± 3.1 years, Hoehn and Yahr stage: 2.0 ± 0.1 in the DOPA-ON condition, Hoehn and Yahr stage: 2.2 ± 0.5 in the DOPA-OFF condition) undergoing neurosurgery for STN-DBS were recruited from the local department of neurology at the University Medical Center Hamburg-Eppendorf (Table 1).

Intraoperative microelectrode recordings during the stepping task

Preoperative behavioural measurements

The day before surgery, Parkinson's disease patients were familiarized with the task and the operating theatre. The patients showed preoperatively a slight freezing in the DOPA-OFF condition (FoG assessment course score 5.8 ± 5.7),[16] which was DOPA responsive (DOPA-ON FoG score 1.5 ± 2.9; $P = 0.008$, Wilcoxon signed rank test). In addition, quantitative gait analysis was performed using a GAITRite® electronic walkway system (details concerning the GAITRite® results are reported in Table 1 and in Horn *et al.*[17]).

Intraoperative stepping task

All data included in this study were collected during the standard neuro-navigation procedure applied for clinical electrode placement (Supplementary material).

During intraoperative neurophysiological testing, the stepping task was performed at each recording site inside the zona incerta (ZI), STN and SN, when stable spike activity with sufficient signal-to-noise ratio was encountered on at least one electrode. The patients were in a supine position on the operating table, with the head fixed in the stereotactic frame. Standard auditory instructions as well as 'start' and 'stop' cues were presented binaurally through inserted foam earplugs (EAR-Tones 3A). The stepping performance was recorded by (i) an ultrasound movement analysis system (CMS20S-System, Zebris) with markers fixed on the knee, lateral malleolus and lateral fifth toe of both limbs; (ii) triaxial accelerometers fixed on the lateral malleolus of each foot (model MMA7260QT, Freescale Semiconductor); and (iii) EMG electrodes (Ag/AgCl gel electrode, model 2282E, 3M-Red Dot) attached over the vastus medialis, the tibialis anterior, the gastrocnemius medialis and the extensor hallucis longus of each leg. After recording of neuronal activity at rest for at least 30 s, patients were prompted to perform internally paced, bipedal stepping movements on a custom-made stepper at a self-paced, comfortable speed for 35 s, this part was preceded by a 10-s steady-state period that was used as pre-stepping baseline activity (Fig. 1B, part 1). After a 10-s pause, patients were asked to perform 10 stepping blocks at a self-paced velocity in response to sudden 'start' and 'stop' signals presented at random, variable latencies (3–10 s). This was intended to simulate unpredictable gait initiation and termination, which are known to provoke FoG in Parkinson's disease patients (Fig. 1B, part 2). The whole task lasted 3 min. The repeated experimental recordings prolonged the surgical time for about 30 min.

Table 1 Clinical and demographic characteristics of Parkinson's disease patients

Patient Age	Gender	Disease duration (years)	H&Y DOPA OFF/ON	LEDD (mg)	UPDRS-III DOPA OFF/ON	L-DOPA response, %	MoCA	BDI-I	Giladi's GFQ	FoG DOPA OFF/ON	Berg balance DOPA OFF/ON	Gait parameters				
												DOPA OFF		DOPA ON		
												(s)	Steps	(s)	Steps	
1	Male	64	7	3/2	600	50/19	62	26	17	53	6/0	50/56	6.4*	12*	5.1*	10.5*
2	Male	60	12	3/2	1475	31/17	45	24	4	7	18/6	50/55	13.8	29	13.5	23.5
3	Male	66	15	2/2	585	38/19	50	28	1	17	7/1	52/55	15.4	27	12.1	22
4	Male	43	10	2/2	850	36/11	69	29	8	8	0/0	54/56	12.5	22	10.1	21
5	Male	49	9	3/2	1500	53/13	75	28	N/A	4	3/0	50/56	24.0	34.5	14.8	21
6	Male	63	11	2/2	1060	54/18	67	25	4	17	0/0	49/53	13.9	26	12.4	22.5
7	Male	57	14	2/2	1510	25/17	32	30	2	36	9/0	54/53	14	25.5	12	22.5
8	Male	57	7	2/2	1455	24/12	50	27	7	13	0/0	27/27#	10.8	19.5	10.6	19.5
9	Male	56	10	2/2	1285	18/8	56	28	14	4	10/0	27/27#	17	26	14.5	25.5
10	Male	51	6	2/2	1640	36/22	39	30	12	8	12/9	27/28#	13.5	24.5	10.5	23.5
11	Male	58	8	1.5/1.5	880	35/21	40	30	4	0	0/0	28/28#	11.2	18	10.5	18
12	Male	54	5	2/2	980	43/24	44	29	7	5	5/2	28/28#	10.7	19	11.6	20

Values were collected a few days before surgery. In the 'Disease duration (years)' column, the disease duration is calculated from the date of the first diagnosis to the date of DBS surgery. In the 'Gait parameters' column, values reported are: mean seconds (s) and steps of 2 × 14 m (7 m 'go' and 7 m 'return') of natural gait in DOPA-OFF and ON condition; *in Case 1 only the first 7 m 'go' were recorded. BDI-I = Becks Depression Inventory; Berg balance scale sum score = #short form of the Berg Balance scale comprehending only items 1, 6, 8, 9, 10, 13, 14; DOPA ON/OFF = ON medication and OFF medication; FoG = Freezing of Gait Assessment Course score; Giladi's GFQ = Giladi's gait and falls questionnaire; H&Y = Hoehn and Yahr scale; LEDD = levodopa equivalent daily dose after Tomlinson *et al.*[15]; MoCA = Montreal Cognitive Assessment score; N/A = not available; Steps = number of steps performed for the distance; UPDRS-III = motor-subscore (part III) of Unified Parkinson's Disease Rating Scale of the Movement Disorder Society.

One main aim of the study was the neuronal characterization of FoG episodes. During the intraoperative stepping task in a supine position, we observed FoG-like stepping irregularities, defined as a reduction of the stepping amplitude by ≥50% of the mean amplitude of the first three steps performed, excluding the very first step (Fig. 1C). Only stepping irregularity episodes longer than 3 s were considered for further analyses. The accuracy of the automatic detection was verified by visual inspection of the data. To validate the concept of stepping irregularities as proxy for FoG episodes during upright walking, the mean stepping irregularity time in seconds has been correlated with the preoperative FoG scores in the DOPA ON and OFF conditions, showing that patients with higher preoperative FoG scores also experienced longer stepping difficulties during the intraoperative pedalling task (Spearman's correlations: preoperative FoG score in the DOPA-OFF condition versus gait irregularities: $r_s = 0.589$; $P = 0.044$; preoperative FoG score in the DOPA-ON condition versus gait irregularities: $r_s = 0.896$; $P < 0.0001$).

Spike sorting

Patients performed a total of 61 recordings, with a duration of ∼5 min each, for a total recording time of ∼300 min. After starting recordings, the initial 30 s of unit activity was discarded to ensure a stable neuronal activity. Offline spike sorting was performed using the Spike2 software version 8.11 (CED, Cambridge, UK), the Neuroexplorer version 4 (NEX Technologies, Littleton, MA, USA), and *ad hoc* written functions using MATLAB 8.6 (MathWorks, Natick, MA, USA). The classification of multi- and single-unit activities (MUAs and SUAs, respectively) was performed applying a voltage threshold method above 3 SD of the background noise, template matching, controlled by shape cluster analysis with principal component analysis and final visual inspection. For each sorted activity, the criteria for the classification as SUA were a threshold >9 SD of the background noise, a stereotypical spike shape and a refractory period between spikes >2 ms.[19,20] Sorted spiking activity >3 and ≤9 SD of the background noise was classified as MUA. Given the high neuronal activity in the STN, we chose to be conservative in spike sorting and in the classification of SUAs. Many recordings classified as MUAs may, therefore, have comprised mostly one or two STN units.[21,22] From each SN recording, we extracted neuronal spiking activity and identified putative dopaminergic neurons and GABAergic neurons based on their baseline firing rates and waveform durations.[23-25] Neurons showing portions of injury discharge or consistent amplitude changes due to electrode drifting or strong cardiac artefacts were excluded from the analysis.

Movement- and event-related unit activity

Movement- and event-related modulation of SUAs and MUAs was investigated by calculating perievent time-histograms (PETH) for heel strike events extracted from the kinematic measurements (Zebris ultrasound movement analysis system and accelerometers), as well as for the 'start' and 'stop' cues.

PETH (bin 0.025 s, post-processing smoothing with boxcar filter of 3 bins, unit: spikes per second) were calculated for epochs from −1.5 to 1.5 s around heel strikes of the right and left leg separately, as well as around the 'start' and 'stop' signals. Movement- and event-related modulation of SUAs and MUAs were considered significant if PETH peaks or troughs exceeded the 95% confidence interval limits of the expected firing rate for the 3 s preceding each 'start' signal, i.e. for the 3 s at rest preceding each movement onset (11 'start' signals for each recording block, 33 s totally; Fig. 1B).

To statistically test the different proportions of units in the ZI, STN and SN significantly modulated by the experimental events, Fisher's exact tests were performed on a 2 × 2 contingency table with categories 'structure' × 'modulation'.

Characterization of neuronal firing pattern

The firing pattern of SUAs was categorized as described previously.[21,26] The firing pattern of each neuron was predetermined based on the visual inspection of the spike train and the characteristics of the inter-spike-interval histogram (ISIH). ISIH (interval 0–0.25 s, bin 0.001 s, smoothed with filter 3 bins) were calculated for SUAs at pre-stepping (10 s prior to the first'start' signal) and during movement (30 of the 35 s of continuous self-paced stepping, i.e. excluding the first and the last 2.5 s). To assess possible differences in neuronal firing characteristics during pre-stepping, continuous stepping and stepping irregularities, we compared the SUA firing rate (Hz), the asymmetry index (AI) of the inter-spike intervals (ISIs; AI: mode ISI/mean ISI)[27,28] and the coefficient of the variance (CV) by means of Wilcoxon signed-rank tests (alpha-level = 0.05). Furthermore, bursts were detected using the Poisson surprise (PS) method.[21,29-31] Higher PS values indicate more improbable events in Poisson probability space. Sequences of spikes with a PS above 5 were considered to be bursts.[21,31] From this analysis, the proportion of spikes that occurred during bursts (%) was calculated.

Characterization of oscillatory activity

Oscillatory activity of units (SUAs + MUAs) were evaluated using fast Fourier transform with 0.5 Hz frequency bins, as described previously.[21,32] A Hanning window filter was used for all spectral analyses and spectra were estimated by averaging across these discrete sections.[32] Significance was evaluated using surrogate data where the spike train was reconstructed by shuffling the ISIs across the record.[21,33,34] Power spectra were calculated on 1000 of these surrogate units and then used to construct 99% confidence limits for each frequency bin. To detect significant peaks, we considered a unit to be oscillating at a given frequency when the power in two contiguous bins (1 Hz total) exceeded the 99% confidence limit within that frequency range. Analysis of shuffled, thresholded spectra from 3 to 90 Hz (where 0 represents spectral values lower than the confidence limit and 1 represents significant values exceeding the confidence limit) showed that the probability of two contiguous bins exceeding the confidence limit by chance was ~0.00007. The combination of the 99% confidence limit and two contiguous bin thresholds therefore gave a conservative estimate of when a unit was oscillating at a defined frequency band and significant peaks were unlikely to represent noise. For reasons of simplification, units that show significant oscillatory activity based on the above-described criteria will be referred to as 'oscillatory units' and units without significant oscillatory activity in their spike trains as 'non-oscillatory units'. In this formalism we would like to highlight that oscillatory units have significant higher oscillatory activity than non-oscillatory units, but that the latter may have weak oscillatory activity that is not captured by this threshold.[35] The units presenting significant peaks in the sub-beta (3–12 Hz), beta (13–35 Hz) and gamma (36–90 Hz) ranges at the three different task states (i.e. at pre-stepping, at stepping and at stepping irregularities) have been counted and normalized expressing them as percentage of oscillatory and non-oscillatory units for three structures considered.

To deal with categorical data (i.e. units defined as significantly oscillating or not oscillating) and uneven sample sizes (number of units recorded at the different task states), a mixed-model approach was chosen. The oscillatory activities (i.e. STN and SN units showing or not showing significant peaks of oscillatory activity and then subdivided in the three defined frequency ranges sub-beta, beta and gamma) were compared at the three different task states (pre-stepping, stepping and stepping irregularities as primary independent variables). The oscillatory activities were analysed using a generalized linear mixed-model approach with a logit-link function assuming binomially distributed data (SPSS routine GENLINMIXED; IBM SPSS Statistics for Mac, version 25.0.0.2, SPSS Inc., Chicago, IL, USA). The three different task states were taken as repeated measures within a cell (stepping state). Model computations were adjusted for the oscillatory state at pre-stepping (baseline). The model-estimated marginal frequencies and their 95% confidence intervals (CI) were computed for all dependent variables at all study stages, followed by post-hoc pairwise comparisons of the three different task states by means of linear contrasts (significance level <0.05). The conservatively Bonferroni-corrected alpha level for the eight computed mixed models was 0.006. As this was an exploratory study, no further adjustments for multiple testing were done.[36]

Data availability

The datasets generated for this study are available on request to the corresponding author.

Results

The aim of this study was to define characteristics of unit activity associated with the different parts of the stepping task ('start' and 'stop' cues, resting, stepping and stepping irregularities) using intraoperative microelectrode recordings. We were able to characterize ZI, STN and SN neurons accordingly to the recording depth in relation to the calculated target. SN SUAs were classified into two subgroups, the 'fast spiking' (SN_{fast}) neurons (mean firing rate ≥25 Hz, probably consisting of GABAergic projection neurons from the SN) and 'slowly firing' (SN_{slow}) neurons (mean firing rate <25 Hz), presumably consisting of dopaminergic cells.[23,24,37] In total, 176 unit activities could be sorted (115 MUAs and 61 SUAs). In particular, 142 units from the STN could be isolated (93 MUAs and 49 SUAs), while 27 units have been ascribed to the SN (17 MUAs and 10 SUAs) and seven to the ZI (five MUAs and two SUAs). The relative proportion of movement-sensitive neurons and cue-related neuronal activity within the left and right STN was comparable between both hemispheres (left STN: 31%, right STN 28%).

Firing rate changes in relation to attentional and motor aspects of the stepping task

The most striking findings were nucleus-specific patterns of task-related activity changes (Fig. 2). Three types of task-related firing rate changes of BG cells could be extracted: (i) movement-related activity changes with recurrent firing rate changes at heel strikes during stepping; (ii) attention-related firing rate changes associated with 'start' and 'stop' cues; and (iii) polymodal neurons with firing rate changes related to both attentional and motor events. Movement-related changes were mostly periodically recurrent firing rate increases associated with each heel strike of the contralateral leg during the stepping task.

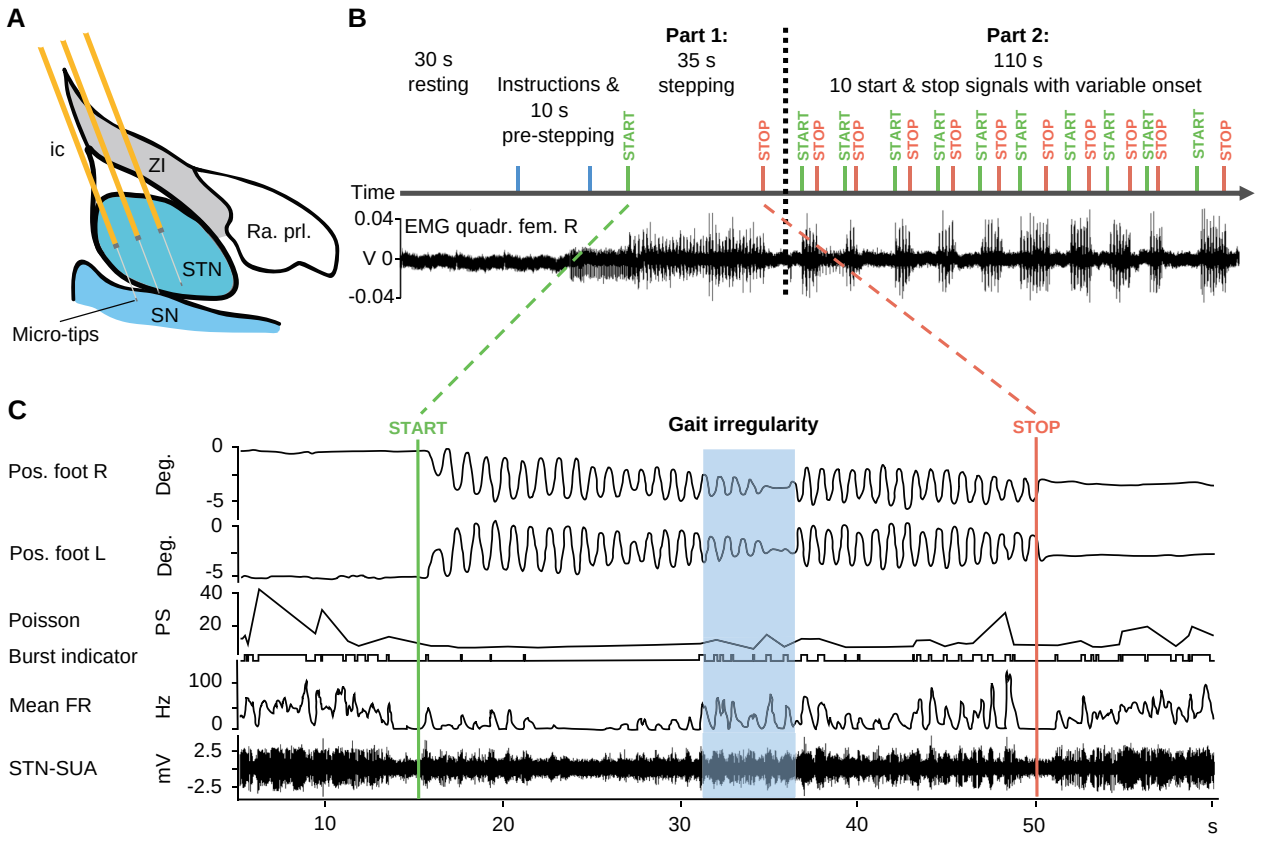

Figure 1 Experimental setup of the intraoperative microelectrode recordings during DBS surgery . (**A**) Surgical setup, sagittal view of the subthalamic area, 11 mm lateral to the midline; modified from Schaltenbrand and Bailey.[18] ic = internal capsule; Ra. prl. = prelemniscal radiation. Three parallel microelectrodes were used as central, anterior, and lateral trajectory in the Ben Gun arrangement. Units along the planned trajectories were recorded from micro-tips within the ZI, STN and SN. (**B**) Outline of the time course of the stepping task. In the *lower* part is an exemplary raw EMG-trace from the right quadriceps femoralis during the stepping task. (**C**) Firing characteristics of an STN neuron during the first part of the stepping task. The two first traces depict the feet position during the task, the transparent box represents the gait irregularity episode as detected by the algorithm.The third trace represents the Poisson surprise (PS) value. The fourth trace is the burst indicator. The fifth trace is the mean firing frequency (FR), while the last trace represents the raw single-unit activity (SUA).

Initially,'start' and 'stop' cues were analysed separately, but as there was no difference in terms of their neuronal response pattern, 'start' and 'stop' stimulus epochs were pooled together for further analyses.

From the ZI units (seven units), only one unit (14%) was modulated by movements, none by attentional cues. Among the 142 STN units, the modulation patterns were heterogeneous. Most of the task-sensitive STN units were modulated by movements (24%), some by attentional cues (8%) and a few units were polymodal (5%). In contrast, for the 27 SN units, there were no observed movement-related activity changes, but only SN units modulated by attentional cues (four SN units (15%); one MUA and three SUAs, of which two were classified as SN_{slow} and one as SN_{fast}). One SN unit revealed a firing pause and three a brisk firing enhancement followed by a firing inhibition. In summary, there was a dorsoventral gradient of firing pattern changes of BG nuclei, movement-related units were predominantly found dorsally within the ZI and the STN, whereas attention-related units were located more ventrally within the SN.

The mean firing rate of included SUAs during pre-stepping periods, continuous stepping and during stepping irregularities is reported in Table 2. Fisher's exact tests revealed significant changes in terms of percentages of modulated units between ZI, STN and SN (Fig. 2). The STN showed a greater proportion of units significantly modulated by stepping than the ZI and the SN ($P = 0.0283$ and $P < 0.0001$, respectively). The percentage of ZI units modulated by stepping was also significantly larger than in the SN ($P < 0.0001$). Complementary, the percentage of SN units significantly modulated by the 'start' and 'stop' signals was significantly larger than in the ZI ($P < 0.0001$), but not when compared to the STN ($P = 0.65$). The STN showed significantly larger percentage of units modulated by the 'start' and 'stop' signals than the ZI ($P = 0.0014$), underlining the observation of a dorsoventral gradient of neuronal responsivity.

Firing pattern modulation in relation to stepping performance

Characterization of the firing pattern of the BG single cells at rest, during stepping and stepping irregularities was performed in SUAs with a stable signal-to-noise ratio over the whole stepping task (i.e. for a total of 155 s, Fig. 1B), resulting in two ZI neurons, 30 STN neurons (hereafter defined as STN_{all}, Fig. 3A–D and Table 2) and eight SN neurons (subdivided in four SN_{slow} and four SN_{fast}). A subset of 17 STN-SUAs showing a significant modulation of firing activity at stepping were analysed separately and defined as STN_{mod} from here on (Fig. 3E–H and Table 2). Because of the low number of ZI neurons, there was no available recording of ZI

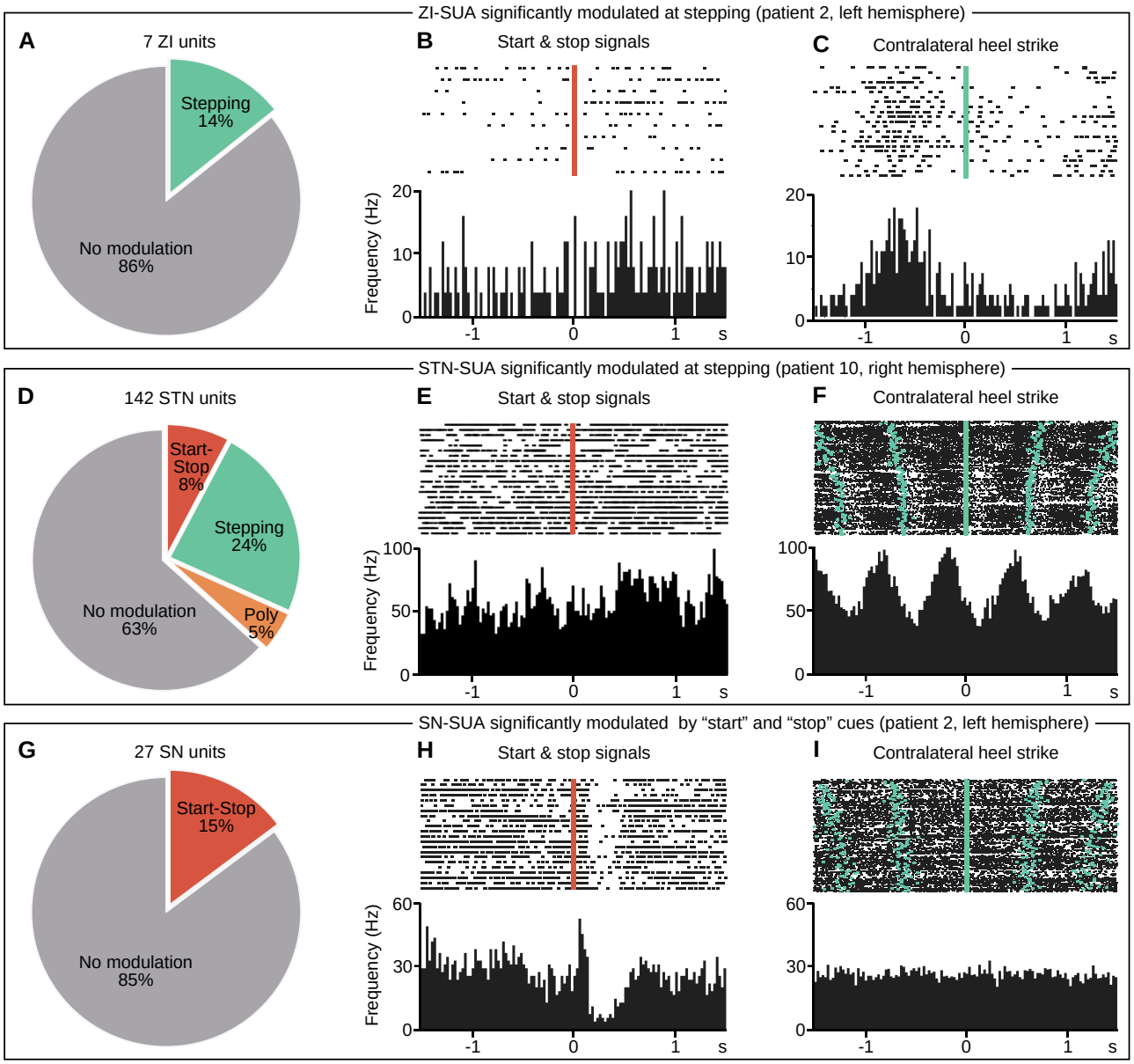

Figure 2 Modulation of cell activity during the stepping task. (**A**, **D** and **G**) Pie charts represent the per cent of ZI, STN and SN neurons modulated by gait and/or 'start' and 'stop' signals (i.e. neuronal firing activity exceeding the 95% CI limits of the expected firing rate at rest). (**B** and **C**) Peri-event raster plots for a SUA from the ZI aligned to the 'start' and 'stop' signals (**B**) and to the contralateral heel strikes (**C**). This SUA was significantly modulated by the heel strikes. (**E** and **F**) Peri-event raster plots for an STN-SUA aligned to 'start' and 'stop' signals (**E**) and to contralateral heel strikes (**F**). This STN-SUA was also clearly modulated by the heel strikes. (**H** and **I**) Peri-event raster plots for a SN_{slow} SUA significantly modulated by the 'start' and 'stop' cues (**H**) but not by the stepping (**I**). Peri-event rasters' bin width = 0.025 s. Note that the exemplary peri-event raster plots for a stepping-modulated ZI SUA in **C**, and for a stepping-modulated STN SUA in **F**, were taken from two different patients (Patients 2 and 10, respectively) and thus represent their individual stepping velocities. Poly = polymodal modulation.

neurons during stepping irregularities. In these two neurons, the low firing rate at rest increased slightly but not significantly during regular stepping, and the firing pattern reflected by high CV and low AI was quite irregular in both activation conditions (Table 2; all *P*-values = 1.0).

The firing pattern of STN_{all} neurons changed depending on the task condition (Fig. 3A–D and Table 2). The comparison of STN_{all} SUA at rest and during regular stepping revealed a significant increase of the firing rate (at rest 30.0 ± 13.6 Hz versus at regular stepping 36.0 ± 19.4 Hz; $P = 0.043$). During freezing-like stepping irregularities, the firing rates remained in the same range as during regular stepping (37.1Hz ± 23.0 Hz; $P = 0.109$). In the subgroup of movement-sensitive STN_{mod} neurons, the CV of ISIHs, as an indirect measure of firing regularity, revealed a predominantly irregular, bursty firing pattern that showed slight but not significant changes between motor conditions. There were more irregular firing patterns at rest (1.59 ± 0.56) and during gait irregularities (1.58 ± 0.35) compared to regular stepping (1.44 ± 0.46; CV at rest *versus* during regular stepping $P = 0.052$; CV at stepping irregularity versus during regular stepping, $P = 0.625$). The irregular, bursty firing pattern was confirmed by low AI of ISIHs of STN_{mod} single cells (rest 0.13 ± 0.07, regular stepping 0.25 ± 0.17, stepping irregularity 0.26 ± 0.13), with a

Table 2 Firing characteristics of STN and SN neurons during the stepping task

Structure	During pre-stepping					During continuous stepping					During stepping irregularities				
	Firing rate (Hz)	PS	% of spikes in burst	CV of ISI	AI	Firing rate (Hz)	PS	% of spikes in burst	CV of ISI	AI	Firing rate (Hz)	PS	% of spikes in burst	CV of ISI	AI
ZI	2.4 ± 2.5	7.3	25.0 ± 35.4	1.79 ± 1.19	0.02 ± 0.01	2.9 ± 3.0	6.7 ± 2.0	31.7 ± 7.9	1.50 ± 0.02	0.23 ± 0.33	N/A	N/A	N/A	N/A	N/A
SN_{slow}	14.8 ± 7.2	7.8 ± 1.4	13.8 ± 15.1	1.05 ± 0.23	0.14 ± 0.19	18.7 ± 5.7	6.7 ± 0.8	17.7 ± 8.9	1.02 ± 0.19	0.10 ± 0.11	14.4 ± 11.2	6.7 ± 0.7	19.0 ± 7.0	1.14 ± 0.31	0.22 ± 0.21
SN_{fast}	64.3 ± 39.7	5.7 ± 0.8	5.8 ± 8.1	0.72 ± 0.13	0.5 ± 0.60	48.2 ± 30.1	5.9 ± 0.7	6.0 ± 7.7	0.70 ± 0.19	0.34 ± 0.30	57.1 ± 41.4	6.2 ± 1.4	9.5 ± 13.0	0.74 ± 0.13	0.47 ± 0.62
STN_{all}	30.0 ± 13.6	7.1 ± 1.4	31.4 ± 18.6	1.42 ± 0.48	0.15 ± 0.11	36.0 ± 19.4	7.5 ± 1.4	29.3 ± 19.0	1.38 ± 0.42	0.18 ± 0.17	37.1 ± 23.0	8.3 ± 2.1	29.8 ± 19.2	1.39 ± 0.38	0.22 ± 0.15
STN_{mod}	27.0 ± 10.7	7.7 ± 1.6	40.2 ± 19.8	1.59 ± 0.56	0.13 ± 0.07	37.9 ± 16.9	7.3 ± 1.1	31.2 ± 20.6	1.44 ± 0.46	0.25 ± 0.17	32.1 ± 19.0	9.2 ± 2.4	34.2 ± 23.6	1.58 ± 0.35	0.26 ± 0.13

Values are given as mean ± SD. AI = asymmetry index (mode ISI/mean ISI; <0.55 bursty neuron; an AI value of 1 represents a Gaussian firing distribution, i.e. a lower AI denote an irregular, burst firing neuron, while a higher AI denote a more regular active neuron); CV = coefficient of variation (>1.25 irregularly firing neuron, <1.25 tonic firing neuron); PS = Poisson surprise values >5; STN_{all} = all STN neurons; STN_{mod} = STN neurons showing a significant modulation of firing activity at stepping.

significant increase of AI from the pre-stepping to regular stepping condition ($P = 0.008$).

SN_{fast} neuron firing characteristics differed from those of the STN. At rest, SN_{fast} neuron firing rates were higher (64.3 ± 39.7 Hz) with a more regular, tonic firing pattern reflected by lower CV (0.72 ± 0.13) and higher AI (0.50 ± 0.60) compared to STN SUAs. In contrast to STN SUAs, SN_{fast} SUA firing characteristics did not change significantly between task conditions with no significant increase of firing rates during stepping (rest: 64.3 ± 39.7 Hz; regular stepping: 48.2 ± 30.1 Hz; stepping irregularities; 57.1 ± 41.4 Hz; all *P*-values ≥0.5) and no significant changes of the firing pattern as reflected by CV and relatively stable AI (Table 2; all *P*-values = 1.0). Comparable findings were obtained for the low-frequency SN_{slow} neurons with relatively stable firing frequencies throughout the different motor conditions (rest: 14.8 ± 7.2 Hz; regular stepping: 18.7 ± 5.7 Hz; stepping irregularities: 14.4 ± 11.2 Hz; all *P*-values = 1.0) and firing patterns (Table 2; all *P*-values ≥ 0.250).

To evaluate irregular neuronal burst activity in more detail, PS values and percentage of spikes in burst were calculated. The mean per cent of spikes in burst value of STN SUAs in the pre-stepping periods was for the STN_{all} 31.4 ± 18.6%, and during regular stepping periods was for the STN_{all} 29.3 ± 19.0% ($P = 0.405$). During stepping irregularities, the per cent of spikes in burst value for the STN_{all} remained at a similar level, 29.8 ± 19.2% (STN_{all} at pre-stepping versus at stepping irregularities, $P = 1.0$; at stepping versus at stepping irregularities $P = 0.945$). PS values differed slightly between rest and regular stepping compared to gait irregularities episodes in the STN. In STN_{all} SUAs, the mean PS value in the pre-stepping periods (7.1 ± 1.4) was similar to that during the continuous stepping periods (7.5 ± 1.4); however, during stepping irregularities, the PS value increased to 8.4 ± 2.0 (all *P*-values ≥ 0.219). This increase of PS value was even more accentuated in the in STN_{mod} SUAs. The mean PS value was similar in the pre-stepping periods (7.7 ± 1.6) and in the continuous stepping periods (7.3 ± 1.1), but clearly increased to 9.2 ± 2.4 during stepping irregularities, but still not reaching a significant level (Table 2; all *P*-values ≥0.375). There were no significant changes of PS values throughout gait conditions in the SN (Table 2; all *P*-values ≥0.250).

Oscillatory neuronal activity in relation to stepping performance

Neuronal oscillatory activity was analysed during the different states of gait to detect a potential oscillatory biomarker for freezing episodes. In a first step, all the stable units in the sample (140 units) were considered. These units were recorded during both resting and regular stepping, but not necessarily during the occasional stepping irregularity episodes. A detailed summary of the oscillatory neuronal activities of all stable units in relation to the stepping performance is reported in the upper part of Table 3. In the pre-movement phase, power spectral analysis revealed significant oscillatory spiking behaviour in 14/113 STN units (12%) and in 4/20 SN units (20%); no oscillating neurons were detected in the low number of ZI units.

With movement onset, the total amount of oscillatory SN neurons remained approximately the same (3/20, 15%). In contrast, in the STN, the number of oscillating units changed considerably depending on the stepping phase: there were smaller amounts of oscillating units during the pre-stepping phase (14/113 = 12%) compared to regular stepping (25/113 = 22%).

Because the group of all units was strongly uneven and unpaired with regard to the rare stepping irregularity episodes, a generalized

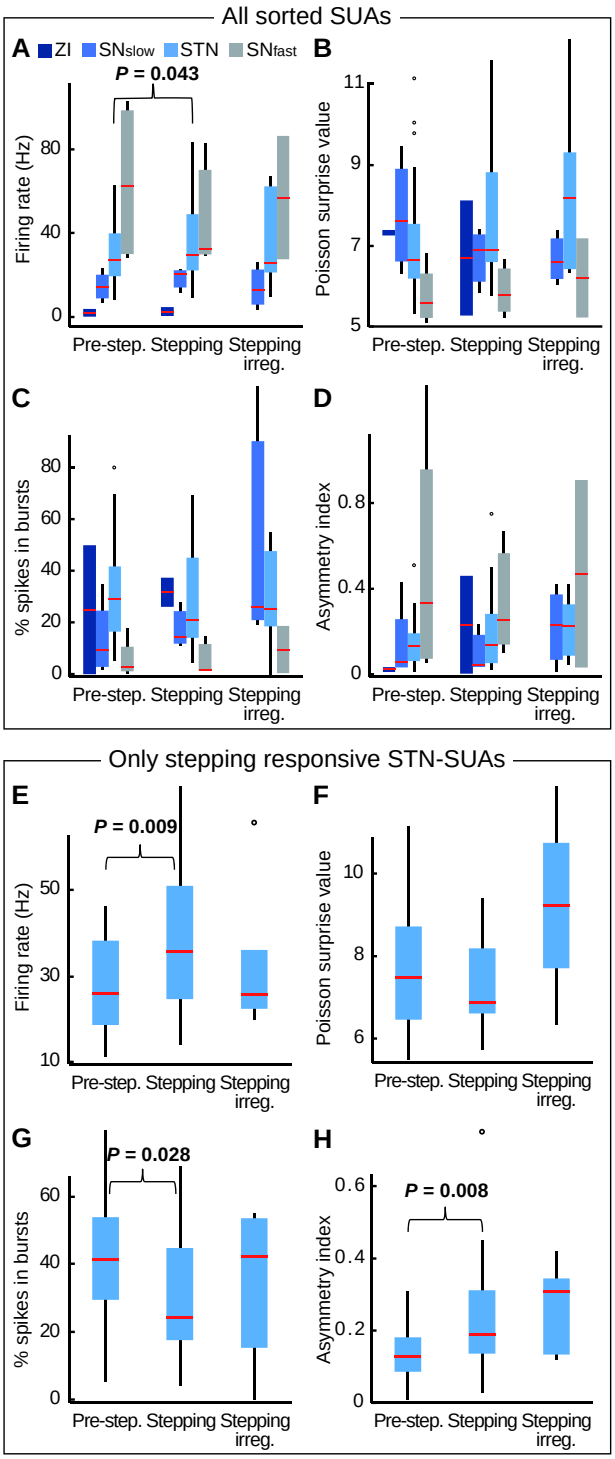

Figure 3 Comparisons of firing characteristics of SUAs. (**A–D**) Comparisons of firing characteristics of all sorted SUAs from the ZI, SN (SN_{slow} and SN_{fast}) and STN during pre-stepping, continuous stepping and stepping irregularities, regardless of whether they were significantly modulated by the task or not. (**E–H**) Comparison of firing characteristics of a subset of STN-SUAs, only included if they were showing a significant modulation of firing activity at stepping (peaks and troughs in PETHs exceeding the 95% CI limits of the expected firing rate at rest), during pre-stepping, continuous stepping and stepping irregularities. Note that only a subset of SUAs were available at stepping irregularities. If asymmetry index (AI= mode ISI/mean ISI) < 0.55,

(Continued)

linear mixed-model approach was used for the core group of 40 neurons, which could be recorded throughout all the three motor stages, i.e. at rest, during regular stepping and during stepping irregularities. The statistical results for this core group are reported in the lower section of Table 3 and in Fig. 4. In this unit subset, certain findings, which were observed in the total population, could be confirmed, such as structure specific oscillatory patterns. SN units displayed stable oscillation patterns irrespective of the movement condition, with 25–27% of units oscillating in the sub-beta (9–17%) and gamma band (8–18%) throughout pre-movement and stepping phases. However, movement-responsive STN units showed a doubling of oscillatory activity through the three different task states (pre-stepping 2/29 < stepping 4/29 < stepping irregularities 8/29). In particular, these units showed an interesting switch within the frequency bands. In the pre-movement phase and during regular stepping, STN units showed significant peaks predominantly oscillating in the sub-beta (0 and 1/29, respectively) and gamma bands (2 and 3/29, respectively), but during gait irregularities there was a novel emerging of units oscillating at beta frequencies (3/29) that were not oscillating in the other task states ($P = 0.003$; Table 3 and Fig. 4).

Discussion

To date, there are no descriptions of SUA firing characteristics during gait freezing episodes in humans. Here, we assessed the role of BG neurons, particularly in the STN and in the SN, during gait and freezing-like gait irregularities. We found structure-specific patterns of task-related activity changes with a dorsoventral gradient. Movement-related units were predominantly found dorsally within the ZI and STN, whereas attention-related units were located more ventrally within parts of the STN and SN. The firing pattern characteristics in the STN changed between the motor states. With the onset of regular stepping, the firing rate increased while the firing pattern became more regular compared to rest. During gait irregularities, a non-significant increase of irregular-burst firing behaviour and an exacerbation of oscillatory beta activity compared to regular stepping were observed.

Limitations

The intraoperative assessment of subcortical network nodes during gait by electrophysiological techniques underlies certain methodological limitations, as unequal numbers of neuronal recordings available across the BG nuclei and movement induced artefacts. Owing to the impossibility to perform intraoperative assessments in the upright position, results from this supine stepping task must be interpreted in light of this technical constraint, not reflecting the natural gait. Nevertheless, to gain insights into the physiology of bipedal locomotion, gait-like tasks in the supine position have been previously validated.[38] We used a definition of gait irregularities relating to dynamic amplitude reduction above 50%, which does not differentiate, but lumps together akinetic FoG and festination and is not commonly used in literature. Despite our effort to establish an intraoperative stepping

Figure 3 Continued
the SUAs are burst firing (ISI = inter-spike intervals). An AI value of 1 represents a Gaussian firing distribution, i.e. a lower AI denotes an irregular, burst firing neuron, while a higher AI denote a more regular active neuron. Poisson surprise values with cut-off above 5. *P*-values: Wilcoxon signed-rank tests. Values reported in the box plots are median, IQR whiskers (highest/lowest values of the data-set within 1.5 times of the IQR) and outliers as dots (<1st percentile and the >99th percentile).

Table 3 Summary of oscillatory neuronal activities in relation to stepping performance

Number of units	Peaks of oscillatory activity at:		
	Pre-stepping	Stepping	Stepping irreg.
STN (113)	15	28	8
STN sub-beta	33% (5/15)	32% (9/28)	12% (1/8)
STN beta	27% (4/15)	25% (7/28)	38% (3/8)
STN gamma	40% (6/15)	43% (12/28)	50% (4/8)
SN (20)	4	3	3
SN sub-beta	25% (1/4)	66% (2/3)	33% (1/3)
SN beta	0% (0/4)	0% (0/3)	0% (0/3)
SN gamma	75% (3/4)	33% (1/3)	66% (2/3)

Number of units	Peaks of oscillatory activity at:			Fixed effects of GLMMs				*P*-values of *post hoc* pairwise contrasts		
	Pre-stepping	Stepping	Stepping irreg.	*F*	df1	df2	*P*	Pre-stepping versus stepping	Pre-stepping versus stepping irreg.	Stepping versus stepping irreg.
STN (29)	2	4	8	2.077	2	47	0.137	0.398	**0.039**	0.202
STN sub-beta	0% (0/2)	25% (1/4)	12% (1/8)	2.737	2	84	0.071	0.198	0.198	1
STN beta	0% (0/2)	0% (0/4)	38% (3/8)	6.098	2	84	**0.003**	N/A	**0.043**	**0.043**
STN gamma	100% (2/2)	75% (3/4)	50% (4/8)	0.349	2	51	0.707	0.647	0.398	0.693
SN (11)	3	3	3	0.148	2	21	0.863	0.631	1	0.631
SN sub-beta	33% (1/3)	66% (2/3)	33% (1/3)	0.250	2	20	0.782	0.557	1	0.557
SN beta	0% (0/3)	0% (0/3)	0% (0/3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SN gamma	66% (2/3)	33% (1/3)	66% (2/3)	0.206	2	22	0.815	0.557	1	0.557

The top section of the table presents overview of all the stable units in the sample recorded during both resting and regular stepping, but not necessarily during the occasional stepping irregularity episodes. The lower section presents the fixed effects of the generalized linear mixed model (GLMM) and *post hoc* tests for the core group of 40 neurons whose oscillatory activities could be recorded throughout all the three motor stages, i.e. in the pre-stepping period, during stepping and during stepping irregularities.

paradigm to trigger difficulty in gait initiation, we provoked only very few such episodes, which were not sufficient for conclusive analyses of that specific FoG subtype. Most units were recorded from the initially operated left hemispheres, because at the beginning of the surgery the patients were in the best condition to adequately perform the stepping task. In only three patients were we able to also record on the second, right hemisphere. Owing to this restriction, a specific differentiation of possible lateralized brain functions during the stepping task was not possible.

The role of STN single neurons during a gait-like task

Although STN single-cell activity has not been investigated specifically during gait-like tasks, there are data on the contribution of subthalamic cells to general motor control, which should be considered in the interpretation of the current single-unit findings during stepping.

Before the interpretation of the unit responsiveness, one needs to consider that there was a considerable portion of neurons, which did not respond to any of the selected cues 'start', 'stop' or 'heel strike'. This apparent neuronal unresponsiveness has been described for other movements and is not yet completely understood. It might be that (i) we missed the neuroanatomically clustered 'leg-associated' cells with the clinically predefined microelectrode trajectories planned for therapeutic DBS electrode implantation; (ii) those unresponsive neurons would react to other movement aspects than the defined, preselected cues in that experimental setting; or (iii) the unresponsive neurons are involved in some sort of 'synfire chain', meaning that their response is not directly related to one specific movement cue, but related to the firing of the first-order STN neuronal pool as some kind of second-order pool.[39]

STN firing rate

In the monkey and in early, intraoperative observations in humans, somatotopically arranged STN single cells revealed an increase of their firing rate during voluntary extension–flexion movements of single upper and lower limbs.[10-12,40-42] Movement-related facilitation of neuronal activity was, in general, more common than inhibition.[13] Here, we found an increase of STN firing rates associated with the contralateral heel strike during bilateral, coordinated stepping in line with those previous observations of facilitation of neuronal subthalamic firing during motor execution. These findings underline the role of the STN in monitoring kinematic, executive motor aspects of movements.

We found a small proportion of STN-cells responding to attentional aspects and few polymodal neurons. In a previous, intraoperative study using a reach-to-grasp task of the right upper limb, STN neurons were also responding to several kinematic aspects of the ongoing movement indicating a polymodal activation profile.[13] Thus, the STN might also be involved in motor aspects beside pure motor execution as previously discussed for feedforward control[43] or feedback processing of movements.[10,11,43]

STN firing pattern and entropy

In this experiment, during regular gait, the firing rate increase was accompanied by a significantly more regular, firing pattern compared to rest, indexed by lower CV and higher AI. During freezing-like stepping episodes, despite comparable high firing rates, the firing pattern seemed to become more irregular and bursty compared to regular stepping. Considering the small number of neurons at a descriptive level, there was a slight, but non-significant increase of CV and PS values reflecting neuronal entropy.[29,44] In information

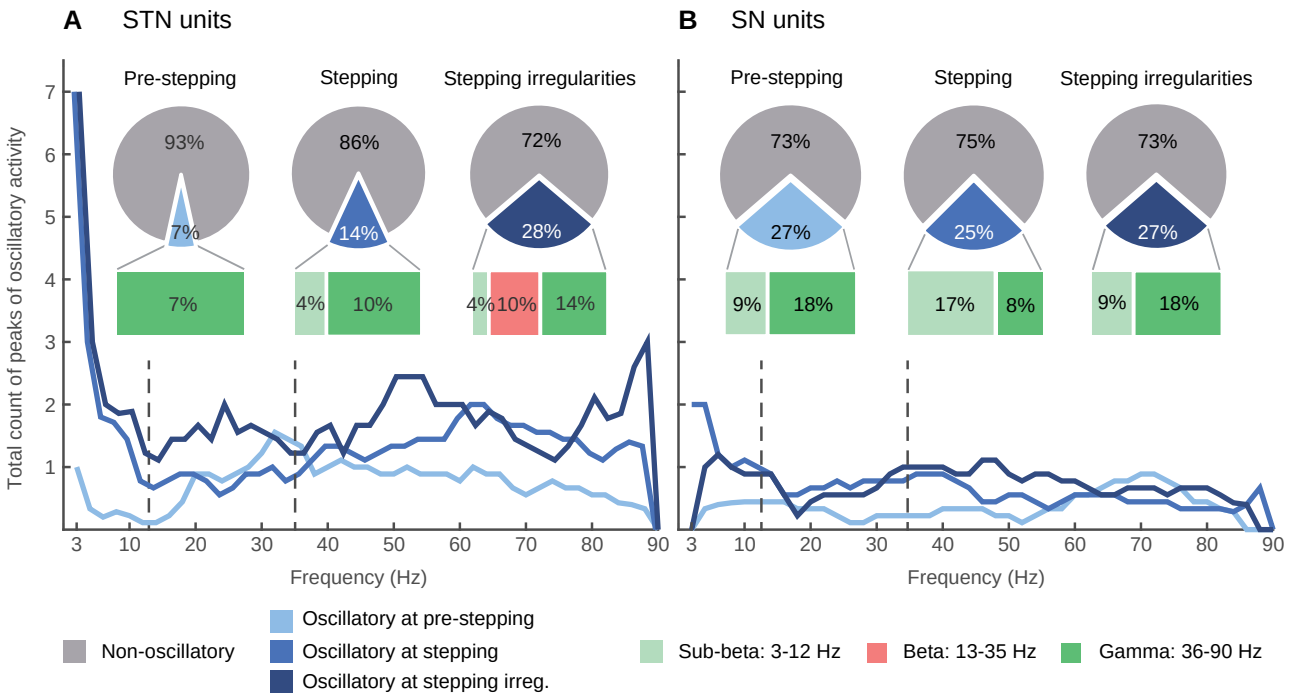

Figure 4 Oscillatory activity of 40 units recorded throughout all the three motor stages, i.e. in the pre-stepping period, during stepping and during stepping irregularities. Please note that, those are a subgroup of all the stable 113 STN and 20 SN units reported in the results section and thus the oscillatory activities reported here may differ. The lines depicted in **A** and **B** represent the spectrograms resulting from the total count of peaks of oscillatory activity in 29 STN and in 11 SN units, respectively. Peaks passing the 99% CI threshold were considered as oscillatory and were counted in the histogram with frequency bin resolution of 1 Hz. Pie charts represent significant peaks of oscillatory activity, i.e. only units showing peaks of oscillatory activity comprehending ≥2 contiguous bins over the 99% CI were considered as significantly oscillating and have been counted. The interrupted lines represent the boundaries of the considered frequency-ranges, i.e. the sub-beta (3–12 Hz), beta (13–35 Hz) and gamma (36–90 Hz).

theory, entropy is assumed to encode information content, but might be inversely associated with information transmission. In this framework, unpredictable, random events with high entropy contain high information,[45] but elevated noise floor interfering with the core signal information[46] lead to decreased information transfer. In 6-OHDA lesioned rats, neuronal entropy of firing patterns was increased in globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNr) compared to the healthy state, indicating increased informational noise and decreased information transfer through BG output nuclei.[46,47] DBS[46,47] or dopaminergic medication[48] decreased neuronal entropy to normal levels in parallel to symptom reduction corresponding to findings that low entropy facilitates efficient information transfer. In Parkinson's disease patients with freezing, local field potential (LFP) recordings during locomotion revealed larger beta entropy during regular walking compared to non-freezers and an additional increase of alpha entropy during periods of FoG.[49] Although our observation of a slight increase of STN-SUA entropy during gait irregularities remain at a non-significant, descriptive level and must be treated with caution, it would fit previous observations of LFP-entropy changes[49] and might confirm the theory of suddenly disrupted, ineffective BG information transfer resulting in motor blocks and gait irregularities.

STN oscillatory firing activity

Ineffective stepping during 'freezing-like episodes' was associated with a significant increase of beta oscillations. We therefore assume that STN single-cell oscillatory activity determines another feature within the control of information transfer. It was hypothesized that during movement, when firing rates increase, the beta oscillations of single cells are progressively dampened to release the information flow of motor programmes resulting in effective movement.[41] The decrease of oscillatory beta activity with gait onset might result in the release of the information flow and gating the motor programme, whereas excessive beta activity blocks the information transfer through the BG and antagonizes motor-related processing, resulting in gait disruption and FoG. This hypothesis is in line with observations of oscillatory activity of neuronal, population signals indexed by LFPs.[50,51] STN beta oscillatory LFP activity was reduced during active walking or the transition phases[52] and revealed pathological synchronization with the motor cortex during FoG episodes accompanied by cortico-subcortical desynchronization within theta band activity reflecting a sudden derangement of locomotor network during FoG.[50] Particularly 'long-bursting' beta oscillatory LFP activity might trigger FoG in freezers, whereas 'short-bursting' beta activity is also observed in non-freezers.[49,53]

At rest, peaks of oscillatory unit activity were mainly found in the high beta band around 30–35 Hz, which decreased during regular stepping. This finding is in line with previously described desynchronization of higher beta oscillations during leg movements.[54] During freezing-like episodes, the rise of subthalamic beta oscillations represented a broader beta frequency band activity, peaking in the higher beta band around 25 Hz. This broad band beta activity could possibly represent the interplay between high beta frequency oscillations generated by an exaggerated hyperdirect pathway, inducing in turn synchrony at lower beta frequencies in the STN, as suggested in a previous work.[55] In summary, single-unit oscillatory behaviour reveals an increase of beta oscillations during FoG-like episodes which is similar to the observed beta activity changes at the STN populational level indexed by LFP.

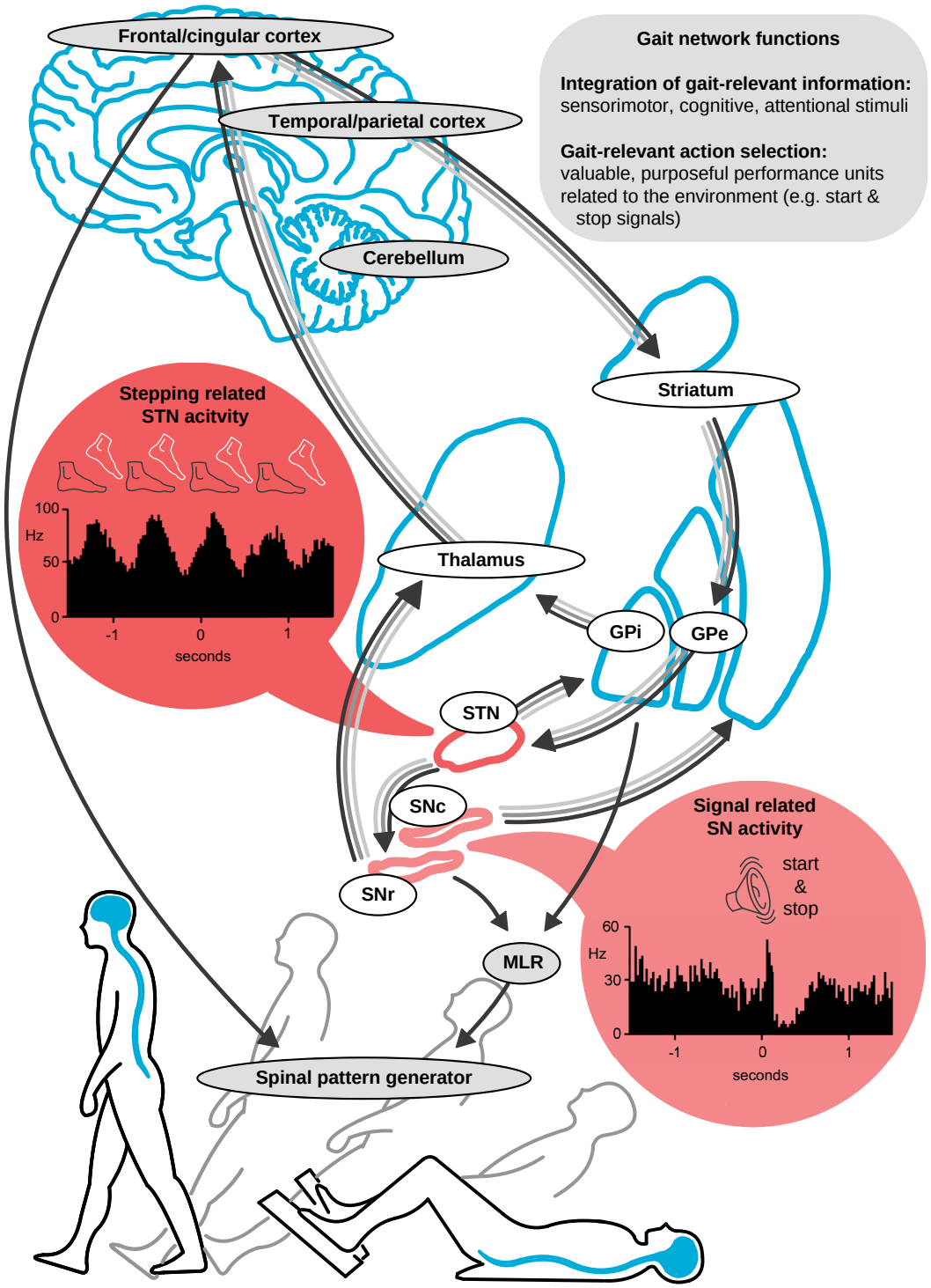

Figure 5 Schematic illustration of signal pathways within the gait network. Integration of the STN and SN unit findings during the intraoperative stepping task of parkinsonian patients in the actual model of gait and FoG. Lines and arrows represent parallel sensorimotor, cognitive and attentional BG projections. We propose the BG to be a cognitive–motor interface for the integration of gait-relevant information for appropriate gait-segment programme selection. Within the BG, the different nuclei vary in their main contribution to motor and attentional signal processing along a dorsoventral gradient.

STN functional role in gait and freezing of gait

In motor control, it is proposed that within the indirect motor loop the STN functions as 'online control'[56] for the proper selection of desired movement segments and inhibition of competing motor mechanisms that would otherwise interfere with the favoured movement.[57] Transferring these assumptions from a general motor model to gait, facilitation and initiation of gait would be induced by the direct BG-loop *via* specific and focused striatopallidal projections resulting in disinhibition of the thalamocortical projections.[58] The indirect BG-loop with broad and widespread STN projections to the GPi would result in inhibition of the thalamocortical projections in terms of a centre surround inhibition[58,59] and suppression of competing motor programmes. When regular gait

is initiated, STN single neurons increase their firing rate while reducing firing irregularities and oscillatory behaviour for optimized information transmission, resulting in effective pallidal surround inhibition, appropriate movement segment selection and undisturbed gait pattern. During FoG, although the STN firing rates remain continuously high as during regular gait, the information transmission is blocked by increased beta oscillatory activity, so that inappropriate action selection results in slurred gait motor patterns.

Another hypothesis of the subthalamic function during gait could be derived from the BG model of motor sequencing of 'chunks' of motor-cognitive performance units.[60] Locomotion represents a sequence of alternating leg movements, which is disturbed in Parkinson's disease with initial normal-sized, larger steps but in the course progressively smaller steps eventually resulting in akinetic freezing. One hypothesis proposes[61] that prior to each component of the movement sequence, a preparatory 'set' signal in the supplementary motor area is transmitted to the striatum. Before the next component of a sequence can be executed, the 'set' signal needs to be turned off to allow the movement to occur by the increase of GPi firing rate prior to the second or following movement sequences.[57,60] We found cyclical, subthalamic firing increase related to the heel strikes of each step within the stepping sequence. This is in line with cyclical, gait-phase–dependent modulations of pedunculopontine[62] and subthalamic[63] LFP activity. The recurrent increase of STN single-cell firing rates might be related to the 'turning off' of the cortical set signal to allow the next step of the other leg to occur. During FoG, the transmission of the STN signal is ineffective by increased, irregular and beta oscillatory activity, so that the interaction with the cortical set command might be disturbed and the release of the next step could be prevented.

The role of substantia nigra neurons within the gait-like task

The firing characteristics of the SN were different in some aspects to those of the STN during gait. At rest, SN spontaneous firing rates were higher, but with a more regular discharge pattern compared to subthalamic activity as described before.[64] SN unit activity was not modulated during motor execution, as observed for STN units, but changed with 'start' or 'stop' signals during the gait-like task. This nucleus-specific, divergent modulation with mostly motor-unresponsive SN neurons is in line with observations in animal models[65] and human recordings,[42] with rare neural responsiveness to sensorimotor stimulation in the SN.[42]

There have been previous considerations of the role of the SN during motor control. On the one hand, the SNr is considered to be one of the BG output nuclei keeping thalamic and brainstem nuclei under tonic inhibitory control through sustained, spontaneous high-frequency firing[66] and facilitating movements by phasic neuronal firing pauses.[67,68] SNr neurons were shown to be involved in movement selection, as it has been generally proposed for subthalamic and BG function.[57,69]

On the other hand, the SNr is proposed to be involved in cognitive, attentional control of purposeful movements and gaze to enhance the valuable outcome of the selected action.[69,70] The SNr is proposed to be organized into dorsolateral and ventromedial subterritories[71] embedded into segregated circuits connecting the caudate nucleus and superior colliculus but also the thalamocortical and brainstem nuclei for integration of sensorimotor-cognitive signals of flexible and stable values.[72] Thus, our observations of attentional-related SN activity changes during gait might fit into the previous observations of cognitive control of valuable purposeful gait modulation.

Besides, these intraoperative observations fit to previous clinical observations with the assessment of STN+SN DBS in postoperative patients in gait conditions with low and high cognitive load.[17] We found improvement of spatial and temporal gait characteristics, with STN+SN DBS, that were emphasized in gait conditions with increased cognitive load such as gait turning or performing dual tasks. The parkinsonian gait disorder and FoG are well known to be affected by cognitive-attentional resources.[73] We therefore propose from clinical and intraoperative observations that combined STN+SN DBS might act by enhanced exploitation of attentional resources to improve gait quality.

Pathophysiological model of gait and freezing of gait: new considerations

From preceding extensive animal and human research, it is assumed that the BG are critically involved in gait control by interactions with remote sites within large-scale subcortico-cortical networks.[74] Particularly, the dense interactions between the STN, SN and the MLR region of the gait network represent a key station in the adaptation of gait[4,74] in the sense of a final common pathway.[3] We found step-related modulation of STN neurons during motor execution, but also modulation of STN and SN neurons with cognitive demands as 'start' and 'stop' signals. In light of these observations and anatomical considerations of highly differentiated, segregated, parallel BG loops encoding motor, limbic and cognitive-associative symptoms,[11] we assume that the STN and SN represent an important cognition–motor interface within the common final pathway to integrate cognitive, emotional and sensorimotor information signals in an activity and history-dependent context for optimized action selection by fine-tuned release or inhibition of particular downstream brainstem nuclei for generation of smooth locomotion.[75]

In conclusion, the observations of nucleus-specific motor- and attentional-related changes of BG firing rates point to an integrative role of attentional and motor aspects of gait along a topographical ventrodorsal gradient within the BG (Fig. 5). The rise of subthalamic beta oscillatory activity during FoG-like episodes compared to regular stepping activity indicates disturbed information transfer within the final common pathway that might result in unspecific, excessive brainstem inhibition, disturbed, slurred movement segment selection and consecutively gait irregularity or FoG.

Acknowledgements

We are indebted to all the patients who agreed to participate in this challenging study during STN-DBS neurosurgery. We are grateful to Marlies Schütte, Maja Kirsten, Beate Schönwald, Claudia Wargel and Eva Tabea Schönfeldt-Reichmann of the Department of Neurology for their support in data acquisition and to Bettina Schwab, Till R. Schneider and Magdalena K. Baaske for valuable scientific discussions.

Funding

This work has been funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation): SFB 936-178316478-C8 (M.P.N. and C.K.E.M.), -A3 (A.K.E.) and -C1 (C.G.).

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships. Some of the authors (A.G., C.K.E.M., W.H.) have been reimbursed for travel expenses from Medtronic Inc. C.G. reports personal fees and other from Bayer Healthcare and Boehringer Ingelheim, personal fees from Abbott, Amgen, BMS, Sanofi Aventis and Prediction Biosciences. C.K.E.M. received lecture fees from Abbott. W.H. received lecture fees and honoraria for serving on advisory boards and travel grants from Boston Scientific, Medtronic, ALEVA and Abbott. M.P.-N. received lecture fees from Abbott, Boston Scientific, Abbvie and Licher, received study-related fees from Boston scientific, Zambon, Abbott and served as consultant for Boston Scientific and Abbvie.

Supplementary material

Supplementary material is available at *Brain* online.

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