Research paper

Overnight unilateral withdrawal of thalamic deep brain stimulation to identify reversibility of gait disturbances

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ABSTRACT

Background: Gait disturbances are frequent side effects related to chronic thalamic deep brain stimulation (DBS) that may persist beyond cessation of stimulation.
Objective: We investigate the temporal dynamics and clinical effects of an overnight unilateral withdrawal of DBS on gait disturbances.
Methods: 10 essential tremor (ET) patients with gait disturbances following thalamic DBS underwent clinical and kinematic gait assessment ON DBS, after instant and after an overnight unilateral withdrawal of DBS of the hemisphere corresponding to the non-dominant hand. The effect of stimulation withdrawal on gait performance was quantitatively assessed using clinical rating and inertial sensors and compared to gait kinematics from 10 additional patients with ET but without subjective gait impairment. DBS leads were reconstructed and active contacts were visualized in relation to surrounding axonal pathways and nuclei.
Results: Patients with gait deterioration following DBS exhibited greater excursion of sagittal trunk movements and greater variability of stride length and shank range of motion compared to ET patients without DBS and without subjective gait impairment. Overnight but not instant unilateral withdrawal of DBS resulted in significant reduction of SARA axial subscore and stride length variability, while tremor control of the dominant hand was preserved. Cerebellothalamic, striatopallidofugal and corticospinal fibers were in direct vicinity of transiently deactivated contacts.
Conclusion: Non-dominant unilateral cessation of VIM DBS may serve as a therapeutic option as well as a diagnostic intervention to identify stimulation-induced gait disturbances that is applicable in ambulatory settings due to preserved functionality of the dominant hand.

1. Introduction

High frequency deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of the thalamus is an impressively effective and safe therapy for patients with severe essential tremor (ET) refractory to medical therapy. (Schuurman et al., 2000) Commonly reported side effects include dysaesthesia, speech disturbances, dysphagia(Pahwa et al., 2006) and gait disturbances(Hwynn et al., 2011). The latter may occur with a delay of several months after activation of DBS and restrain its efficacy. On the other hand, increased variability of gait(Roemmich et al., 2013) with clinically evident impairment of gait and balance (Kronenbuerger et al., 2009; Rao and Louis, 2019; Stolze et al., 2001)

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can be a feature in the advanced stages of ET unrelated to DBS, which further complicates the differentiation from disease progression(Favilla et al., 2012) or microlesion effects after DBS(Roemmich et al., 2019). Studies investigating the prevalence of gait worsening following DBS report up to 58% of patients with deterioration of gait performance following DBS, with similar proportions in patients with unilateral and bilateral DBS.(Hwynn et al., 2011).

Recently, inadvertent activation of mid-line cerebellar structures, arguably mediated antidromically via cerebello-thalamic fibers was identified as a possible correlate of stimulation-associated gait disturbances in a study using FDG-PET(Reich et al., 2016). The delayed onset of such gait disturbances may distract the clinician from diagnosing them as DBS-side effects and distinguishing them from other concomitant comorbidities affecting gait, such as peripheral neuropathy. Nevertheless, this diagnostic step is critical to select potential therapeutic strategies(Kroneberg et al., 2019b) that can be restricted by the implanted type of electrode (i.e. directional)(Bruno et al., 2021) or pulse generator(Choe et al., 2018). The interval used in previous studies to reverse these gait disturbances by a "washout" of the bilateral DBS was several days long. (Kroneberg et al., 2019b; Reich et al., 2016; Reich et al., 2017).

In clinical practice, a multi-day withdrawal of deep brain stimulation poses a significant challenge for the patient. Firstly, symptom severity in patients with ET that underwent DBS can be assumed relevant enough to impact activities of daily living. Hence, withdrawing stimulation will lead to reemergence of an incapacitating tremor, likely requiring hospitalization for this period. This may be even aggravated by transient occurrence of rebound tremor of even greater severity(Hariz et al., 1999). In our experience, patients who have experienced transient deactivation of their DBS, e.g. during monopolar reviews, therefore often express resentment towards scenarios involving prolonged withdrawal of effective stimulation.

We therefore sought to explore if a paradigm for unilateral withdrawal of DBS that allows maintaining functionality of the dominant hand may be sufficient to modulate gait performance to a degree detectable to kinematic, quantitative assessment. Moreover, the strategy of unilateral DBS could be applied chronically to improve gait in severely affected patients with remaining effects of tremor suppression for the dominant hand. This paradigm would be safely applicable in an outpatient clinic or ambulatory setting. Additionally, we aim at characterizing how changes of gait characteristics unfold after withdrawal of unilateral deep brain stimulation and which neuroanatomical structures may be of relevance.

2. Patients and methods

2.1. Study population

Ten ET patients (7 female, age 71.7 ± 6.1 yrs., average disease duration 34.0 ± 15.0 yrs) with documented and patient-reported deterioration of gait performance following activation of thalamic DBS (average time of chronic stimulation at time of study: 57.8 ± 34.3 months) were recruited for the study. Patients with comorbidities affecting gait, such as musculoskeletal conditions or peripheral neuropathy, were excluded.

Patients were recruited from the outpatient clinic in which deterioration of gait and balance is routinely queried. Prior to this study, patients had undergone multiple attempts to refine programming settings with monopolar review sessions, adjustments of active contacts, including the use of advanced programming settings such as bipolar and interleaving stimulation to address gait disturbances. The setting yielding most efficient tremor control and least side effects on gait in each individual is reported in Table 1. None of these patients were programmed with shorter pulse width at the time of the study due to limited range of parameter settings of the pulse generators used (Activa PC). However, 7 of the 10 patients reported here had been selected for a reprogramming with shorter pulse widths in a later study (Kroneberg et al., 2019b).

Table 1
Clinical details of withdrawal cohort.

Patient	Sex	Age	Disease duration in years	Months since DBS surgery	Stimulation parameter ON DBS					Medication relevant for tremor
						Contacts	Hz	V	µs	
Patient 1	F	72	50	15	R	0-,1-,2+	130	2.0	60	Metoprolol 100 mg 1–0-1
					L	1-*/2-*	130	1.4/2.0	60	
Patient 2	F	72	38	19	R	0-*/1-*	130	0.9/0.8	60	Propranolol 80 mg 1–0-1
					L	0-*/1-*	130	1.2/2.7	60	
Patient 3	M	72	17	69	R	0-,1-,2+	125	1.9	60	none
					L	0-*/1-*	125	1.6/1.6	60	
Patient 4	M	76	16	60	R	1-*/2-*	130	1.5/1.2	60	none
					L	0-*/1-*	130	1.7/1.5	60	
Patient 5	F	73	20	117	R	2-*/3-*	110	1.6/1.6	60	Primidone 250 mg 0–0-1 Metoprolol 47.5 mg 1–1-0
					L	0-, 3-	110	2.4	60	
Patient 6	M	54	40	67	R	2-,3-	130	2.3	60	none
					L	4-,5-	130	2.0	60	
Patient 7	F	75	19	48	R	1-	160	2.5	60	Propanolol 40 mg 1–1-1 Primidone 250 mg 0–0-1
					L	5-	160	3.7	60	
Patient 8	F	77	52	61	R	1-, 2+	160	4.3	90	Metoprolol 95 mg 1–0-0
					L	8-	160	3.0	90	
Patient 9	F	74	30	13	R	0-	200	2.1	60	Pregabalin 100 mg 0–0-1
					L	8-	200	3.4	60	
Patient 10	F	72	58	109	R	1-, 2+	160	3.1	60	None
					L	4-	160	2.5	60	
Average		71.7 ± 6.1	34.0 ± 15.0	57.8 ± 34.3		* = interleaved DBS				

Clinical details of patients with essential tremor that underwent unilateral withdrawal of deep brain stimulation.
DBS – deep brain stimulation, ON DBS – initial stimulation parameter setting, ET – Essential tremor, R – right hemisphere, L – left hemisphere, F- female; M - male.

For comparison of gait characteristics, ten additional non-DBS patients with ET and no subjective impairment of gait were recruited (4 female, age 63.4 ± 10.4 yrs., average disease duration 43.3 ± 13.7 yrs). Of note, these patients were under evaluation for DBS.

2.2. Study protocol

Handedness was determined using Edinburgh handedness inventory (Oldfield, 1971) with a cutoff of ±50.

Clinical assessment and gait analysis were conducted with the following sequence of DBS conditions 1) ON bilateral VIM-DBS with empirically determined best setting for tremor suppression 2) one hour (INSTANT) after unilateral pausing of DBS, and 3) unilateral withdrawal overnight for 10–16 h (OVERNIGHT). We chose to switch off stimulation of the hemisphere corresponding to the non-dominant hand, so tremor control would be maintained in the patient's dominant hand. As all subjects were right-handed, the right-hemispherical electrode was deactivated in all subjects. The study was approved by the institutional review board of Charité – Universitätsmedizin Berlin and written informed consent was obtained from all subjects.

2.3. Clinical assessment

Tremor severity was assessed using Fahn-Tolosa-Marin tremor rating score (TRS) items 1–13(Fahn et al., 1988), including functional testing of drawing and pouring water. Axial items (1–3) of the Scale for assessment and rating of ataxia (SARA) (Schmitz-Hubsch et al., 2006) were used to score ataxia of gait and trunk.

2.4. Gait assessment

Gait performance was assessed with a commercially available gait analysis system (Mobility Lab V1 hardware, APDM, Oregon USA) using six body worn, inertial sensors (Opals) attached to both wrists and shanks and medially placed over sternum and lower back. Data was sampled at 128 Hz and processed within Mobility Lab software V1.0.0.201503302135 (Mancini et al., 2011) to determine trial validity and generate an export of stridewise timecoded values of gait parameters per trial after excision of turns as defined by manufacturer's algorithms as this would be the expected scenario when using a commercial device in a clinical setting. Accuracy and repeatability of algorithms for delineation of gait parameters have been validated against other motion analysis technologies by third parties (Washabaugh et al., 2017) and through numerous studies. (https://apdm.com/publications) From these exports of individual trials, lengths and times of strides were plotted against time stamps to verify proper turn detection and excision. (Kroneberg et al., 2019a).

Gait performance was assessed on a walkway of 10 m length, a total distance of 20 m was covered in 2 walking bouts of 10 m each at patient's self-selected, preferred comfortable gait speed. Starting- and stopping point was marked with colored tape. Spatial and temporal parameters obtained from Mobility Lab software were: stride length, stride velocity (corresponding to gait speed), stride time, cadence, double support, swing and stance time and ranges of motion (RoM) of knees, shanks and trunk. Parameters reflecting asymmetry and peak velocities, that are reported to have a low reliability and agreement between different measurements(Cabral et al., 2017) were not included in further analysis. Coefficients of Variation (CoV) were calculated for gait parameters in all trials as standard deviation divided by the respective mean. Reported gait parameters and their variability were previously shown to reflect cerebellar dysfunction (Ilg et al., 2007) and susceptibility to modulation by supratherapeutic DBS (Fasano et al., 2010) and reflect different domains of gait performance factors (pace, rhythm and variability)(Lord et al., 2012; Roper et al., 2019).

2.5. Statistical analysis

Group data were tested for normal distribution using Shapiro-Wilk-test. Given small cohort sizes and as not all parameters were normally distributed, non-parametric Friedman-ANOVA was used to compare scores and gait measures across stimulation conditions (ON, INSTANT, OVERNIGHT), Wilcoxon-sign-rank-tests were used for respective post-hoc analyses and *p*-values were adjusted for multiple comparisons using false discovery rate (FDR)(Benjamini and Hochberg, 1995) for each measure. Mann-Whitney-*U* tests were conducted to compare scores and gait measures of ET control group and ET patients with gait disturbances. To adjust for multiple comparisons here, p-values were adjusted using the FDR. Results are reported as mean ± standard deviations. An alpha level of 0.05 was considered significant.

2.6. Electrode localization and connectivity analysis

DBS electrodes were localized using the advanced processing pipeline of the Lead-DBS toolbox (V2.1.0, RRID:SCR_002915)(Horn et al., 2019b) using pre-operative MRI and post-operative CT (*n* = 5) or MRI. Individual stimulation settings were used to model volumes of tissue activated following methods previously described(Horn et al., 2017) (Horn et al., 2019a). In short, postoperative MRI or CT were linearly coregistered to preoperative MRI using advanced normalization tools (Avants et al., 2011) (http://stnava.github.io/ANTs/), then visually inspected and refined if necessary. Brain shift correction was applied as a built-in function of Lead-DBS. Preoperative volumes were used to estimate multispectral normalization to ICBM2009n NLIN asymmetric ("MNI") standard space(Fonov et al., 2011) using the ANTs SyN Diffeomorphic Mapping with presets "effective: low variance default + subcortical refinement" (Avants et al., 2008).

Electrode contacts were automatically pre-reconstructed using PaCER(Husch et al., 2018) method or the TRAC/CORE approach and manually refined if necessary. Group visualization were performed with the Lead group toolbox(Treu et al., 2020). Modulated fiber tracts were visualized using the built-in pipeline of Lead DBS V2.3 (Horn et al., 2019b) based on an approach described previously in (Irmen et al., 2020). A detailed description can be found as supplemental material.

To visually inspect distribution of active contacts in relation to those of another cohort of patients with ET and DBS, we used the 24 patients previously reported from this group (Al-Fatly et al., 2019) that had no documented gait pathology. (15 female, average age at DBS OP 75.33 years, average TRS pre OP 34.29, average improvement of TRS following DBS: 66,7%).

Unpaired *t*-tests were used to compare active x, y and z coordinates of ET DBS patients from both cohorts. If multiple contacts were active in a patient, an average was calculated.

3. Results

3.1. Clinical scores

The comparison between ET DBS patients at baseline (DBS ON) and the ET control group showed a significantly lower tremor score (*p* = 0.022, Fig. 1A) and higher SARA score (*p* < 0.0001, Fig. 1B) in patients with DBS ON.

In the DBS group, tremor scores significantly increased for total TRS (17.0 ± 9.0) with INSTANT (25.3 ± 10.1; *p* = 0.0002) and OVERNIGHT unilateral withdrawal of DBS (23.2 ± 8.9; *p* = 0.0004). This was also observed in TRS subscore for the non-dominant hand contralateral to the transiently deactivated DBS electrode (ON DBS 9.2 ± 3.7; INSTANT withdrawal 16.7 ± 5.8, *p* = 0.0003; OVERNIGHT withdrawal 14.7 ± 4.6, p = 0.0002), while for the dominant hand (contralateral hemisphere not deactivated at any time) tremor severity did not increase significantly with INSTANT (5.7 ± 4.1, *p* = 0.87) and OVERNIGHT ipsilateral withdrawal (5.8 ± 4.3, *p* = 0.78) compared to bilateral ON DBS (5.6 ±
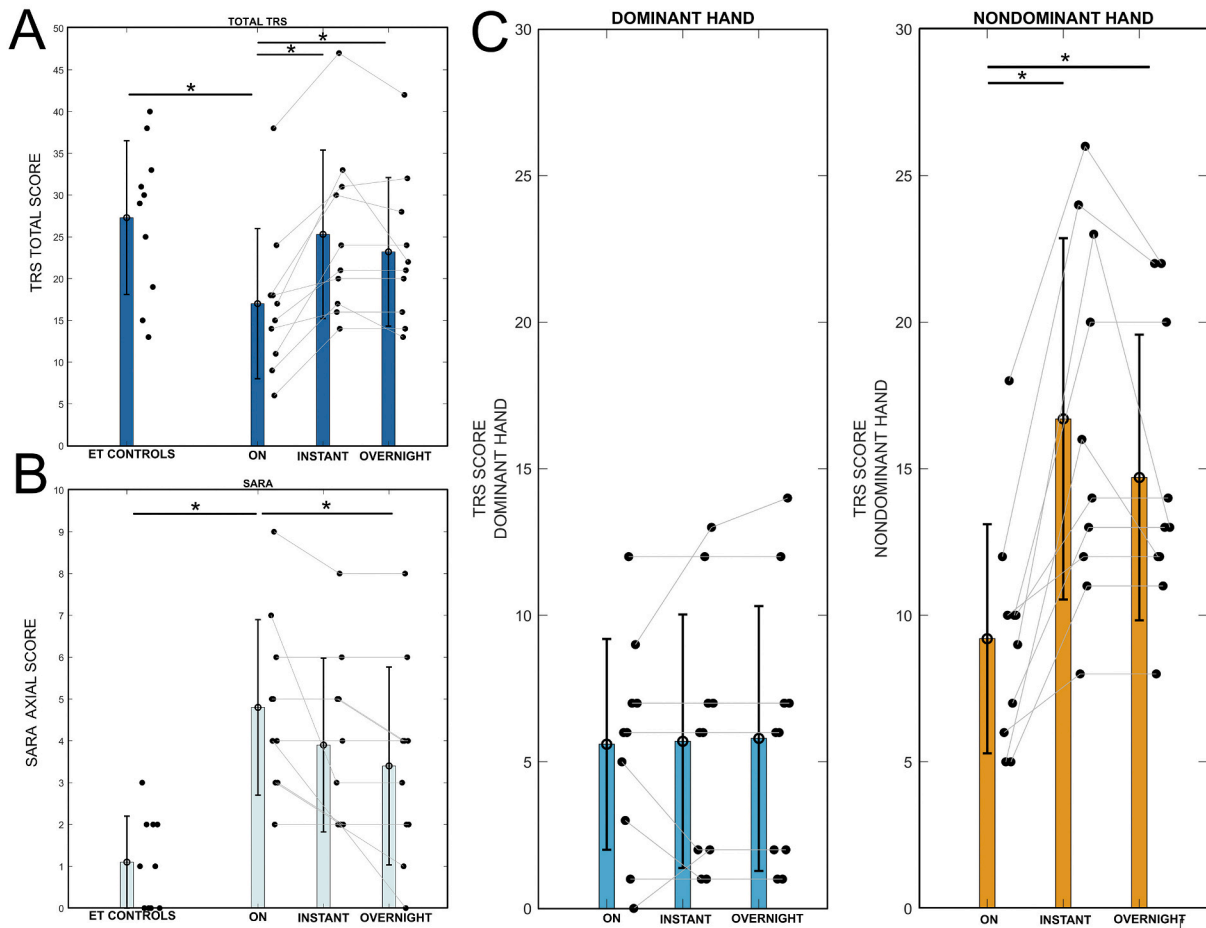
Fig. 1. Clinical scores corresponding to the stimulation conditions ON bilateral deep brain stimulation, instantly after unilateral deactivation of the DBS lead corresponding to the non-dominant hand (INSTANT) and after prolonged deactivation over night (OVERNIGHT). A: TRS: Fahn-Tolosa-Marin Tremor Rating Score (items 1–13) B: axial items (1–3) of SARA score C: left panel displays TRS-hemiscore for the dominant, right panel for the non-dominant hand. * indicates significant change of scores across stimulation conditions ($p < 0.05$, *p*-value adjusted for multiple comparisons using false discovery rate) or significant difference between controls and patients with gait disorder ON DBS ($p < 0.05$).

3.4, Fig. 1C).

SARA axial items (1–3) were significantly lower after overnight withdrawal (3.4 ± 2.4, Fig. 1B) compared to DBS ON (4.8 ± 2.1; $p = 0.0078$), but not instant withdrawal (3.9 ± 2.1; $p = 0.31$). On an individual basis, two out of ten patients had no change in SARA axial sub-score overnight. No falls were reported or documented during the assessments of the study.

3.2. Kinematic assessment

Kinematic analysis revealed that the ET DBS group showed significantly larger trunk movements in the sagittal plane ($p = 0.020$) during DBS ON compared to ET controls (Supplementary Fig. 1). Variability measured in CoV was significantly higher for stride length ($p = 0.021$) and RoM of shanks ($p = 0.021$, both FDR-adjusted).

Friedman ANOVA revealed a significant effect of "stimulation condition" on CoV of stride length ($p = 0.007$), on Cadence ($p = 0.03$) and stride time ($p = 0.03$) as well as proportions of stride phases (Swing, Stance, Double support each $p = 0.0405$). Post-hoc tests confirmed a significant reduction of CoV stride length at overnight withdrawal ($p = 0.0039$) compared to DBS ON. Furthermore, a significant decrease of cadence and stride time were observed at instant withdrawal compared to DBS ON (both $p = 0.02$), but not for overnight withdrawl (Fig. 3).

Averages of all spatiotemporal gait parameters at group level and for all DBS conditions are reported in online Supplementary Tables 1&2.

3.3. Localisation of DBS electrodes

Active contacts of ET patients undergoing stimulation withdrawal were all located in the posterior subthalamic area and ventral thalamus. (Fig. 2).

Visualization of surrounding axonal pathways from a normative atlas of 28 pathways of the basal ganglia (Petersen et al., 2019) showed cerebellothalamic, corticospinal, hyperdirect motor and pallidosubthalamic pathway in direct vicinity of the contacts that had been transiently deactivated. Upon visual inspection, there was large spatial overlap with a cohort of patients with ET where no side effects were reported(Al-Fatly et al., 2019) (Fig. 4). Comparison of x, y and z dimensions of both cohorts showed active contacts of ET patients of this study (x: 13.65 ± 1.6; y: -13.94 ± 1.43; z:-2.21 ± 2.78) to be more anterior in y-dimension ($p = 0.026$) compared to the cohort from Al-Fatly et al. (x:13.17 ± 1.1; y: -15.68 ± 2.2; z: -3.70 ± 2.91). x and z dimensions were not different when compared across cohorts.

4. Discussion

Our study reports on the temporal dynamics of reversibility of gait disturbances following withdrawal of DBS and proposes a procedure of unilateral cessation of DBS as a clinical routine assessment. We demonstrated that DBS-induced gait disturbances as measured by specific kinematic parameters are partially reversible following unilateral
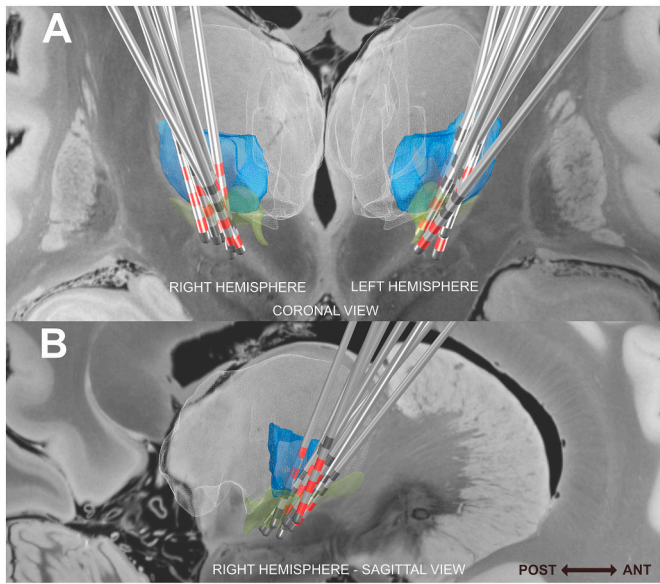
Fig. 2. 3D-visualization of DBS leads of the cohort. A: coronal view B: sagittal view. In both panels, active stimulation contacts are highlighted as red. The thalamus as defined by the DISTAL Atlas (Ewert et al., 2018) is displayed as translucent white mesh, the ventral intermediate nucleus (VIM) as blue and the zona incerta (Zi) as green, superimposed on a slice of 7 Tesla MRI of ex vivo human brain at 200 μm resolution (Edlow et al., 2019). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
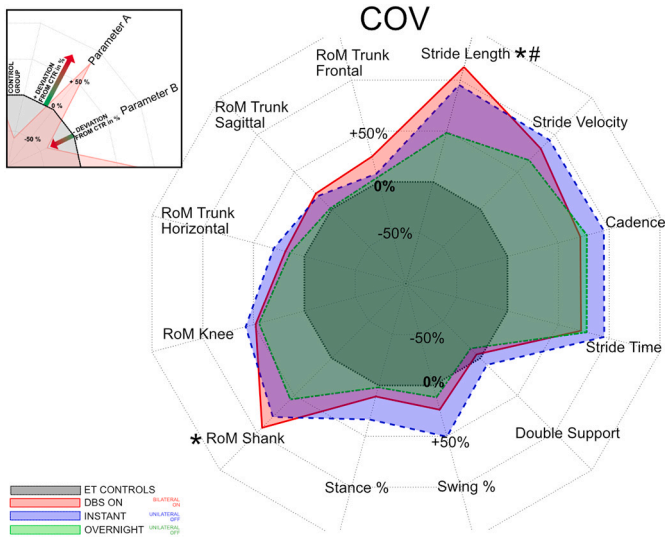

Fig. 3. Coefficient of Variability (CoV) of spatiotemporal gait parameters as relative deviations from respective measures obtained from patients with ET and no subjective gait disorder. (ET CONTROLS, black dotted line). Three stimulation conditions are depicted: ON bilateral deep brain stimulation (red line and area), instantly after unilateral deactivation of the DBS lead corresponding to the non-dominant hand (INSTANT – blue dashed line and area) and after prolonged deactivation over night (OVERNIGHT – green dashed line and area). * Indicates significant differences of gait parameters ON DBS compared with ET CONTROLs, # Indicates significant change of gait parameters OVERNIGHT compared with ON DBS. *p*-values were adjusted for multiple comparisons using false discovery rate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
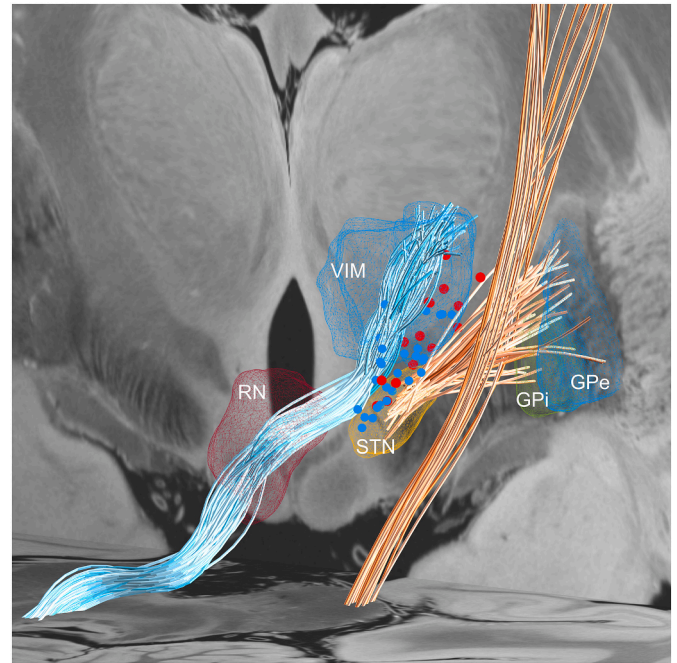

Fig. 4. Fibertracts and anatomical structures surrounding active contacts. Red dots represent active contacts of the right hemisphere that were transiently deactivated in this study. Blue dots represent active contacts from a cohort of ET patients with DBS where no gait disability was documented previously published from our group (Al-Fatly et al., 2019). Active contacts of patients with gait disturbances from this study were located slightly more anterior compared to the cohort of Al-Fatly et al. Shown tracts represent the cerebellothalamic (blue fibers), corticospinal, motor hyperdirect pathway and pallidosubthalamic pathway (orange fibers). Fibers were extracted from a normative atlas of 28 pathways of the basal ganglia (Petersen et al., 2019). Red mesh structure represents the right hemispherical red nucleus (RN), light blue mesh structure the right VIM, orange mesh represents the subthalamic nucleus (STN) and green and turquoise mesh structures represent internal (GPi) and external globus pallidus (GPe) as defined by the DISTAL atlas (Ewert et al., 2018) superimposed on a section of 7 Tesla MRI of ex vivo human brain at 100 μm resolution (Edlow et al., 2019). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

overnight DBS withdrawal that preserved tremor control of the dominant hand.

In our cohort, patients with DBS-induced gait disturbances exhibited increased variability of lower limb gait parameters as well as larger trunk movements along the sagittal plane during chronic thalamic stimulation. This finding is in line with studies reporting changes of gait performance after long-term thalamic stimulation (Hwynn et al., 2011), increased variability of lower limb joint movements (Fasano et al., 2010; Fasano et al., 2012) and reports of gait ataxia. (Reich et al., 2016; Reich et al., 2017) Age differences between ET CONTROLS and DBS ON group should be considered given gait speed changes over time in ET (Roper et al., 2019), yet there was no statistical difference for stride velocities between groups after correction for multiple comparisons. With regard to gait speed as a general indicator of gait performance level ("sixth vital sign"), stride velocities in our control cohort were well within the range of those reported for healthy elderly subjects (Bohannon and Andrews, 2011; Lord et al., 2011), indicating unaffected gait in these individuals. Despite subjectively unaffected gait, clinical testing revealed a very mild impairment measured by SARA axial subscore in 6 patients from the control cohort, which is in line with previous reports on gait and balance in advanced ET.(Stolze et al., 2001).

After overnight withdrawal of unilateral DBS, a reduction of axial symptoms as assessed by the SARA score was observed, paralleled by a

reduction of variability of spatiotemporal gait parameters. Both changes were not present instantly after unilateral cessation of DBS but only after a prolonged withdrawal interval of at least 10 h. Consistent with previous work from our group (Kroneberg et al., 2019b), stride length variability was increased in patients with gait disturbances compared to controls. Moreover, clinical improvement of gait was paralleled by normalization of this gait parameter when DBS settings were changed, thus representing dynamic changes over repeated measurements within the same group following the intervention suggesting a causal relation to DBS. At the same time, the preservation of tremor control for the dominant hand was illustrated by lateralized TRS subscores that did not show a significant increase, indicating preserved functionality of the dominant hand over the course of the diagnostic intervention. On the long term, 7 of the 10 patients reported here were selected for reprogramming of DBS parameters with shorter pulse widths. Two of the remaining patients received programs allowing for self-administration of unilateral DBS as required. In line with previous work from our group (Kübler et al., 2021) highlighting a dissociation of adverse effects and their impact on activities of daily living, none of the patients opted for a chronic decrease of tremor control over improvement of gait.

4.1. Reversibility of gait disturbances

Our results add to previous studies demonstrating reversibility of gait abnormalities after bilateral withdrawal of DBS. Prior reports (Reich et al., 2016) (Kroneberg et al., 2019b) have applied withdrawal intervals of 72 h which required hospitalization and staff - support for activities of daily living. This may not be generally practicable due to limited hospital capacities, resulting costs or lack of coverage from health insurers for such interventions. Investigating short intervals of DBS cessation, Roemmich and colleagues (Roemmich et al., 2019) reported no improvement of gait performance one hour after DBS deactivation. In their study, the subgroup of patients with gait deterioration showed decreased step length and walking speed as well as increased step time with both ON and OFF DBS when compared to pre-operative measures.

Similarly, in our cohort, patients with gait disturbances showed shorter stride length and reduced stride velocity compared to the ET CONTROLS, though not statistically significant. Yet, the degree of stride length variability in our patients with gait disturbances was at comparable level to that found by Roemmich et al. Increased variability of lower limb ranges of motion have been reported as a kinematic feature in patients with ET and impaired gait ON DBS, consistent with an increased CoV of shank RoM in our cohort. (Fasano et al., 2012).

Congruent with kinematic assessments following stimulation withdrawal over 3 days (Kroneberg et al., 2019b), the variability of stride length and RoM of shanks were sensitive to modulation towards renormalization after overnight withdrawal of unilateral DBS. As mentioned and confirming the data from Roemmich et al., these changes could not be detected instantly after deactivating DBS corresponding to the non-dominant hand, pointing out the importance of extended withdrawal intervals.

Given the prolonged washout of ataxic symptoms after deactivation of DBS seen in our cohort as well as other studies (Kroneberg et al., 2019b; Reich et al., 2016) it is likely that adaptive mechanisms and neuroplasticity may be involved. The sustained persistence of ataxia well after deactivation may also be one reason why stimulation induced gait disturbances have possibly been underdiagnosed in studies where gait changes were attributed to other pathologies such as microlesion effects (Roemmich et al., 2019). In this regard it is important to note that new ablative therapy approaches (focused ultrasound) producing a permanent lesion in the same target area as DBS may also cause side effects such as gait disturbances. The lack of possibility for later adaptation can lead to permanent disability especially in bilateral approaches (Jackson et al., 2021).

4.2. Quantitative gait assessment in the management of stimulation-induced gait disorders

Differentiating stimulation-induced and therefore reversible gait disturbances from irreversible etiologies is an essential prerequisite to guide therapeutic strategies. Quantitative kinematic assessment of gait may provide key information additive to clinical assessment and should therefore be routinely used in the management of patients with gait difficulties following DBS. Moreover, the use of the SARA score has not been validated for patients with ET although it has been used in various studies, and patients with ET exhibit a gait disorder qualitatively similar to diseases with cerebellar pathology(Rao and Louis, 2019). Nevertheless, kinematic assessment allows additional quantitative characterization of the gait disorder. The gait disorder occurring as a side effect of DBS or due to supratherapeutic simulation amplitudes has been reported to be associated with increased variability of spatiotemporal gait parameters(Fasano et al., 2010) (Kroneberg et al., 2019b; Roemmich et al., 2019; Roemmich et al., 2013), which can be conveniently assessed using quantitative methods (Kroneberg et al., 2019a), but may be difficult to capture with qualitative or semiquantitative clinical scores. Although further studies must focus on refining assessments and parameters that are sensitive and specific to stimulation withdrawal, we have repeatedly (Kroneberg et al., 2019b) identified the variability of stride length as a parameter susceptible to modulation and showing a tendency towards normalization after stimulation withdrawal. In contrast, parameters representing the independent gait domain "rhythm"(Lord et al., 2012), such as cadence and stride time showed no consistent change after overnight stimulation withdrawal despite an increase instantly after DBS deactivation. In line with this observation, these parameters have not been discriminative of the gait disorder induced by DBS in other studies. (Fasano et al., 2012).

Thus, our findings suggest that a unilateral stimulation withdrawal together with quantitative kinematic assessment may be a useful clinical tool in outpatient or ambulatory settings for the management of patients with gait disturbances following DBS who cannot be hospitalized for a multi-day withdrawal of stimulation for personal or economic reasons. Kinematic assessment may further elucidate subtle changes of gait performance that may not be detected by commonly used semiquantitative clinical scores. Unlike a clinical examination, kinematic parameters can be recorded independent from the clinical experience of the examiner, thus evading problematic inter- and interrater reliabilities at follow ups.

If the gait disorder can be classified as reversible and associated with DBS, further steps of the management include directional steering of the electric field, adjustment of pulse width and stimulation amplitudes to reduce inadvertent current spread into adjacent fiber tracts(Bruno et al., 2021) or enlarge the therapeutic window (Choe et al., 2018; Moldovan et al., 2018; Reich et al., 2017). If quantitative kinematic assessment shows a clear improvement of characteristic gait parameters after withdrawal of stimulation, this may even justify efforts of using adapter kits to connect pulse generators and electrodes from different manufacturers(Soh et al., 2018) to allow for programming of shorter pulse widths. Ultimately, unilaterally deactivated DBS may be used as a chronic or selectable programming setting when aforementioned measures are insufficient to reduce stimulation induced gait impairment.

4.3. Anatomical correlates

The etiology of stimulation-induced gait disturbances is not fully understood to date. Stimulation amplitudes above therapeutic levels ('supra-therapeutic') have been found to worsen gait and balance (Fasano et al., 2010; Fasano et al., 2012) and induce ataxic movement trajectories of upper extremities (Groppa et al., 2014). From decomposition of strength-duration-relationships for tremor alleviation and dysmetria as a surrogate of ataxia, Groppa and colleagues(Groppa et al., 2014) concluded that effects could be mediated by axonal populations with different chronaxies. Specifically, the authors concluded that tracts

within the cerebello-rubro-spinal system with varying thickness and degrees of myelination could be involved. Correspondingly in this study, fiber filtering of axonal pathways that are connected to VTAs and associated with a reduction of stride length variability, hints to fibers of the superior cerebellar peduncle following the course of DRTT, passing through the red nucleus. As previously suggested by Groppa et al., we speculate that inadvertent perturbance of the rubro-olivo-cerebellar system and the cerebello-rubro-spinal system along with modulation of the dentato-thalamo-cortical system may contribute to the manifestation of gait disturbances. In a recent cohort study, gait disturbances were reported to occur more frequently in bilateral DBS and only with stimulation in the posterior subthalamic area (PSA), (Kim et al., 2021) which contains cerebellothalamic and pallidothalamic fibers.(Gallay et al., 2008b). Cerebellar involvement has further been suggested by imaging studies using FDG PET showing an association of metabolic changes in the cerebellar vermis with the occurrence of gait ataxia (Reich et al., 2016) as well as an investigation of functional connectivity patterns of patients with ataxia (Al-Fatly et al., 2019).

Innovative methods used to model discriminative fiber tracts (Irmen et al., 2020; Li et al., 2020) from DBS targets depend on much larger samples than available for this study or data from multiple centers for cross-validation of identified pathways. Since in our study we focused on clinical assessment rather than exploring pathway-specific activation patterns for gait disturbances, we only provide a visualization of the distribution of active contacts in relation to surrounding anatomical structures and pathways that connect to their respective VTAs and therefore might play a role in the pathophysiology of gait disturbances following VIM DBS. In addition to DRTT, bundles of the corticospinal/corticopontine, motor hyperdirect pathway and pallidosubthalamic pathway were connected to the VTAs of the cohort and may hypothetically also contribute to a perturbation of motor performance. The cerebellar cortex receives massive projections from pyramidal neurons of the motor cortex via the pontine nuclei and projects back via deep cerebellar nuclei and core-thalamic nuclei. Pyramidal neurons further receive input from the basal ganglia via matrix thalamic nuclei distributed to a wider array of cortical regions, thus injecting an "element of randomness" in the otherwise deterministic, feed-forward processing mode of the cerebellar loop.(Shine, 2021) Future models for the pathophysiology of gait disturbances following DBS may further investigate the role of these projections.

Distribution of the active contacts of patients with gait disability show large spatial overlap with a previously published cohort without documented gait pathology (Al-Fatly et al., 2019), yet slight differences of distribution of active contacts in y-dimension with a more anterior position of contacts associated with gait disturbances. Surrounding pathways include cerebellothalamic, corticospinal, motor hyperdirect pathway and pallidosubthalamic pathways as possible candidates involved in the development of gait disturbances. The atlas of axonal pathways used here (Petersen et al., 2019) represents the consensus of expert knowledge in the field and describes the spatial course of thin fibers that are otherwise not identifiable (i.e. could not be reconstructed from patient specific diffusion MRI data). Still, the set of tracts does not account for individual anatomical differences and variability.

One factor contributing to an inadvertent activation of tracts other than the DRTT might be habituation to the tremor suppressive effect (Fasano and Helmich, 2019) of DBS which clinicians may address by increasing stimulation amplitudes. Hariz et al. report an increase of 64% for the stimulation amplitude after 12 months of DBS compared to the postoperative amplitude that initially was sufficient for tremor suppression.(Hariz et al., 1999) An increased stimulation amplitude would result in an increase of the stimulation volume(Butson et al., 2007) which has previously been attributed to inadvertent disruption of cerebellar inflow to the motor thalamus (Groppa et al., 2014) due to the high density of functionally segregated fibers running as cerebello-thalamo-cortical projections within the subthalamic area and the ventrolateral border of the thalamus(Gallay et al., 2008a).

Clearly, understanding the pathophysiology of gait disturbances associated with DBS in ET and involved neuroanatomical may ultimately refine standard procedures in the emerging field of ablative therapies using focused ultrasound in the same target area as DBS. Despite the obvious advantages of this non-invasive approach, lesions and side effects remain permanent (Jackson et al., 2021). The potential reversibility of side effects in DBS should therefore always be considered when selecting therapies for patients who are at risk for developing gait disability.

5. Conclusion

We have demonstrated that a unilateral stimulation withdrawal paradigm may suffice to reveal the reversibility of gait disturbances. As tremor control is preserved for the dominant hand, this approach may be applied both as a diagnostic as well as a therapeutic intervention in an outpatient clinical setting. Future trials should focus on refining and validating sensitive and specific physiomarkers of stimulation induced gait disturbances as well as assessments that facilitate differentiation of gait disorders.

Authorship statement

All authors state that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

CRediT authorship contribution statement

Daniel Kroneberg: Investigation, Writing – original draft, Visualization, Formal analysis. **Bassam Al-Fatly:** Formal analysis, Visualization, Writing – review & editing. **Tanja-Schmitz Hübsch:** Investigation, Writing – review & editing. **Florin Gandor:** Resources, Writing – review & editing. **Doreen Gruber:** Resources, Writing – review & editing. **Georg Ebersbach:** Resources, Writing – review & editing. **Andreas Horn:** Formal analysis, Writing – review & editing. **Andrea A. Kühn:** Conceptualization, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors state that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Appendix A. Supplementary data

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