Gait ataxia in essential tremor is differentially modulated by thalamic stimulation

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Patients with advanced stages of essential tremor frequently exhibit tandem gait ataxia with impaired balance control and imprecise foot placement, resembling patients with a cerebellar deficit. Thalamic deep brain stimulation, a surgical therapy for otherwise intractable cases, has been shown to improve tremor, but its impact on cerebellar-like gait difficulties remains to be elucidated. Eleven patients affected by essential tremor (five females; age 69.8 ± 3.9 years; disease duration 24.4 ± 11.2 years; follow-up after surgery 24.7 ± 20.3 months) were evaluated during the following conditions: stimulation off, stimulation on and supra-therapeutic stimulation. Ten age-matched healthy controls served as the comparison group. Locomotion by patients and controls was assessed with (i) overground gait and tandem gait; (ii) balance-assisted treadmill tandem gait and (iii) unassisted treadmill gait. The two treadmill paradigms were kinematically analysed using a 3D opto-electronic motion analysis system. Established clinical and kinesiological measures of ataxia were computed. During stimulation off, the patients exhibited ataxia in all assessment paradigms, which improved during stimulation on and worsened again during supra-therapeutic stimulation. During over ground tandem gait, patients had more missteps and slower gait velocities during stimulation off and supra-therapeutic stimulation than during stimulation on. During balance-assisted tandem gait, stimulation on reduced the temporospatial variability in foot trajectories to nearly normal values, while highly variable (ataxic) foot trajectories were observed during stimulation off and supra-therapeutic stimulation. During unassisted treadmill gait, stimulation on improved gait stability compared with stimulation off and supra-therapeutic stimulation, as demonstrated by increased gait velocity and ankle rotation. These improvements in ataxia were not a function of reduced tremor in the lower limbs or torso. In conclusion, we demonstrate the impact of thalamic stimulation on gait ataxia in patients with essential tremor with improvement by stimulation on and deterioration by supra-therapeutic stimulation, despite continued control of tremor. Thus, cerebellar dysfunction in these patients can be differentially modulated with optimal versus supra-therapeutic stimulation. The cerebellar movement disorder of essential tremor is due to a typical cerebellar deficit, not to trembling extremities. We hypothesize that

deep brain stimulation affects two major regulating circuits: the cortico-thalamo-cortical loop for tremor reduction and the cerebello-thalamo-cortical pathway for ataxia reduction (stimulation on) and ataxia induction (supra-therapeutic stimulation).

Keywords: ataxia; cerebellum; cerebellar loop; supra-therapeutic stimulation; deep brain stimulation

Abbreviations: DBS = deep brain stimulation; ICARS = International Cooperative Ataxia Rating Scale; TRS = Fahn-Tolosa-Marin Tremor Rating Scale

Introduction

Essential tremor is a slowly progressive movement disorder of yet unknown origin. Clinically, core symptoms of the disease are action and postural tremor of head and arms while voice, leg and trunk tremor is less prevalent (Deuschl *et al.*, 1998; Louis, 2005). In recent years, perception of essential tremor as a pure tremor disease has been challenged, because a subgroup of severely affected patients with essential tremor exhibit a broader spectrum of motor dysfunction, such as ataxia in reach-to-grasp hand movements (Deuschl *et al.*, 2000) and abnormalities of tandem gait (Stolze *et al.*, 2001).

Interestingly, kinematic features of upper limb movements in patients with essential tremor closely resemble abnormalities found in patients suffering from cerebellar disease, as targeted hand movements exhibit delayed deceleration, target overshoot and intention tremor (Deuschl *et al.*, 2000; Herzog *et al.*, 2007). During tandem gait, patients with essential tremor have increased frequency of missteps and lower-limb ataxia that are qualitatively indistinguishable from abnormalities in patients with cerebellar disease (Stolze *et al.*, 2001).

In line with animal studies (Botterrell and Fulton, 1938*a*, *b*; Chambers and Sprague, 1955*a*, *b*), cerebellar locomotor abnormalities in humans might be due to impaired balance, limb coordination or both. In some studies, impaired balance seemed to play a greater role (Palliyath *et al.*, 1998; Stolze *et al.*, 2002; Morton and Bastian, 2003; Ilg *et al.*, 2007), leading to the conclusion that leg coordination dysfunction might be of minor importance in ataxic gait. These paradigms, however, were relatively easy to perform and therefore might have failed to reveal all relevant cerebellar deficits. More complex gait paradigms, such as stepping onto visual targets (Armstrong and Marple-Horvat, 1996; Marple-Horvat and Criado, 1999; Crowdy *et al.*, 2000), might demonstrate that limb ataxia is more important than previously believed (Morton and Bastian, 2003).

Despite the description of Purkinje cell degeneration (Louis *et al.*, 2007), there is no evidence of gross cerebellar damage in essential tremor (Daniels *et al.*, 2006). As a counter argument to the hypothesis that essential tremor is a neurodegenerative disease, it has been proposed that symptoms of essential tremor are due to pathologic oscillations that interfere with cerebellar function. Consistent with this 'functional disturbance' hypothesis, deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (thalamic DBS) has been shown to efficaciously reverse symptoms of essential tremor. Accordingly, thalamic DBS not only suppresses tremor but also reduces the ataxic features of hand movements (Herzog *et al.*, 2007). However, some studies have anecdotally reported that increasing stimulation intensity above the usual therapeutic range (supra-therapeutic stimulation) can worsen ataxia (Benabid *et al.*, 1996; Kumar *et al.*, 2003; Pahwa *et al.*, 2006).

The consequences of thalamic DBS on gait performance in essential tremor are not yet clear. In the present study, we therefore examined the effect of thalamic DBS on balance while walking (attributed to the medial cerebellum), precise foot placement (attributed to the lateral cerebellum) and routine walking (probably involving multiple cerebellar zones). Furthermore, we characterized the consequences of normal versus supra-therapeutic stimulation on these three aspects of locomotion and compared the results with the performance of healthy control subjects. Based on the results of our study, we hypothesize that therapeutic thalamic DBS beneficially suppresses tremor and reduces ataxia, while supra-therapeutic stimulation increases ataxia, despite continued suppression of tremor.

Subjects and methods

Subjects

Eleven consecutive patients with essential tremor treated with bilateral thalamic DBS at our centre for medically intractable tremor participated in this study. Demographic and disease-related details of the patients are summarized in Table 1.

Entry criteria for this study were diagnosis of essential tremor according to the criteria of the Tremor Investigation Group and the consensus statement of the Movement Disorder Society Group (Deuschl *et al.*, 1998), a stable clinical response to thalamic DBS for $\geq$3 months, and complete mobility scoring 14/14 on the Rivermead mobility index (Collen *et al.*, 1991). Medications for the treatment of essential tremor (propranolol and primidone in the majority of cases) were allowed since they have been previously demonstrated not to interfere with the gait performance of patients with essential tremor (Stolze *et al.*, 2001).

Ten age- and gender-matched individuals (four females), with a mean age of 67.3 $\pm$ 5.0 years, served as healthy controls. Body size, weight and leg length were not significantly different from values in both patient groups. Healthy controls underwent a full clinical neurological examination to exclude neurological disease and gait impairment.

Surgical procedure

The surgical procedure has previously been described in detail (Herzog *et al.*, 2007). In the present essential tremor patient group, based on intraoperative mapping with $\leq$5 microelectrodes, the permanent

Table 1 Demographic and clinical data of patients with essential tremor and healthy controls

Case	Gender	Age (years)	Disease duration (years)	Follow-up after DBS (months)	Lower limb tremor	Tremor rating scale (Part A + Part B; max 116)			Oral therapy at latest visit (daily dosage)
						Pre-DBS	Post-DBS	Per cent improvement	
ET1	F	69	30	6	–	65	26	60.0	–
ET2	M	66	20	36	+	80	19	76.3	–
ET3	F	69	34	6	+	72	12	83.3	–
ET4	M	76	10	48	–	40	17	57.5	Primidone 100 mg, propranolol 40 mg
ET5	F	76	20	3	+	62	5	91.9	Primidone 250 mg, propranolol 120 mg
ET6	M	70	50	36	–	66	12	81.8	–
ET7	F	64	20	48	+	34	26	23.5	–
ET8	M	67	12	8	+	69	7	89.9	Gabapentin 1600 mg, metoprolol 95 mg, primidone 750 mg
ET9	F	72	22	54	–	62	34	45.2	Propranolol 80 mg
ET10	M	72	30	3	–	66	12	81.8	Primidone 250 mg, propranolol 160 mg
ET11	M	67	20	24	–	53	8	84.9	–
Mean ± SD	6M 5F	69.8 ± 3.9	24.4 ± 11.2	24.7 ± 20.3		60.8 ± 13.6	16.2 ± 9.2	70.6 ± 21.5	–
HC1	F	65	–	–	–	–	–	–	–
HC2	F	75	–	–	–	–	–	–	–
HC3	F	62	–	–	–	–	–	–	–
HC4	M	65	–	–	–	–	–	–	–
HC5	F	59	–	–	–	–	–	–	–
HC6	M	65	–	–	–	–	–	–	–
HC7	M	73	–	–	–	–	–	–	–
HC8	M	69	–	–	–	–	–	–	–
HC9	M	69	–	–	–	–	–	–	–
HC10	M	71	–	–	–	–	–	–	–
Mean ± SD	6M 4F	67.3 ± 5.0	–	–	–	–	–	–	–

Tremor rating scale score 'post-DBS' refers to the first follow-up visit following surgery (performed after 3–6 months).
F = female; M = male; HC = healthy control.

macroelectrode (model 3389, Medtronic, Minneapolis, MN, USA) was implanted into the following trajectories: 17/22 were implanted into the central trajectory, 3/22 into the medial and 2/22 into the posterior trajectory.

Evaluation of electrode position in stereotactic space

The stereotactic coordinates of each contact of the quadripolar macroelectrode related to the midpoint of the intercommisural line were calculated based on fusion of the preoperative stereotactic and postoperative MRI. The mean coordinates of the active contacts were $x = 11.2 \pm 0.8$ mm, $y = -6.1 \pm 1.3$, $z = -2.5 \pm 1.4$ mm for the right side and $x = -11.9 \pm 0.7$ mm, $y = -5.8 \pm 1.8$, $z = -1.4 \pm 1.2$ mm for the left side. Thus, we found that all the patients were stimulated below the thalamic border within the prelemniscal radiation according to anatomy of the Schaltenbrand-Wahren-atlas (Schaltenbrand and Wahren, 1977).

Tremor and ataxia rating scales

In patients with essential tremor, we assessed tremor severity using a modified version of the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) (Fahn *et al.*, 1988). On a 5-point scale (0–4), tremor was rated for axial body regions (face, voice, head and trunk) and bilateral upper and lower extremities, corresponding to items 1–9 of Part A of the TRS. Additionally, patients were requested to draw large and small Archimedes spirals and three straight lines (items 11–13 of Part B of the TRS, maximum 24). The maximum score of the total TRS was 104, with higher values indicating more severe tremor. TRS subscales for intention and postural tremor were calculated from items 5, 6, 8 and 9 (each subscale with a maximum of 16). Moreover, subscales for tremor in axial body parts (items 1–4 and 7; maximum 24), upper (items 5, 6, 11, 12 and 13; maximum 48) and lower extremities (items 8 and 9; maximum 24) were computed.

We rated the severity of ataxia using the International Cooperative Ataxia Rating Scale (ICARS), a 100-point ordinal scale that quantifies ataxia in four categories of movement: posture and gait, limb kinetics, speech and eye movements. Higher scores indicate increased impairment (Trouillas *et al.*, 1997).

Tremor recording

Six patients with essential tremor did not present with clinically visible tremor in their lower extremities. In these patients, we performed surface EMG recording to exclude subtle tremor activity within leg and paraspinal muscles that might influence gait performance. EMG

was recorded in stimulation off and on conditions while standing and performing tandem gait. Under each of these conditions, the EMG was bilaterally recorded for 30 s from lumbar paraspinal and gastrocnemius muscles using bipolar Ag-AgCl electrodes. EMGs were bandpass filtered between 50–350 Hz, full-wave rectified and digitized at 800 Hz.

Spectral analysis was performed using a standard mathematical algorithm implemented in a tremor analysis software (Lauk *et al.*, 1999). The EMG spectra were calculated between 1 and 30 Hz. Tremor peaks in the power spectra were tested for statistical significance using the methods described by Lauk *et al.* (1999).

Assessment of overground gait

Before treadmill analysis, gait speed of patients and healthy controls was measured during overground locomotion. Subjects were requested to walk a distance of 11 m at a freely selected comfortable speed. Gait velocity was calculated by measuring the time each subject needed to cover the distance (mean of two runs). As a measure of balance function (Bastian *et al.*, 1998), tandem gait was evaluated by requesting the subjects to walk 5.5 m by placing one foot exactly in front of the other on a red line. Subjects were instructed to walk safely rather than fast and with both arms close to the body to prevent compensating balance control strategies, like walking with horizontally outstretched arms. We assessed tandem gait velocity (mean of two runs) and number of missteps, which were defined as steps taken with the whole foot outside the bounds of the red line.

Assessment of treadmill gait

Gait analysis was performed on a motor-driven treadmill (Woodway, Weil am Rhein, Germany) of length 2.2 m and width 0.7 m. The treadmill speed was adjusted exactly to the subject's individual gait velocity measured during overground gait tasks for each stimulation condition.

All subjects performed two tasks: balance-assisted tandem gait (as a precision foot placement task) and unassisted uninterrupted gait.

Balance-assisted tandem gait was specifically designed to examine the foot trajectory of the swing limb with much less demand on balance than during overground unassisted tandem gait (Morton and Bastian, 2003). Previous studies have shown that even slight hand contact on a support surface significantly reduces postural sway due to various balance disorders (Holden *et al.*, 1994; Lackner *et al.*, 1999; Morton and Bastian, 2003). Therefore, all subjects performed the task while holding onto a rail bar with one hand, thus compensating disease-related balance dysfunction.

The balance-assisted tandem gait was recorded after a training period of 5 min. Afterwards, we assessed unassisted treadmill uninterrupted gait following another 5 min training period. During unassisted treadmill uninterrupted gait, subjects were instructed to let their arms swing freely and were allowed to walk with a spontaneously chosen step length and width.

Gait was recorded with an infrared movement analysis system (Qualisys, Sandvälen, Sweden) consisting of six infrared cameras and video processors (240 Hz sampling rate) connected to a computer. Seven infrared light-reflective spherical markers (1.8 cm diameter) were attached to specific points of each leg (anterior superior iliac spine, major trochanter, lateral thigh, knee joint, lateral malleolus, calcaneus, fifth metatarsal bone). During balance-assisted tandem gait, two additional markers were placed on the acromion of both shoulders for assessment of postural sway.

During these two tasks, two trials of 20 s duration were recorded at identical treadmill velocity. From these trials, 15–20 consecutive walking cycles were analysed offline. Using customized software (Stolze *et al.*, 1997), we calculated the following standard spatio-temporal gait variables: stride length, step width, gait cycle time and duration of swing phase. To quantify ataxia of gait, we computed an ataxia ratio. This ratio is an index of spatial regularity of recorded strides and was used previously for assessment of patients with essential tremor and cerebellar disease (Stolze *et al.*, 2001, 2002; Klebe *et al.*, 2005). The ataxia ratio was calculated based on the standard deviation (SD) of foot placement in all three room directions according to the following formula:

$$\frac{(\text{SD of step length} + \text{SD of step width} + \text{SD of step height})}{3}$$

In addition, the coefficients of variation (coefficient of variation) of gait cycle time (for unassisted uninterrupted gait) and swing phase duration (for balance-assisted tandem gait) were calculated to assess ataxia (Hausdorff *et al.*, 1997). Coefficient of variation was expressed as (SD/mean) $\times$ 100. To verify that the support bars provided sufficient stability during balance-assisted tandem gait, we estimated the coefficients of variation of shoulder excursions measured with infrared markers on the acromions. Foot-, hip-, knee- and ankle rotations were assessed during unassisted treadmill uninterrupted gait (Stolze *et al.*, 1997, 2001). For each joint, the maximum and minimum values, the range of motion, and coefficients of variation were computed.

Stimulation conditions

In patients with essential tremor, all above specified assessments (TRS, ICARS, overground and treadmill gait) were performed during three stimulation conditions: thalamic DBS on with chronically used parameters (Supplementary Table A), thalamic DBS off and supra-therapeutic DBS. The order of stimulation conditions was randomly chosen. Thalamic DBS was switched off 30 min before assessment of stimulation off. There were rest intervals of 30 min between the different stimulation conditions.

Supra-therapeutic stimulation was obtained by slowly increasing amplitude and, if needed, pulse width (Supplementary Table A) until proximal decomposition of the contralateral upper limb movements appeared during the finger to nose test. The severity of stimulation-induced ataxia was rated using ICARS (Trouillas *et al.*, 1997).

The following morning, six randomly chosen patients were additionally evaluated after a prolonged stimulation off condition of 12 h during the night to exclude the impact of so-called rebound tremor on gait performance. Rebound tremor is the clinical phenomenon of increased tremor immediately after a stimulator is turned off (Dowsey-Limousin, 2002).

Statistical analysis

For statistical analysis, we tested for normal distribution of variables using the Kolmogorov-Smirnov test. All variables except the kinematic variables were normally distributed. Values were expressed as mean $\pm$ standard error of the mean (except for clinical and demographic data, which were expressed as mean $\pm$ SD) or median (25th–75th percentile) according to data distribution.

We looked first at the stimulation effect in the essential tremor group: the influence of the factor 'stimulation condition' was explored by means of one-way ANOVA or Friedman ANOVA and Kendall Coefficient of Concordance for kinematic variables, and in case of significant effect (defined with a level of significance set at $P < 0.01$), *post hoc* comparisons were calculated using Student's *t*-test paired or Wilcoxon matched pair test for kinematic variables. Then, we compared essential tremor cases and healthy controls by using

one-way ANOVA, and in case of significant effect (defined with a level of significance set at $P<0.01$), *post hoc* comparisons were calculated using Dunnett's test, a tool specifically designed to compare different treatment approaches with a control group (Dunnett, 1955). Kinematic variables were compared with the Kruskal–Wallis one-way analysis of variance, and in case of a significant influence of the group factor on the dependent variables, *post hoc* Mann–Whitney U-tests were performed.

We used repeated measures of covariance (ANCOVA) to perform the correlation analyses between dependent variables (clinical and instrumental gait parameters), continuous predictors (disease duration and tremor scores) and the stimulation condition (stimulation off, stimulation on and supra-therapeutic stimulation) as the categorical factor. Statistica 7.0 (StatSoft, Tulsa, OK, USA) software was used for all statistical analyses. All *post hoc* tests were two-sided with a level of significance set at $P<0.05$.

Results

Clinical assessment of tremor and ataxia

One-way ANOVA showed a significant effect of the factor 'stimulation condition' on different sections of TRS ($P<0.001$). Specifically, thalamic DBS led to a $66.1\pm15.7\%$ reduction of the TRS in stimulation on ($P<0.001$, *t*-test paired) (Fig. 1A) compared with the stimulation off condition (Table 1). Intention and postural tremors were similarly improved (Fig. 1A and B). Supra-therapeutic stimulation also reduced tremor severity compared with stimulation off, but it worsened spiral drawing compared with stimulation off due to stimulation-induced ataxia (Fig. 1A).

No patient complained of gait difficulties or unsteadiness. Ataxia was objectively assessed with ICARS in patients and controls. Patients during the stimulation off and stimulation on conditions did not display any obvious cerebellar abnormalities except for the items assessing intention tremor and spiral drawing. In contrast, supra-therapeutic stimulation induced clinically visible limb ataxia despite reducing tremor severity. Therefore, one-way ANOVA showed a significant effect of the factor 'stimulation condition' on ICARS total score and ICARS item 10 (decomposition and dysmetria of the upper limbs, $P<0.001$) but not on items 5 and 6 (body sway with eyes open or closed, $P>0.06$). *Post hoc* analysis revealed that ICARS total score (17.9 ± 6.2) was significantly higher than during stimulation on (10.8 ± 5.9, $P=0.01$, *t*-test paired), and ICARS item 10 (decomposition and dysmetria of the upper limbs) was significantly increased to 1.0 ± 0.6 and 1.3 ± 0.6 for the right and left upper extremities ($P=0.01$, *t*-test paired).

Tandem gait

In an earlier study (Morton and Bastian, 2003), 'balance deficit' and 'leg-placement deficit' (lower limb ataxia) were found to represent different aspects of cerebellar gait ataxia. Therefore, we assessed the effect of thalamic DBS on both aspects.

Overground tandem gait

Number of missteps and velocity in overground tandem gait were evaluated as measures of dynamic balance. One-way ANOVA revealed a significant effect of the factor 'stimulation condition' on the number of missteps in the patient group ($P<0.005$). Stimulation on significantly reduced the number of missteps compared with stimulation off and supra-therapeutic stimulation ($P<0.01$, *t*-test paired; Fig. 2). Healthy controls had a significantly lower number of missteps compared with patients with essential tremor during all three stimulation conditions ($P<0.001$, one-way ANOVA; $P<0.01$ as compared with each stimulation condition, Dunnett's test; Fig. 2). A significant effect on velocity was found for the 'stimulation condition' within the patients ($P<0.01$, one-way ANOVA): the mean overground velocities of patients

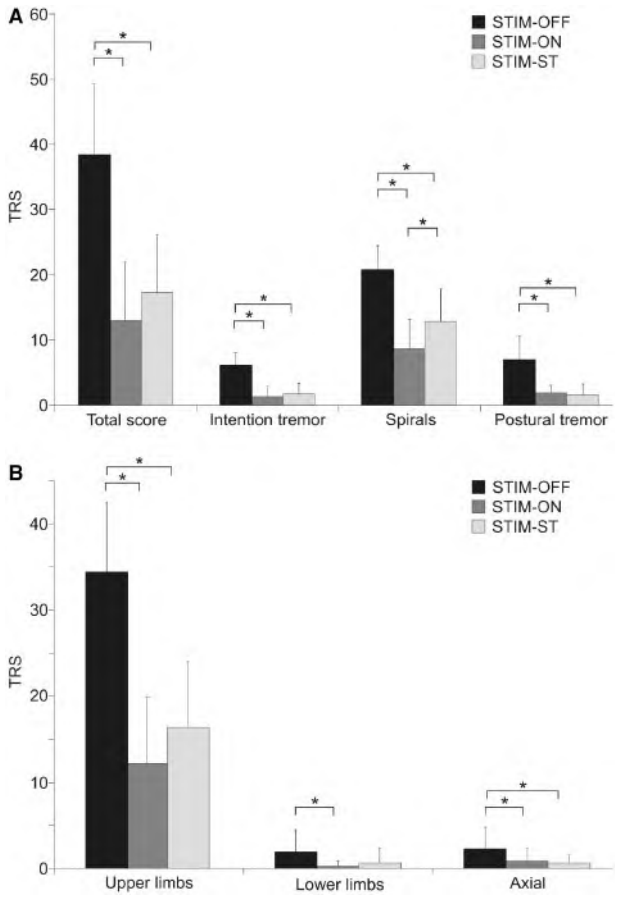

Figure 1 Thalamic DBS either using postoperatively optimized therapeutic stimulation parameters (STIM-ON) or supra-therapeutic stimulation (STIM-ST) was highly effective in reducing tremor when compared with no stimulation (STIM-OFF). Both types of stimulation significantly reduced the Tremor Rating Scale (TRS) total score and all subscores (tremor location-severity and drawings) except for the lower limbs during supra-therapeutic stimulation (STIM-ST). Supra-therapeutic stimulation effect did not significantly differ from stimulation on (STIM-ON) except for the drawing (spiral) scores. *$P<0.05$.

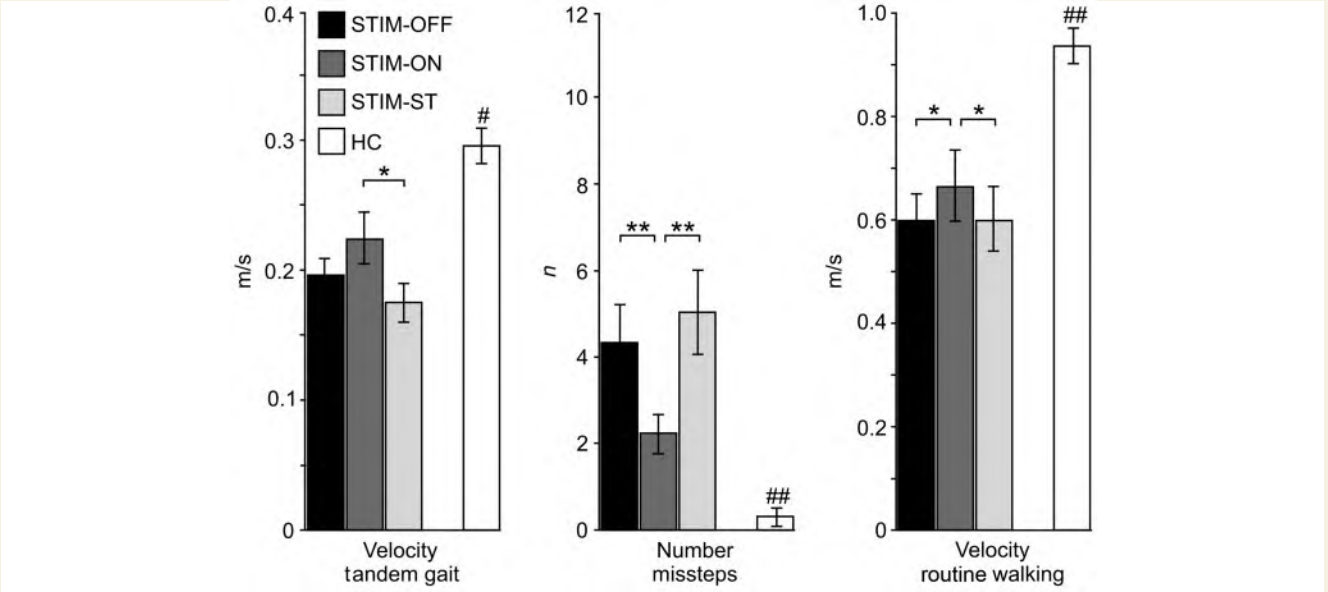

Figure 2 Overground walking in patients with essential tremor and healthy controls (HC): mean velocity during routine walking, during tandem gait and number of missteps during tandem gait. *$P<0.05$, **$P<0.01$; #significantly different from each stimulation condition of patients with essential tremor ($P<0.05$); ##significantly different from each stimulation condition ($P<0.01$).

with essential tremor were 0.20 ± 0.01 m/s, 0.22 ± 0.02 m/s and 0.18 ± 0.01 m/s for stimulation off, stimulation on and supra-therapeutic stimulation, respectively, with a significant difference between supra-therapeutic stimulation and stimulation on conditions ($P=0.02$; *t*-test paired; Fig. 2). Healthy controls had a significantly faster overground tandem gait than patients with essential tremor ($P<0.001$, one-way ANOVA; $P<0.05$ as compared with each stimulation condition, Dunnett's test; Fig. 2). Thus, patients with essential tremor were slower and had more missteps than healthy controls, and these measures of ataxia improved but did not completely normalize during stimulation on and severely worsened during supra-therapeutic stimulation.

Balance-assisted tandem gait on a treadmill

The role of lower limb ataxia was assessed with the balance-assisted tandem gait paradigm, specifically designed to examine the joint kinematics and foot trajectories of the swinging limb without the balance requirements needed for overground tandem gait (Morton and Bastian, 2003). All subjects held onto a bar to reduce the effect of impaired balance and with this aid, patients did not commit any missteps during all three stimulation conditions, indicating that the effect of impaired balance was strongly reduced.

However, the foot trajectories were still very abnormal in the patients, as illustrated in Fig. 3. These foot trajectories moved in a straight line when the foot was in contact with the treadmill (positive foot transport in Fig. 3), followed by motion in a half-circle during the active swing phase of each step. Healthy controls exhibited very little variability in foot trajectories. By contrast, the foot trajectories of patients with essential tremor were highly variable (ataxic) during stimulation off, thereby confirming our previously published study (Stolze *et al.*, 2002). During stimulation on, foot trajectories improved and were indistinguishable from controls in some patients. The trajectories became ataxic again in the supra-therapeutic stimulation condition.

These abnormalities were quantified with the ataxia ratio and the coefficient of variation of the swing phase. A significant effect on these variables was found for the factor 'stimulation condition' in the patient group ($P<0.01$, one-way ANOVA). *Post hoc* analysis revealed that during stimulation on, the ataxia ratio and the coefficient of variation during swing phase were significantly lower than during stimulation off and supra-therapeutic stimulation ($P<0.01$, *t*-test paired; Fig. 4). Interestingly, the ataxia ratio and the coefficient of variation of swing phase were not different between patients with essential tremor during stimulation on and healthy controls, but patients with essential tremor showed significantly higher values for both parameters during stimulation off and supra-therapeutic stimulation ($P<0.01$, one-way ANOVA; $P<0.05$ as compared with each stimulation condition, Dunnett's test; Fig. 4). Thus, the patients with essential tremor exhibited ataxic foot trajectories that improved to almost normal values during stimulation on, but this ataxia returned during supra-therapeutic stimulation.

Unassisted uninterrupted gait on a treadmill

The patients with essential tremor had no gross abnormalities of gait by clinical exam (Stolze *et al.*, 2001). However, subtle abnormalities may escape routine clinical observation.

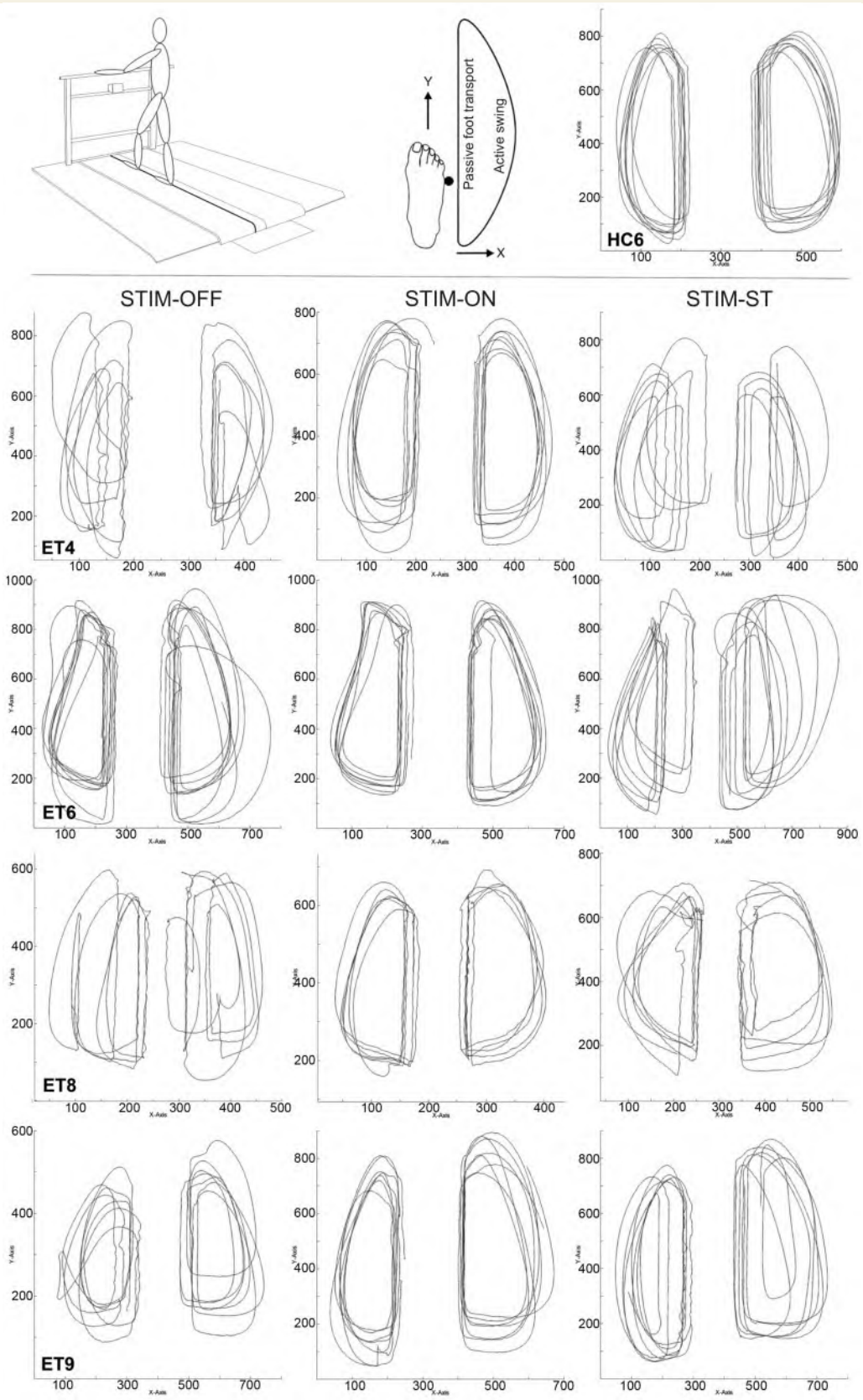

Figure 3 Motion of markers attached over the distal head of the fifth metatarsal bone of each foot, viewed from above (see schematic drawing at the top) for healthy controls (HC) and patients with essential tremor (ET). Recordings were made during tandem walking on the treadmill for 20 s. Note and the variable ataxic foot movements in essential tremor during stimulation off (STIM-OFF) and supra-therapeutic stimulation (STIM-ST) and relative normalization during stimulation on (STIM-ON).

During unassisted uninterrupted gait on the treadmill, patients with essential tremor walked significantly slower than healthy controls, irrespective of the stimulation condition ($P<0.001$, one-way ANOVA; $P<0.01$ as compared with stimulation off and supra-therapeutic stimulation, Dunnett's test; Fig. 2). In the patient group, the factor 'stimulation condition' did not significantly influence velocity, stride length, step width or coefficient of variation of cycle duration (Table 2).

For patients with essential tremor, thalamic DBS significantly influenced the range of motion within the ankle joint, with an increase during stimulation on [23.6° (19.0–28.4°)] compared with stimulation off [21.1° (16.7–27.2°), $P<0.001$] and supra-therapeutic stimulation [21.5° (16.8–24.8°), $P<0.001$]. In addition, supra-therapeutic stimulation significantly increased range of motion variability of foot, ankle and knee joint (Fig. 5). No significant differences were found when comparing patients with essential tremor and healthy controls except for range of motion variability of knee joint, which was significantly higher in essential tremor during supra-therapeutic stimulation (Fig. 5).

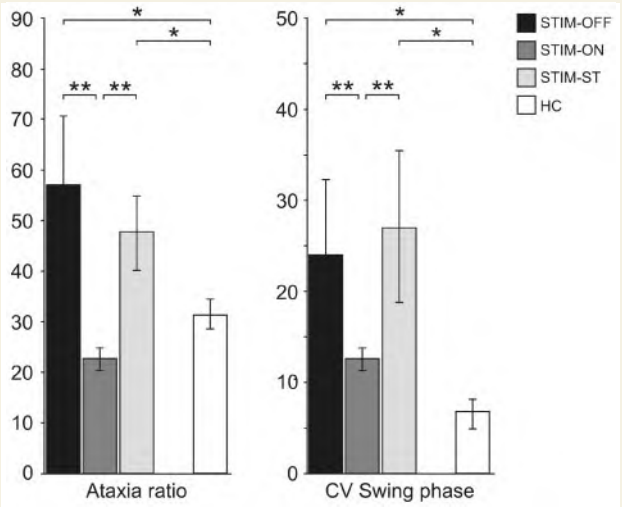

Figure 4 Mean ataxia ratio and coefficient of variation (CV) of swing phase measured during the tandem gait task on the treadmill revealed an increase in spatial and temporal variability of foot movements of patients with essential tremor during stimulation off (STIM-OFF) and supra-therapeutic stimulation (STIM-ST). Stimulation on (STIM-ON) significantly reduced variability of both variables leading to values within the range of healthy controls (HC). *$P<0.05$; **$P<0.01$.

Assessment of confounders

We examined tremor as a possible confounder in our study. First, we hypothesized that a more pronounced tremor would cause a more severe ataxia. To exclude ataxia as the result of a rebound effect due to cessation of stimulation, we examined six patients following a 12 h discontinuation of stimulation. There was no significant difference in motor performance during overground and treadmill gait tasks compared with the assessment following 30 min of stimulation discontinuation (Supplementary Table B). Secondly, our patients did not have overt trunk or leg tremor, but to exclude a contribution of a subtle tremor, we assessed six patients with essential tremor during standing and tandem gait with surface EMG recording and spectral analysis of paraspinal, quadriceps and hamstring muscles. These recordings did not

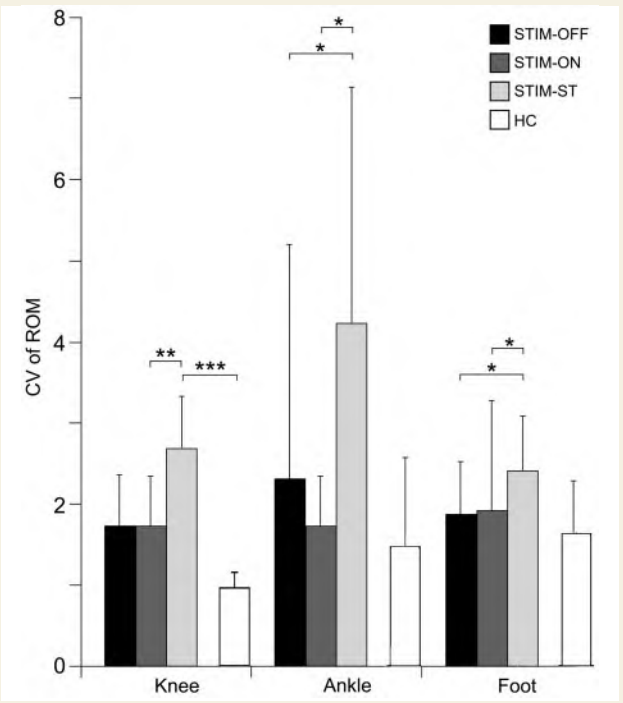

Figure 5 The coefficient of variation (CV) of the mean range of motion (ROM) of the lower limb joints was significantly increased in patients with essential tremor during supra-therapeutic stimulation (STIM-ST). Values are medians +75° percentile. Significant differences are indicated: *$P=0.04$; **$P=0.02$; ***$P=0.005$. HC = healthy controls.

Table 2 Main parameters during unassisted treadmill uninterrupted gait

	Essential tremor (stimulation off)	Essential tremor (stimulation on)	Essential tremor (supra-therapeutic stimulation)	Healthy control
Stride length (cm)	69.0 ± 30.5	74.4 ± 24.9	73.4 ± 24.8	82.2 ± 23.8
Step width (mm)	147.4 ± 0.3	132.1 ± 0.4	161.2 ± 0.3	125.5 ± 0.3
CV-cycle duration	13.9 ± 3.2	12.5 ± 2.4	15.8 ± 4.0	8.1 ± 1.2

No statistically significant differences were found in essential tremor cases during the different stimulation conditions and between patients and healthy controls except for velocity (Fig. 2).
CV = coefficient of variation.

reveal a statistically significant spectral (tremor) peak in the 3–16 Hz band during any stimulation condition. We also performed Fourier analysis on the 3D foot trajectories and found no spectral peak compatible with tremor.

In order to exclude a significant involvement of compensating postural trunk movements during the balance-assisted tandem gait on the treadmill, we simultaneously measured the coefficient of variation of shoulder trajectories. Coefficient of variation of shoulder trajectories did not differ during the three stimulation conditions (*t*-test paired; data not shown). Finally, primidone did not bias the effects induced by DBS since the main parameters under analysis behaved in the same manner in the subgroup of seven patients with essential tremor not taking the drug (data not shown).

Correlation analysis

The ANCOVA correlation analysis between disease duration and the main gait parameters showed significant correlations with uninterrupted gait velocity ($\beta = 0.45$, $P < 0.01$), tandem gait velocity ($\beta = 0.49$, $P < 0.01$) and number of missteps ($\beta = 0.48$, $P < 0.005$). The next question was whether gait abnormalities in essential tremor and the DBS effect were related to any specific clinical or stimulation-related features of essential tremor. ANCOVA analysis showed that velocity, number of missteps and ataxia ratio during overground and treadmill tandem gait correlated positively with the severity of intention tremor (Table 3). The analysis of unassisted uninterrupted gait revealed that velocity, step width and kinematic features of the ankle joint all positively correlated with severity of intention tremor (Table 3). This is evidence that the intention tremor is a valid surrogate parameter for the ataxic gait abnormalities.

Discussion

Abnormalities of gait in patients with essential tremor: a pancerebellar ataxia

A cerebellar gait disorder in advanced essential tremor has been shown with simple clinical tests (Singer *et al.*, 1994; Hubble *et al.*, 1997) and was later confirmed with more sophisticated laboratory tests (Stolze *et al.*, 2001; Klebe *et al.*, 2005; Parisi *et al.*, 2006; Earhart *et al.*, 2008; Kronenbuerger *et al.*, 2009). Also, impaired balance in essential tremor has been shown to produce increased body sway (Bove *et al.*, 2006) and decreased functional mobility, performance and self-reported measures of stability (Parisi *et al.*, 2006). These abnormalities are independent of tremor severity and distribution (Bove *et al.*, 2006; Parisi *et al.*, 2006; Kronenbuerger *et al.*, 2009).

We demonstrated a generalized cerebellar-like gait disorder in our patients with the stimulation off condition. Invisible trunk tremor, subtle leg tremor and compensation for abnormal trunk movements were excluded as possible causes of these gait abnormalities. Therefore, we feel confident in suggesting that our data reflect true cerebellar ataxia that is not confounded by another movement disorder.

Physiological studies in monkey and man (Diener *et al.*, 1984; Ito, 1984; Hallett and Massaquoi, 1993; Armstrong and Marple-Horvat, 1996; Cooper *et al.*, 2000; Ilg *et al.*, 2007) have provided evidence that the medial and intermediate zones of the cerebellum are mainly responsible for gait and balance disturbances. Recently, balance and leg coordination have been separated as two different contributions to gait ataxia (Morton and Bastian, 2003). We demonstrated a significant improvement in tandem gait when patients were allowed to reduce the contribution of impaired balance by holding on to a handrail while tandem walking on a treadmill. However, there remained a significant amount of lower limb ataxia during balance-assisted treadmill walking, so both impaired balance and limb ataxia are important in the gait disturbance of essential tremor. Standardization of gait velocity across subjects and conditions might have more specifically examined gait effects caused by disease and stimulation conditions. However, we preferred self-chosen rather than externally imposed walking speed to assess compensation mechanisms such as reduced velocity and increased step width (Stolze *et al.*, 2002; Morton and Bastian, 2007).

The cerebellum has been separated into three functional divisions: the vestibulocerebellum, spinocerebellum and cerebrocerebellum (Ito, 1984; Barlow, 2002). All three divisions appear to function abnormally in essential tremor. Impaired vestibulocerebellar function is reflected by subtle abnormalities of eye movement (Helmchen *et al.*, 2003). Gait abnormalities (Stolze *et al.*, 2001; Earhart *et al.*, 2008; Kronenbuerger *et al.*, 2009) and eye-blink

Table 3 Effect of tremor and stimulation on clinical and instrumental features of normal and tandem gait

	Tandem gait				Balance-assisted tandem gait				Unassisted treadmill uninterrupted gait							
	Velocity		Missteps		Ataxia score		CV-swing phase		Velocity		Step width		Ankle ROM		CV-Ankle ROM	
	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P
TRS: lower limb subscore	−0.24	0.067	−0.13	0.406	0.04	0.807	0.12	0.537	−0.20	0.177	−0.14	0.267	−0.25	0.117	−0.25	0.144
TRS: axial subscore	−0.03	0.825	0.01	0.946	0.26	0.106	0.31	0.129	−0.14	0.385	0.06	0.659	−0.03	0.848	−0.24	0.191
TRS: intentional subscore	**0.59**	**0.010**	**0.74**	**<0.001**	**0.61**	**0.025**	0.43	0.196	**0.66**	**0.015**	**0.86**	**<0.001**	**0.72**	**0.013**	**0.62**	**0.045**
TRS: postural subscore	**0.64**	**0.007**	0.28	0.293	0.08	0.773	−0.03	0.936	0.45	0.085	0.14	0.505	0.33	0.223	0.44	0.144
Stimulation condition		**<0.001**		**<0.001**		**0.044**	−0.29	0.131		**<0.001**		**<0.001**		**<0.001**		**0.001**

ANCOVA with the following dependent variables: velocity and missteps during tandem gait, ataxia score and coefficient of variation (CV) of swing phase duration during the alternating foot placement task, and velocity, step width, ratio single/double support time, ataxia ratio, ankle range of motion (ROM) and coefficient of variation of ankle range of motion during routine walking. TRS with its various subscores and stimulation conditions were covariates. Significant impact of covariates is indicated with bold font.

conditioning deficits (Kronenbuerger *et al.*, 2007) are consistent with vestibulo- and spinocerebellar impairment. Impaired reaching (Deuschl *et al.*, 2000) and hand function (Farkas *et al.*, 2006) suggest spino- and cerebrocerebellar dysfunction. Therefore, the available data are consistent with pancerebellar dysfunction in essential tremor.

The effect of thalamic neurostimulation on gait performance in patients with essential tremor

The most important result of our study is that suppression of tremor with stimulation on is combined with an improvement of ataxia and that ataxia returns without recurrence of tremor when stimulating excessively (supra-therapeutic stimulation) in the same place.

In this study, stimulation on significantly reduced the temporospatial variability in lower limb movement, which is a widely accepted measure of cerebellar ataxia. A similar improvement of upper limb ataxia of patients with essential tremor with thalamic DBS has been previously shown for reach-to-grasp hand movements (Herzog *et al.*, 2007). Our present results demonstrate first that the ataxia-reducing effect of neurostimulation is not limited to the upper extremities but involves the lower limbs as well. Ataxia is therefore a separate component of essential tremor that can be influenced by neurostimulation, irrespective of the affected body part. In addition, the neurostimulation effect on ataxia is independent of coexisting tremor. We feel confident with this conclusion because surface EMG in calf and paraspinal muscles did not reveal subclinical tremor, despite the presence of ataxia. Patients with essential tremor walked in a more physiological manner with stimulation on. Supra-therapeutic stimulation re-established the cerebellar-like movement profile but did not produce a return of tremor, as measured by the total TRS.

The lack of blinding might have biased our results. However, the majority of outcomes have been objectively measured under highly standardized conditions and, due to the reappearance of tremor, the patients were only able to detect the stimulation off condition.

Our study is at variance with a recent paper (Earhart *et al.*, 2008) reporting no significant impact of thalamic stimulation on the gait disorder of patients with essential tremor. However, their stimulating electrode was implanted more dorsally, and the stimulation site is therefore probably far away from the electrode position in our study. Another recent paper reported a reduction of missteps during tandem gait and improved ICARS gait score, but due to the small sample size (four patients with bilateral implants), these results did not reach statistical significance (Kronenbuerger *et al.*, 2009). A study using computerized posturography during quiet standing and support-surface motion revealed improved balance in patients with essential tremor treated with DBS (Ondo *et al.*, 2006). Concurrently, falls lessened with activation of the stimulator. These studies collectively support our interpretation that the postural instability in essential tremor is amenable to thalamic DBS, independent of the effect on tremor.

Pathophysiological implications

Our study confirmed the presence of subtle gait ataxia in patients with essential tremor and, for the first time, the gait ataxia of essential tremor was shown to be corrected by thalamic neurostimulation. The profound and independent influence of neurostimulation on ataxia and tremor is new and must be explained pathophysiologically. In particular, we must put forth a hypothesis that explains why advanced essential tremor causes a pancerebellar deficit; therapeutic stimulation suppresses tremor and cerebellar malfunction; and supra-therapeutic stimulation suppresses tremor but causes a return of cerebellar dysfunction.

Many investigators have proposed that essential tremor originates in the olivocerebellar system. This 'olivocerebellar hypothesis' of tremorogenesis is supported by many data summarized in a recent review (Elble, 2009). Rhythmic neuronal synchronization is believed to be conducted through the cerebellothalamic and cerebelloreticular fibres and from there to the cerebral cortex and spinal cord (Fig. 6A). The DBS electrode was located within the area prelemniscalis in our patients (Herzog *et al.*, 2007), beneath the thalamus in a zone of white matter containing cerebellothalamic and pallidothalamic fibres. Therapeutic stimulation of the cerebellothalamic fibres could mediate its beneficial effect on tremor and ataxia by interrupting rhythmic cerebellothalamic entrainment that is tremorogenic and that produces a functional impediment of normal neuronal traffic in Loop 1 of Fig. 6. Supra-therapeutic stimulation of the same fibre bundle is hypothesized to disrupt rhythmic tremorogenic activity and normal physiologic activity in Loop 1, which produces continued suppression of tremor with the return of ataxia.

The olivocerebellar hypothesis assumes that essential tremor originates in olivocerebellar oscillation, which may not be true. The genetic defects in essential tremor could cause more widespread neuronal oscillation in motor pathways and elsewhere. Furthermore, thalamic DBS suppresses tremor of many different aetiologies (Elble, 2009). Therefore, it is possible that the thalamocortical loop (Loop 2 in Fig. 6B) simply mediates the amplification of tremor and that DBS reduces deleterious oscillation within this loop and deleterious entrainment of other motor pathways. Excessive (supra-therapeutic) stimulation of this loop could impede the function of Loop 2 and other motor pathways, producing ataxia while still suppressing tremor.

In our study, stereotactic evaluation of the stimulating electrodes revealed localization of the most efficacious contacts within the subthalamic fibre tract of the prelemniscal radiation. The pallidothalamic (Tepper *et al.*, 2007) and cerebellothalamic (Herzog *et al.*, 2007) pathways are known to be in this subthalamic region, and other neighbouring structures could also be affected (Plenz and Kital, 1999; Middleton and Strick, 2000; Hoshi *et al.*, 2005). Nevertheless, our results suggest that the ventrolateral thalamus and its afferent inputs play critically important roles in the phenomena observed in our study (Fig. 6).

Our network models (Fig. 6) of DBS-induced tremor suppression, improved coordination and ataxia are supported by a number of previously published observations. For example, it has been shown that extensive synchronization between the cerebellum and motor cortex is of major functional importance in normal

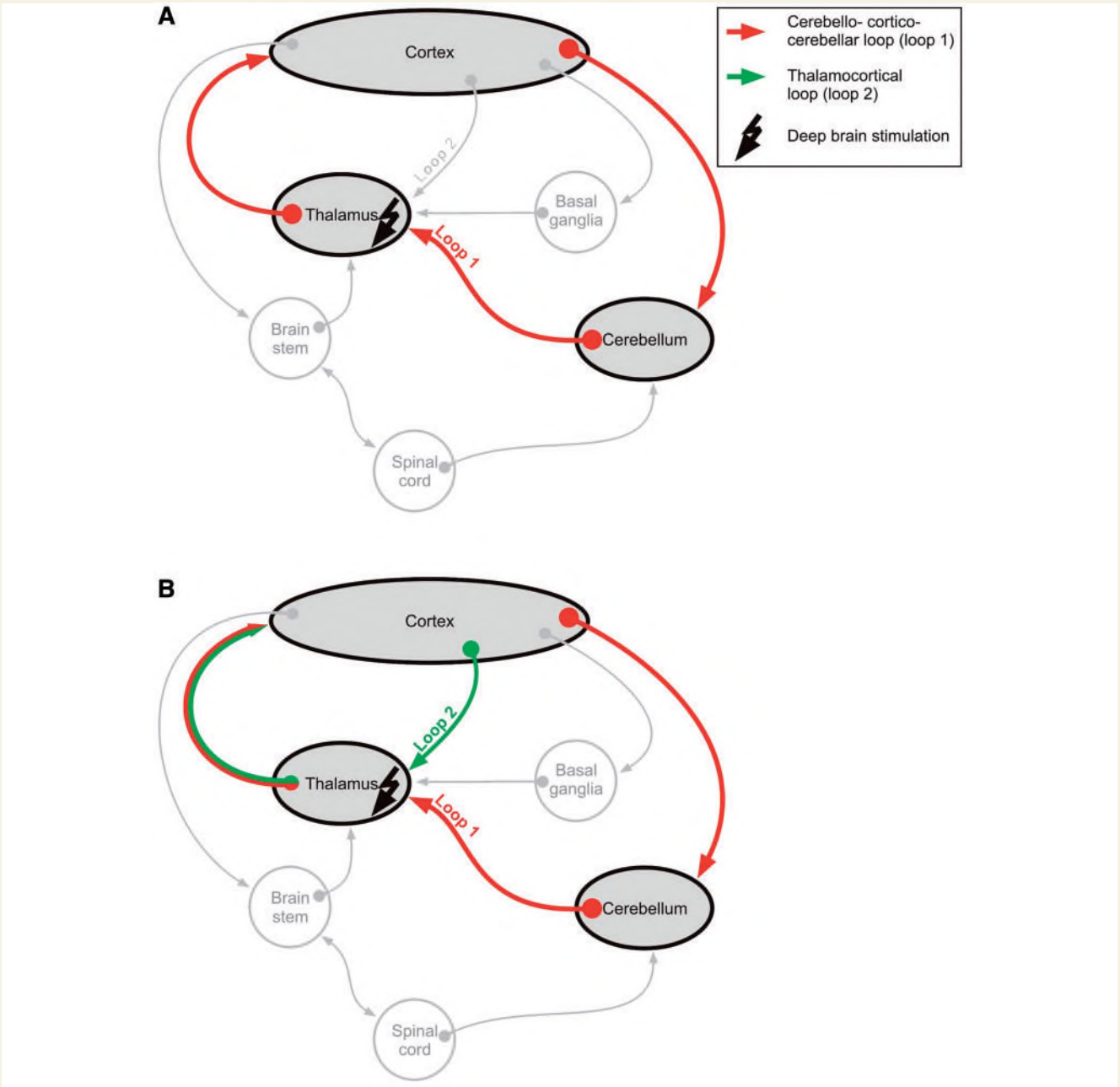

Figure 6 (**A**) The results of our study suggest that DBS reduces ataxia by reducing the functional impairment of cerebellar pathways. DBS within the thalamus/subthalamic fibre tract area could interrupt the tremorogenic oscillatory entrainment of the cerebello-cortico-cerebellar loop (loop 1), resulting in less tremor and more physiologic function of cerebellar pathways. (**B**) Alternatively, DBS at therapeutic ranges might beneficially modulate the thalamocortical loop (loop 2), which non-specifically amplifies tremor, regardless of its origin. Supra-therapeutic stimulation of either loop could produce ataxia by impeding normal function of the cerebello-cortico-cerebellar loop (loop 1).

sensory processing and execution of a precision grip (Schwarz and Thier, 1999; Soteropoulos and Baker, 2006). The superimposition of a pathological oscillatory signal (as in patients with essential tremor) might impede normal interaction between these structures, with the consequence of cerebellar-like deficits. Support for this hypothesis comes from an independent study in which 10–30 Hz transcranial magnetic stimulation caused a 5–8 Hz intention tremor in normal people (Topka *et al.*, 1999). The normalization of upper limb coordination and motor learning (Herzog *et al.*, 2007; Kronenbuerger *et al.*, 2008) with thalamic DBS in patients with essential tremor and the reduced tandem gait ataxia in these patients after alcohol intake (Klebe *et al.*, 2005) support a functional impairment of the cerebellum in essential tremor.

Additional support for our models comes from the observation that stimulation within the cerebellothalamic fibre tract favourably

modulates the ascending side of the cerebellocortical loop and, as a consequence, releases the motor cortex from pathological activity originating from the thalamus (Ceballos-Baumann *et al.*, 2001; Perlmutter *et al.*, 2002; Haslinger *et al.*, 2003; Fukuda *et al.*, 2004). The change in cortical activity might subsequently influence the descending side of the loop, which reaches the cerebellum through pyramidal tract collaterals (Ugolini and Kuypers, 1986), corticopontine fibres (Kawamura and Chiba, 1979; Ugolini and Kuypers, 1986) and strong cortico-rubro-olivary projections via the central tegmental tract (Nathan and Smith, 1982; Humphrey *et al.*, 1984; Schmahmann and Pandya, 1997; Middleton and Strick, 2000; Habas and Cabanis, 2006). Following this hypothesis, suppression (disruption) of the pathological signal within the ascending arm of the cerebellocortical loop might restore the physiological state of the system and thereby improve ataxic symptoms.

Finally, increased stimulation charge broadens the electric field radius and changes the composition of stimulated neuronal elements (Kiss *et al.*, 2002). This is likely to change the cortical stimulation effects. Indeed, a positron emission tomography study in patients with essential tremor (Haslinger *et al.*, 2003) has shown that variations in voltage of thalamic stimulation has differential effects in the thalamocortical circuitry: when therapeutic amplitudes are used, the cortical metabolic activity is reduced, whereas a further increase in the amplitude enhances it. Therefore, increased DBS charge might impose the abnormal ~130 Hz frequency on cerebellar pathways to such an extent that cerebellar function is impaired. The tremor-desynchronizing effect however is still maintained. Other effects of DBS in our patients cannot be excluded, such as a local effect on the thalamus causing contralateral ataxia (Boiten and Lodder, 1990; Melo and Bogousslavsky, 1992; Tanaka *et al.*, 1992; Lehericy *et al.*, 2001) or deafferentation of vestibular information to the cortex, as recently described in humans (Dieterich *et al.*, 2005; Zwergal *et al.*, 2008). Another possibility would be that the cerebellorubral fibres are activated in the supra-therapeutic stimulation condition, thereby contributing to the observed ataxia.

Clinical implications

We found a U-shaped correlation between stimulation strength and ataxia with optimal results at stimulation parameters of medium range and return of ataxia at parameters of high range. In other words, the beneficial effect of thalamic DBS on ataxic symptoms is limited to a narrow therapeutic window. This might explain disadvantageous consequences of thalamic stimulation reported by some studies including increased likelihood to fall (Pahwa *et al.*, 2006), impaired fine motor skills (Benabid *et al.*, 1996; Kumar *et al.*, 2003) and malfunctioning motor adaptation (Chen *et al.*, 2005). In these studies, the stimulation charges were significantly higher than in studies with improved cerebellar function: e.g. malfunctioning motor adaptation [3.4 ± 1.1 V, 139.9 ± 73.9 μs, 183 ± 7.8 Hz, (Chen *et al.*, 2005)] compared with reduced hand ataxia [2.5 ± 0.6 V, 72.0 ± 15.1 μs, 140.5 ± 16.7 Hz, (Herzog *et al.*, 2007)]; normalization of eye blink conditioning [2.7 ± 0.9 V, 98.2 ± 55.5 μs, 145.9 ± 27.5 Hz, (Kronenbuerger *et al.*, 2008)]; and no effect on gait performance [3.3 ± 0.9 V, 84.2 ± 26.9 μs, 181 ± 13.9 Hz (Earhart *et al.*, 2008)] compared with the improved gait in the present study (2.8 ± 0.8 V, 70.9 ± 20.2 μs, 165 ± 32 Hz). The parameters of beneficial versus detrimental stimulation and their relation to the anatomical site of stimulation need further study.

Conclusion

Therapeutic subthalamic stimulation improves and supra-therapeutic stimulation impairs particular components of gait ataxia in patients with essential tremor. The results of our study suggest that DBS reduces ataxia by reducing a functional impairment of the cerebello-cortico-cerebellar loop caused by abnormal tremorogenic entrainment of cerebellar pathways. Excessive DBS is hypothesized to disrupt normal neuronal traffic in this loop, resulting in a return of ataxia without tremor. This suggests that the complex and multi-component motor dysfunction of ataxia is amenable to the remote effects of focal neurostimulation.

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