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Specific influences of cerebellar dysfunctions on gait

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Cerebellar ataxic gait is characterized by unsteady movements and variable gait patterns. Previous studies have successfully identified pathological changes of balance-related gait parameters. However, it has been difficult to demonstrate deficits of joint coordination and the control of limb dynamics. This has motivated the hypothesis that cerebellar ataxic gait might be affected predominantly by balance impairments. We investigated the influences of different types of cerebellar dysfunction on the gait patterns of patients suffering from degenerative cerebellar disease (13 patients, five females, 50.4 ± 14.4 years). Walking patterns were quantitatively analysed combining standard gait measures and novel measures for the characterization of the spatial and the temporal variability of intra-joint coordination patterns. The temporal variability of gait patterns was significantly correlated with a subscale of the clinical ataxia scale (ICARS) that rates deficits of the control of limb dynamics and intra-limb coordination for goal-directed movements. This suggests that common cerebellar mechanisms might be involved in coordination during voluntary limb control and ataxic gait. The tested standard gait parameters correlated predominantly with clinical measures for balance-related abnormalities. These results imply that ataxic gait is influenced by both balance-related impairments and deficits related to limb control and intra-limb coordination. Applying the same analysis to gait patterns from patients with peripheral vestibular failure (six patients, four females, 47.8 ± 14.3 years) and Parkinson's disease (eight patients, two females, 60.7 ± 10.6 years), we found comparable abnormalities in balance-related gait parameters and general gait variability, but significantly lower increases of temporal variability. This implies that increased temporal variability of intra-limb coordination is a specific characteristic of cerebellar dysfunction, which does not arise for other movement disorders that also cause balance deficits and increased gait variability.

Keywords: cerebellum; locomotion; ataxic gait; gait variability; intra-limb coordination

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Introduction

Cerebellar ataxic gait is typically characterized by an instable stumbling walking path, increased step width and high variability of gait (Holmes, 1939; Hallett and Massaquoi, 1993; Diener and Dichgans, 1996; Morton and Bastian, 2004). Such variability might be caused by different factors: On the one hand, it might reflect that cerebellar disorders cause deficits of dynamic limb control and intra-limb coordination. On the other hand, this variability might be induced by deficits in balance control. A detailed understanding of the factors and specific deficits causing variability in ataxic gait is still lacking (Stolze *et al.*, 2002; Morton and Bastian, 2003; Morton *et al.*, 2004; Thach and Bastian, 2004).

Clinical studies addressing the question of how cerebellar ataxia affects ataxic gait have yielded partially conflicting results: Comparing cerebellar patients with normal controls, Palliyath *et al.* (1998) report significant changes for gait velocity and stride length, while Stolze *et al.* (2002) found almost no differences for the same gait parameters. Similarly, a number of studies report significant differences for the step width (Hudson and Krebs, 2000; Stolze *et al.*, 2002), while others did not (Palliyath *et al.*, 1998; Ebersbach *et al.*, 1999; Mitoma *et al.*, 2000; Morton and Bastian, 2003). Mitoma *et al.* (2000) divided their patient population into two groups with moderate and severe ataxia. Only for patients with severe ataxia they found

significant changes for several parameters, including step width, step length, speed and periods of ground support. Other studies report differences between patients and controls for gait parameters, like angle ranges, stance time or cadence (Palliyath *et al.*, 1998; Stolze *et al.*, 2002).

A recent study by Morton and Bastian (2003) tried to dissociate influences of balance deficits and voluntary leg coordination deficits on cerebellar ataxic gait. Based on their performance in a balance task and a leg-placement task, patients were assigned to two groups with dominantly balance-related and coordination-related impairments. Patients with dominant balance-related deficits showed significant deviations from normal controls for several gait parameters, including stride length and its variability as well as the peak angles of lower limb joints. Patients with coordination-related impairments did not show significant deviations from normal controls for all tested gait parameters except for a movement decomposition index (Earhart and Bastian, 2001; Morton and Bastian, 2003). This result has motivated the hypothesis that cerebellar ataxic gait might be predominantly influenced by balance impairments, while leg coordination impairments might have only a minor influence.

This hypothesis seems consistent with the fact that the control of walking is strongly dependent on pattern generators in the spinal cord (Grillner, 1975; Dietz, 1992, 2003; Duysens and Van de Crommert, 1998; Orlovsky *et al.*, 1999), and might thus be less influenced by higher centres, like the cerebellum, that are important for the control of goal-directed and visually guided movements (Armstrong *et al.*, 1997; Crowdy *et al.*, 2002; Morton and Bastian, 2003; Morton *et al.*, 2004). It seems also consistent with physiological studies showing that in animals the control of balance in stance and locomotion is dependent on the medial part of the cerebellum (Chambers and Sprague, 1955*a*, *b*; Dichgans and Diener, 1984; Thach *et al.*, 1992; Thach and Bastian, 2004), while the control of goal-directed movements and perturbed or visually guided walking is influenced by the intermediate and lateral parts of the cerebellum (Schwartz *et al.*, 1987; Marple-Horvat *et al.*, 1998; Marple-Horvat and Criado, 1999; Cooper *et al.*, 2000).

Other studies in cats, however, show that lesions of the intermediate cerebellum can induce impairments of limb dynamics during walking, e.g. resulting in hypermetria (Udo *et al.*, 1980; Yu and Eidelberg, 1983). This suggests that the cerebellum might be constantly involved in locomotion, e.g. by adjustment of intra- and inter-limb coordination patterns and the modulation of reflex patterns (Ito, 1984; Orlovsky *et al.*, 1999).

The difficulty to demonstrate coordination deficits in human ataxic gait raises the question whether standard measures from clinical gait analysis are sensitive enough for picking up the relevant changes. Applying methods, like 'angle–angle plots', that provide a qualitative description of the whole trajectory shape it has been possible to demonstrate qualitative changes in intra-limb coordination patterns of cerebellar patients, e.g. systematic abnormalities and increased variability of coordination patterns (Hallett and Massaquoi, 1993; Palliyath *et al.*, 1998; Stolze *et al.*, 2002). However, so far it remains unclear how far these abnormalities reflect specific cerebellar-induced deficits in intra-limb coordination, or if they are an indirect consequence of balance deficits, which are also typical for other types of movement disorders.

To determine specific influences of cerebellar dysfunctions on cerebellar ataxic gait, this study investigates gait patterns from different classes of neurological patients. The analysis combines standard gait parameters and new measures for the spatial and temporal variability of multi-joint coordination patterns. The comparison between these gait measures and standard clinical measures for different types of deficits in cerebellar ataxia revealed that deficits related to intra-limb coordination and control of limb dynamics are associated with increased temporal variability of inter-joint coordination patterns in gait. The comparison between different patient groups demonstrated further that increased temporal variability is a specific sign of cerebellar dysfunction, which was not observed for other movement disorders.

Material and methods

Subjects

Thirteen patients (CP1-13) with degenerative cerebellar disease (five females and eight males; 50.4 ± 14.4 years), eight patients with idiopathic Parkinson's disease (two females and six males; 60.7 ± 10.6 years), six patients with peripheral vestibular failure (four females and two males; 47.8 ± 14.3 years) and nine healthy control subjects (three females and six males, 48.1 ± 13.8) participated in our study (*see* Table 1). All patients gave informed consent prior to participation. All participants were able to walk without external help or walking aids during the data collection. The study had been approved by the local institutional ethical review board.

Clinical evaluation

Prior to gait analysis, the severity of the cerebellar ataxia was rated using the International Cooperative Ataxia Rating Scale (ICARS) (Trouillas *et al.*, 1997). This 100-point ordinal scale quantifies ataxia in the four subcategories posture and gait, limb kinetics, speech and oculomotor deficits. The ICARS score has been applied in numerous clinical studies on ataxia (Maschke *et al.*, 2004; Konczak *et al.*, 2005; Richter *et al.*, 2005), and in particular in studies on the quantification of gait deficits (Morton and Bastian, 2003; Morton *et al.*, 2004).

Recent studies have tested the reliability and the validity of this scale, demonstrating high inter-rater reliability for the whole score and for the subscores measuring deficits of posture and gait, and limb kinetics (Storey *et al.*, 2004; Schmitz-Hubsch *et al.*, 2006).

Since our study tried to distinguish the influences of balance control and joint coordination on ataxic gait, we did not include two gait items (walking capacities, gait speed) in the ICARS 'posture' subscore that measure rather the general walking

Table 1 Diagnoses and clinical scores for the patients taking part in the study

Subject	Age (years)	Gender (F/M)	Velocity (m/s)	Diagnosis	ICARS			
					Total score	Gait	Posture	Limb kinetics
CP1	43	F	1.01	Idiopathic pancerebellar atrophy	5/100	0/12	1/22	4/52
CP2	49	F	0.7	Idiopathic pancerebellar atrophy	32/100	5/12	8/22	12/52
CP3	58	M	0.99	Idiopathic pancerebellar atrophy	21/100	0/12	2/22	13/52
CP4	36	M	1.01	Gluten associated ataxia	35/100	5/12	6/22	19/52
CP5	53	M	0.8	Idiopathic pancerebellar atrophy	27/100	3/12	4/22	14/52
CP6	29	M	1.13	Idiopathic pancerebellar atrophy	34/100	3/12	6/22	19/52
CP7	44	M	0.6	Gluten associated ataxia	30/100	5/12	11/22	9/52
CP8	66	F	0.66	SCA 6	22/100	5/12	5/22	9/52
CP9	25	M	1.0	Idiopathic pancerebellar atrophy	31/100	3/12	5/22	13/52
CP10	55	F	0.78	Idiopathic pancerebellar atrophy	12/100	2/12	3/22	3/52
CP11	63	M	0.58	Arteriovenous angiom, pancerebellar atrophy	45/100	5/12	7/22	25/52
CP12	63	M	0.74	SCA 6	37/100	5/12	7/22	15/52
CP13	71	F	0.71	SCA 6	38/100	5/12	9/22	19/52
						UPDRS		
						Total score	Motor	Gait
PP1	46	M	1.04	Idiopathic Parkinson's disease		39/124	10/56	1/4
PP2	72	M	1.12	Idiopathic Parkinson's disease		41/124	20/56	1/4
PP3	72	M	0.8	Idiopathic Parkinson's disease		46/124	14/56	1/4
PP4	73	M	0.85	Idiopathic Parkinson's disease		36/124	10/56	2/4
PP5	50	M	0.87	Idiopathic Parkinson's disease		33/124	17/56	1/4
PP6	62	F	0.86	Idiopathic Parkinson's disease		41/124	28/56	1/4
PP7	55	M	0.87	Idiopathic Parkinson's disease		25/124	13/56	1/4
PP8	56	F	0.83	Idiopathic Parkinson's disease		36/124	17/56	2/4
					StepL (cm)	StepL var	StepW (cm)	Lateral sway (cm)
VP1	54	F	0.96	Unilateral vestibulopathy (left)	54.64	14.89	12.23	32.95
VP2	63	F	0.91	Unilateral vestibulopathy (right)	49.95	10.61	13.02	38.13
VP3	31	F	0.86	Unilateral vestibulopathy (right)	48.40	11.57	13.65	59.00
VP4	38	F	1.03	Unilateral vestibulopathy (right)	53.90	4.43	15.22	48.26
VP5	64	F	1.10	Bilateral vestibulopathy	49.32	6.32	17.54	45.06
VP6	37	M	1.14	Bilateral vestibulopathy	53.75	6.26	18.66	50.84

Cerebellar patients were rated using the ICARS score (Trouillas *et al.*, 1997). The table lists the total ICARS scores and the subscores for posture, gait and limb kinetics. Higher scores indicate more severe ataxia. The second number signifies the maximum value of the corresponding score. SCA 6: spinocerebellar ataxia type 6. The Parkinson patients were rated using the UPDRS score. The table lists the UPDRS total score using sections I–III, the motor examination score (section III) and the specific gait item. The gait patterns of the vestibular patients were quantified by the most important balance-related gait parameters: step length, StepL; step length variability, StepLVar; step width, StepW and lateral sway (see section 'Standard gait parameters').

capability than specific posture or balance deficits (but *see* Table 1 for the gait score). We tested that the results of our study were only marginally different when these two gait items were included.

The 'limb kinetics' subscore includes items like movement decomposition, dysmetria and intention tremor, mainly rated for goal-directed movements of individual limbs (e.g. heel-to-shin test or finger-to-nose test). Since the kinetics subscore contains only two items for the lower limbs, we used the whole kinetic subscore, including items characterizing the behaviour of the upper limbs, in order to obtain more robust ratings. As justification of this proceeding, we verified that for our patient population the lower limb items correlate significantly with the complete kinetic subscore (Spearman's rank correlation $r = 0.63$, $P = 0.02$). The correlation between the posture and the kinetic subscore did not reach significance ($r = 0.33$, $P > 0.05$). The total ICARS score correlated highly with the two subscores used in our experiment (posture $r = 0.69$, $P < 0.01$; kinetic $r = 0.85$, $P < 0.01$).

Parkinson patients were scored using the Unified Parkinson's Disease Rating scale (UPDRS) (Table 1). Described here are the total score (section I–III), the motor examination score (section III) and the specific gait item. Balance impairments of the vestibular patients were characterized by assessing the most important balance-related gait parameters (*see* Table 1 and subsection Standard gait parameters).

Recording and preprocessing of gait trajectories

For gait analysis, the patients were instructed to walk normally at a self-determined pace. All patients were walking barefoot without additional aids. The three-dimensional movement trajectories of

the patients were recorded with a sampling rate of 120 Hz using a Vicon 612 motion capture system with six cameras and 41 reflecting markers. The marker trajectories were preprocessed using commercial software provided by Vicon. This software fits a clinically evaluated kinematic model to the marker trajectories and extracts velocities, joint angles and the course of the centre of mass.

Gait cycles were automatically determined from the trajectories by detection of heel-strike events, based on the vertical components of the heel marker positions. Results of the automatic detection were verified manually using a stick figure animation in order to correct for different types of foot placements.

From each patient, 8–12 gait cycles were recorded, assessed within 2–3 experimental trials. The reconstructed joint angle trajectories were smoothed with a Savitzky–Golay polynomial filter (of order 4 and with a window size of 41 sampling points) and resampled equidistantly with 100 data points per gait cycle by linear time interpolation. Our analysis was based on the joint angles of the lower limbs in the sagittal plane (flexion/extension). In order to compensate for amplitude variation between different joints, the angle trajectories were normalized to the angle interval $[0, 1]$.

Computation of standard gait parameters

We computed 16 common parameters from clinical gait analysis (Kirtley, 2006) (Table 2). Step length was normalized by body height. Lateral body sway was defined as the medial–lateral component of the path of the centre of mass, normalized by the anterior–posterior component. In addition, we computed the decomposition indices for several joint pairs. The decomposition index of a joint pair was defined as the percentage of time of the swing phase during which one of the joints was moving, while the other one remained stationary (Earhart and Bastian, 2001).

Separation of spatial and temporal trajectory characteristics

For the detailed analysis of the variability of multidimensional joint coordination patterns, we applied a new method for the modelling of the space–time characteristics of multijoint movements. This method is based on the computation of spatio-temporal correspondence between trajectory pairs (Giese and Poggio, 2000). Such correspondence is defined by a set of spatial and temporal displacements that map the first trajectory onto the second. This is illustrated in Fig. 1A that shows a reference trajectory $x_{\mathrm{ref}}(t)$ and a test trajectory $x_{\mathrm{test}}(t)$. The circles on the trajectories that are connected by dashed lines indicate points that are in spatiotemporal correspondence, for example the maxima of the two trajectories. Each point $x_{\mathrm{ref}}(t_n)$ on the reference trajectory corresponds to a point $x_{\mathrm{test}}(t_n)$ of the test trajectory.

Table 2 Elementary gait parameters for control subjects and cerebellar patients

Gait parameter	Control (mean ± SD)	Patient (mean ± SD)	*P* from *t*-test
Step length (cm)	56.7 ± 7.8	47.5 ± 9.5	0.03
Step width (cm)	6.7 ± 0.9	14.4 ± 4.9	<0.001
Velocity (m/s)	1.2 ± 0.14	0.83 ± 0.18	<0.001
Lateral sway (cm)	19.5 ± 1.3	52.26 ± 7.4	<0.001
Swing time (s)	0.39 ± 0.07	0.42 ± 0.04	0.32
Gait cycle time (s)	1.02 ± 0.2	1.2 ± 0.09	0.08

The points are displaced against each other in space by the spatial vector $\xi(t_n)$ and in time by the (scalar) time shift $\tau(t_n)$, formally:

$$x_{\mathrm{test}}(t_n) = x_{\mathrm{ref}}(t_n + \tau(t_n)) + \xi(t_n) \quad (1)$$

The two displacement functions $\xi(t)$ and $\tau(t)$ characterize the spatio-temporal deviation of the test trajectory from the reference trajectory and decompose it into a spatial and a temporal component. The displacement functions were computed automatically using an algorithm (Giese and Poggio, 2000) that is briefly described in the Supplementary material.

Quantification of spatial and temporal variability

We applied different methods for characterizing the variability of the joint coordination patterns over multiple repetitions of the same movement (gait cycles). A common approach for the quantification of movement variability (Winter, 1984; Borghese *et al.*, 1996; Stergiou, 2004) is to normalize the total durations of the individual movements (steps) by linear rescaling of the time axis.

From the time-normalized trajectories $x_k(t)$, an average trajectory $\bar{x}(t)$ is then computed by averaging separately for each time point. A measure for the variability of the movement can be defined by integrating the deviations of the individual trajectories from the average trajectory over the gait cycle time T, and averaging over K gait cycles (*see* Supplementary material for details):

$$\mathrm{var}_{\delta} = \frac{1}{K}\sum_{k=1}^{K}\int_0^T |x(t) - \bar{x}(t)|\,\mathrm{d}t \quad (2)$$

More accurate variability measures can be constructed by exploiting the separation into spatial and temporal trajectory characteristics as discussed in the last section. Accurate measures of temporal variability seem particularly interesting for the study of cerebellar ataxic gait, since animal studies have shown that impairments of the control of limb dynamics are often associated with abnormalities of the temporal coherence between different joints and by abnormalities in joint kinematics (Milak *et al.*, 1997; Cooper *et al.*, 2000).

Measures for the spatial and the temporal variability of the movements can be constructed by averaging separately the spatial and temporal deviations from appropriately chosen reference trajectories. Reference trajectories $x_{\mathrm{ref}}(t)$ were computed separately for each participant, and were defined by the space–time average of all gait cycles $x_k(t)$ from the same subject (*see* Supplementary material for further details). Exploiting equation (1), the movement (joint angle trajectory) of each gait cycle can then be represented by its spatial and temporal displacement $\xi_k(t)$ and $\tau_k(t)$ relative to the reference trajectory. Separate measures for the spatial and the temporal variability of the movements were constructed by averaging the absolute values of the spatial shifts $\xi_k(t)$, and of the temporal shifts $\tau_k(t)$ over all gait cycles (K signifying the number of recorded gait cycles and T the gait cycle time):

$$\mathrm{var}_{\xi} = \frac{1}{K}\sum_{k=1}^{K}\int_0^T |\xi_k(t)|\,\mathrm{d}t \quad (3)$$

$$\mathrm{var}_{\tau} = \frac{1}{K}\sum_{k=1}^{K}\int_0^T |\tau_k(t)|\,\mathrm{d}t \quad (4)$$

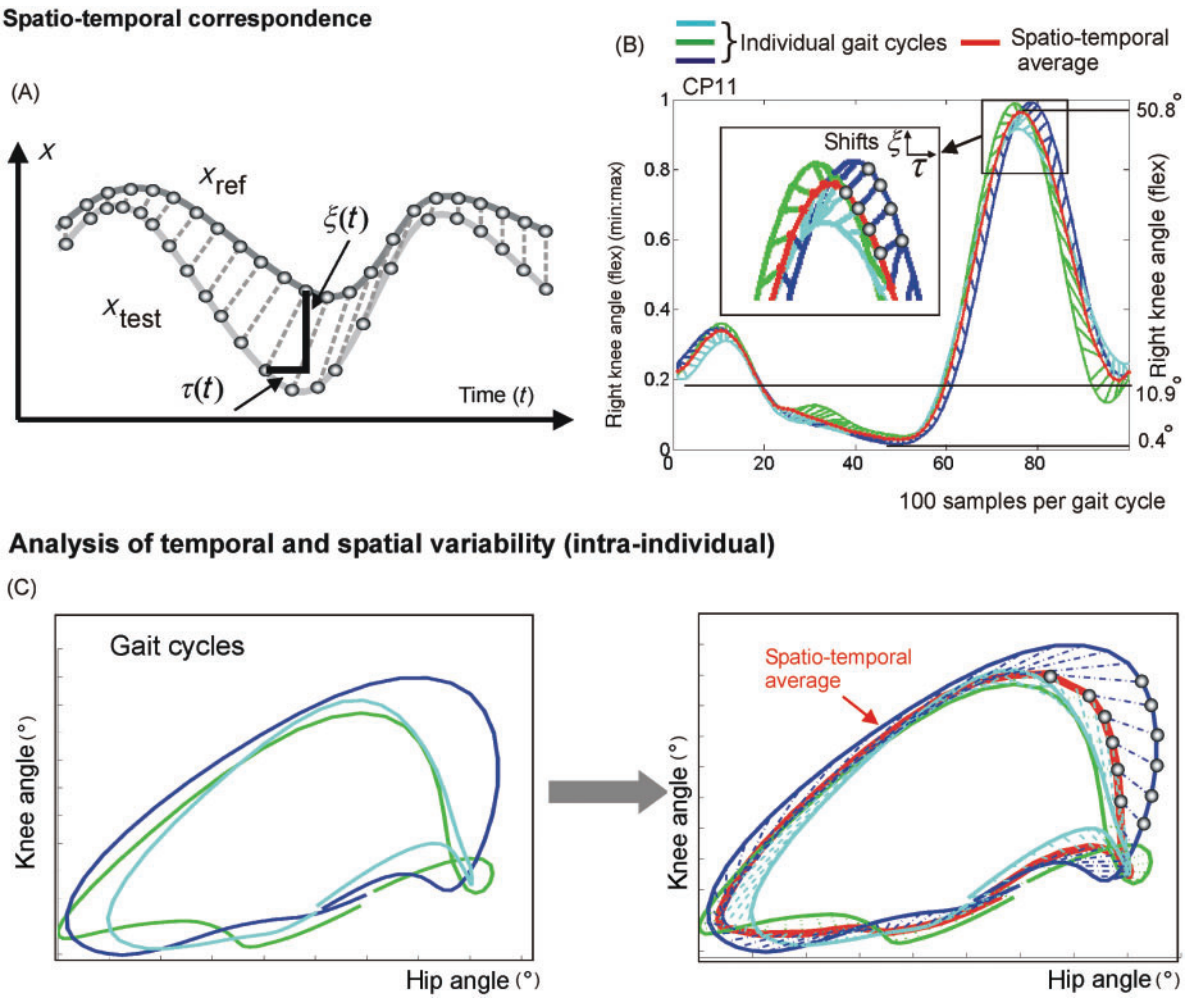

Fig. 1 (**A**) Spatiotemporal correspondence and spatial and temporal variability. Illustration of the spatial–temporal correspondence between a reference trajectory and a test trajectory. Small circles indicate corresponding points of the two trajectories. The spatiotemporal displacements between corresponding points (indicated by dotted lines) have spatial and temporal displacement components, defining the correspondence fields $\xi(t)$ and $\tau(t)$. (**B**) Illustration of spatial and temporal variability for real data and computation of the average movement for the gait trajectories of a cerebellar patient. Joint angle trajectories (100 time samples) are shown for the right knee flexion angle for three subsequent gait cycles. Thin lines between the trajectories connect points that are in spatiotemporal correspondence. (**C**) Analysis of the spatial and temporal intersubject variability of two-dimensional joint angle trajectories. Trajectories are illustrated as angle–angle plots. From the three trajectories from individual gait cycles of the same patient (left), a spatiotemporal average trajectory is computed (right).

Since the trajectories $x_k(t)$ can have in principle an arbitrary number of spatial dimensions, these stability measures can be applied to multidimensional joint coordination patterns. In this study, we applied the method to pairs and triples of normalized joint angle trajectories from the same lower limb.

Figure 1B illustrates the reference trajectory (red) and the spatial and temporal displacements (thin lines) for one joint of a cerebellar patient. Figure 1C illustrates the application to applied multidimensional combinations of joint angles, where the space–time correspondences between trajectories of two joints are indicated in the angle–angle plane. The left panel shows the original gait cycle trajectories. In the right panel, the red curve illustrates the reference trajectory, and the dashed-dotted lines indicate space–time correspondences between the trajectories of the individual recorded gait cycles and the reference trajectory.

Statistical analysis

Group differences between patients and normal controls were confirmed by unpaired *t*-tests for unequal group sizes and variances. Differences between the patients groups were confirmed by independent measures ANOVAs. For the 13 cerebellar patients (CP1–CP13), Spearman rank correlations between gait measures and the clinical ataxia rating scale ICARS and its subscores for posture and limb kinetic deficits were computed. Significances are reported for the individual gait parameters with the significance level $P<0.05$. In addition, we report significance values that are Bonferroni-corrected over all 16 standard gait parameters (corresponding to the uncorrected significance level $P<0.00315$), and over eight different joint angle combinations (corresponding to the uncorrected significance level $P<0.00625$).

In order to verify that our results were not induced by confounding biomechanical factors, we also performed a partial

correlation analysis to remove the influences of gait velocity and step width from the correlations between gait measures and clinical scores. For this purpose, gait velocity (respectively step width) was treated as an additional predictor whose influence was removed from the correlations with the clinical ratings. The statistical analysis was performed using the software packages MATLAB and SPSS.

Results

Analysis of standard gait parameters

As baseline for the further analysis, we first verified how far balance-related and coordination-related cerebellar deficits are reflected by changes of common standard gait parameters. The correlations between the gait parameters and the ICARS score, and its two subscores for posture and limb kinetics, are listed in Table 2. The complete ICARS score correlated significantly only with the step width ($r = 0.66$, $P = 0.018$). The posture subscore correlated positively with step width ($r = 0.74$, $P = 0.003$), the mean duration of the swing phase ($r = 0.70$, $P < 0.007$) and the lateral body sway ($r = 0.86$, $P = 0.0001$), and negatively with gait velocity ($r = -0.65$, $P = 0.018$) and the step length ($r = -0.56$, $P = 0.04$). The limb kinetics subscore correlated significantly only with the variability of the swing phase duration ($r = 0.62$, $P < 0.05$). The correlations for all other gait parameters were non-significant (*see* Table 2). With Bonferroni correction, over all tested 16 gait measures only the correlations between posture subscore and step width and lateral sway remain significant.

Comparing cerebellar patients and normal controls, we found significant differences for a number of standard gait parameters, including step length ($t_{20} = 2.4$, $P = 0.03$), step width ($t_{20} = -5.30$, $P < 0.001$), gait velocity ($t_{20} = -5.5$, $P < 0.001$), lateral body sway ($t_{20} = -5.416$, $P < 0.001$) and variance of the peak time of the knee joint angle (normalized to gait cycle time; $t_{20} = -4.11$, $P < 0.001$). Means and standard deviations of the most important gait parameters for patients and controls are listed in Table 3.

Comparing all three patient groups employing standard gait parameters, we did not find significant differences between cerebellar and vestibular patients for balance-related measures, specifically step width, step width variability and lateral body sway [ANOVA, $F(1,20) < 2.93$, $P > 0.11$] (Fig. 2). Parkinson patients show significantly smaller values for these balance-related measures [$F(2,25) > 34.89$, $P < 0.0001$]. Compared with normal controls, all three patient groups showed significantly increased step length variability ($t < 3.12$, $P < 0.01$). This was comparable between the patient groups [no significant between-group differences [$F(2,25) = 1.2$, $P = 0.32$]. These results suggest that cerebellar patients were (i) comparable to vestibular patients with respect to balance-related deficits and (ii) with respect to vestibular and Parkinson patients in terms of general variability measures (step-length variability).

Table 3 Correlations between different standard gait parameters and the clinical ataxia scale ICARS for 13 patients

Correlation coefficients *r*	ICARS	ICARS posture	ICARS kinetics
Gait parameters			
Step length (M)	−0.14	−0.56*	0.17
Step length (SD)	−0.06	−0.43	0.22
Step width (M)	0.65*	0.73**	0.45
Step width (SD)	0.12	−0.14	0.18
Lateral sway	0.47	0.86**	0.14
Velocity (M)	−0.25	−0.66*	0.06
Gait cycle time (M)	0.13	−0.1	0.24
Gait cycle time (SD)	−0.23	0.05	−0.25
Swing phase time (M)	0.40	0.70*	0.17
Swing phase time (SD)	0.50	0.30	0.62*
H-AmaxV (SD)	0.21	−0.05	0.3
K-AmaxV (SD)	0.15	0.11	0.1
A-AmaxV (SD)	0.22	−0.05	0.26
Decomposition HK	0.21	−0.06	0.38
Decomposition HA	−0.03	−0.11	−0.03
Decomposition KA	0.10	−0.12	0.19

The second column indicates the total ICARS scores, and the right columns the subscales for posture and kinetic deficits. Significances were assessed using Spearman's rank correlation coefficients. Significance levels are indicated by asterisks (*$P < 0.05$ for single pairwise correlation; **$P < 0.05$ with Bonferroni correction for the 16 different gait measures, corresponding to the uncorrected level $P < 0.00315$). The abbreviations H-Amax, K-Amax and A-Amax indicate the variances of the relative timing of the peak angles for hip, knee and ankle joint, respectively. The correlations for the decomposition indexes were tested for combinations of lower limb joints, the last letters specifying angle combinations of (H)ip, (K)nee and (A)nkle. For the individual gait parameters, means (M) and standard deviations (SD) are listed.

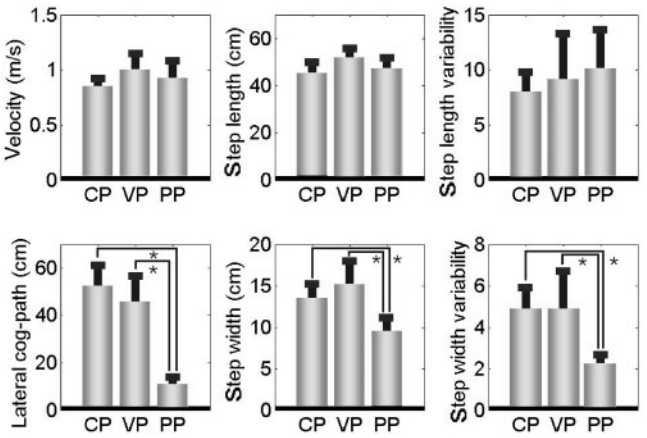

Fig. 2 Comparison of the most important gait parameters for cerebellar patients (CP), vestibular patients (VP) and Parkinson patients (PP). The links between different bars represent significant group differences (*$P < 0.05$). Cerebellar and vestibular patients are comparably impaired in balance-related parameters like step width, step width variability and lateral sway. The values of the Parkinson patients group are not significantly changed for the balance-related parameters in comparison with healthy controls, but their step length variability is increased and comparable with the other patient groups.

Qualitative analysis of joint coordination patterns

The fact that the time of the swing phase showed a significant (uncorrected) pairwise correlation with the limb kinetics subscore motivated a more detailed investigation whether impairments of intra-limb coordination in ataxic gait might be associated with increased temporal variability. A more complete analysis of the joint coordination patterns seems to require more accurate measures, which are sensitive for changes of the whole trajectory shape rather than of individual events during the walking cycle. A qualitative analysis of this type can be based on angle–angle plots.

The panels of Fig. 3 show angle–angle plots for different joint angle pairs of the lower limbs for: (A) a normal control subject (female, 54 years), (B) patient CP11 with pancerebellar atrophy, (C) patient PP1 with idiopathic Parkinson's disease and (D) patient VP3 with unilateral vestibulopathy. Compared with the control subject, the patients PP1 and VP3, and CP11 show increased variability. For the patients VP3 and PP1 this variability seems to be predominantly caused by variations of the joint angle amplitudes (labels 2 and 3). Contrasting with this observation, the variability of the cerebellar patient (CP11) seems to reflect more complex intra-limb coordination changes, especially during the swing phase (label 1).

Polar angle plots provide another qualitative method which emphasizes more the temporal aspects of inter-joint coordination (used e.g. by Ivanenko *et al.*, 2003). Individual joint angles, normalized to the interval [0, 1], are plotted in polar coordinates against normalized time within the gait cycle. Figure 4 shows the polar angle plot for the right hip, knee and ankle joints for a control subject (panel A), two cerebellar patients (panels B + C), a Parkinson patient (panel D) and a vestibular patient (panel E). Patient CP7 suffered from a balance-dominated impairment (*see* ICARS scores, Table 1). While her polar angle plot (panel B) shows systematic abnormalities, like a deformation of the hip angle trajectory (label 1) and an increased stance phase with a delay of the ankle angle (label 2), the variability of her angle trajectories is almost normal. Contrasting with this result, the joint angle patterns of patient CP11 (panel C) with a limb kinetic-dominant impairment (according to the ICARS score) show high spatial and temporal variability especially for the knee and ankle joints (label 3). This indicates that balance-dominated and kinetic-dominant impairments might induce distinguishable changes in the inter-joint coordination patterns. The corresponding plots of Parkinson patient PP 1 and vestibular patient VP3 show lower variability than those of CP11. High temporal variability might thus to be indicative for kinetics-dominant cerebellar dysfunctions.

Variability of joint coordination patterns of cerebellar patients

A more accurate quantitative characterization of the variability of coordination patterns can be accomplished with the variability measures var_ξ, var_τ and var_δ (*see* Material and methods). For obtaining a sufficient characterization of the intra-limb coordination patterns of the knee, hip and ankle joints, we computed these measures for two- and three-joint combinations from each individual leg. These combinations included the knee (K), hip (H) and ankle (A) angles in the sagittal plane. The joint combinations are indicated by the letter combinations in Table 4, with L signifying the left leg and R the right leg.

Figure 5A exemplifies our results for the cerebellar patients for a characteristic set of joint angles, including the hip and knee angles of the left leg. The temporal variability measure var_τ is shown as a function of the ICARS kinetic subscore, separately for 13 patients and the nine control subjects. The temporal variability measure for this angle combination was significantly higher for the patients than for the normal controls ($t_{20} = 8.06$, $P < 0.001$). Within the group of patients, the temporal variability measure increased almost linearly with the ICARS kinetic subscore, confirmed by a significant correlation between these two variables ($r = 0.69$, $P = 0.007$). Contrasting with this result, the temporal stability measure var_τ did not correlate significantly with the posture subscore from the ICARS scale ($r = 0.33$, $P = 0.26$) (Fig. 5B).

For the same combination of joint angles, the spatial variability measure var_ξ was not significantly different between patients and normal controls ($t_{20} = -0.31$, $P = 0.63$) and did not correlate with the ICARS kinetic subscore ($r = 0.03$, $P = 0.94$). Also, the simple standard variability measure var_δ (*see* Material and methods) for this joint angle combination (Fig. 5C) failed to show significant differences between patients and controls ($t_{20} = 1.16$, $P = 0.14$), and did not correlate significantly with the ICARS kinetic subscore ($r = 0.11$, $P = 0.67$).

The same results remain valid for other joint angle combinations. We tested all two- and three joint combinations of the hip, knee and ankle joints (Table 4). We found significant pairwise correlations ($P < 0.05$) between the temporal variability measure var_τ and the ICARS kinetic subscore for six of the eight tested angle combinations. The correlation for the joint combination L-KA remained significant with Bonferroni correction over all eight tested angle combinations (uncorrected $P < 0.00625$). Like for the example in Fig. 5, the temporal variability measure var_τ never correlated significantly with the posture subscore (maximum correlation: $r = 0.41$, $P = 0.16$), and the correlations between the variability measures var_ξ and var_δ and the ICARS and its subscores were non-significant for all tested joint angle combinations. These results were additionally confirmed by a step-wise multiple regression analysis (*see* Supplementary material for details).

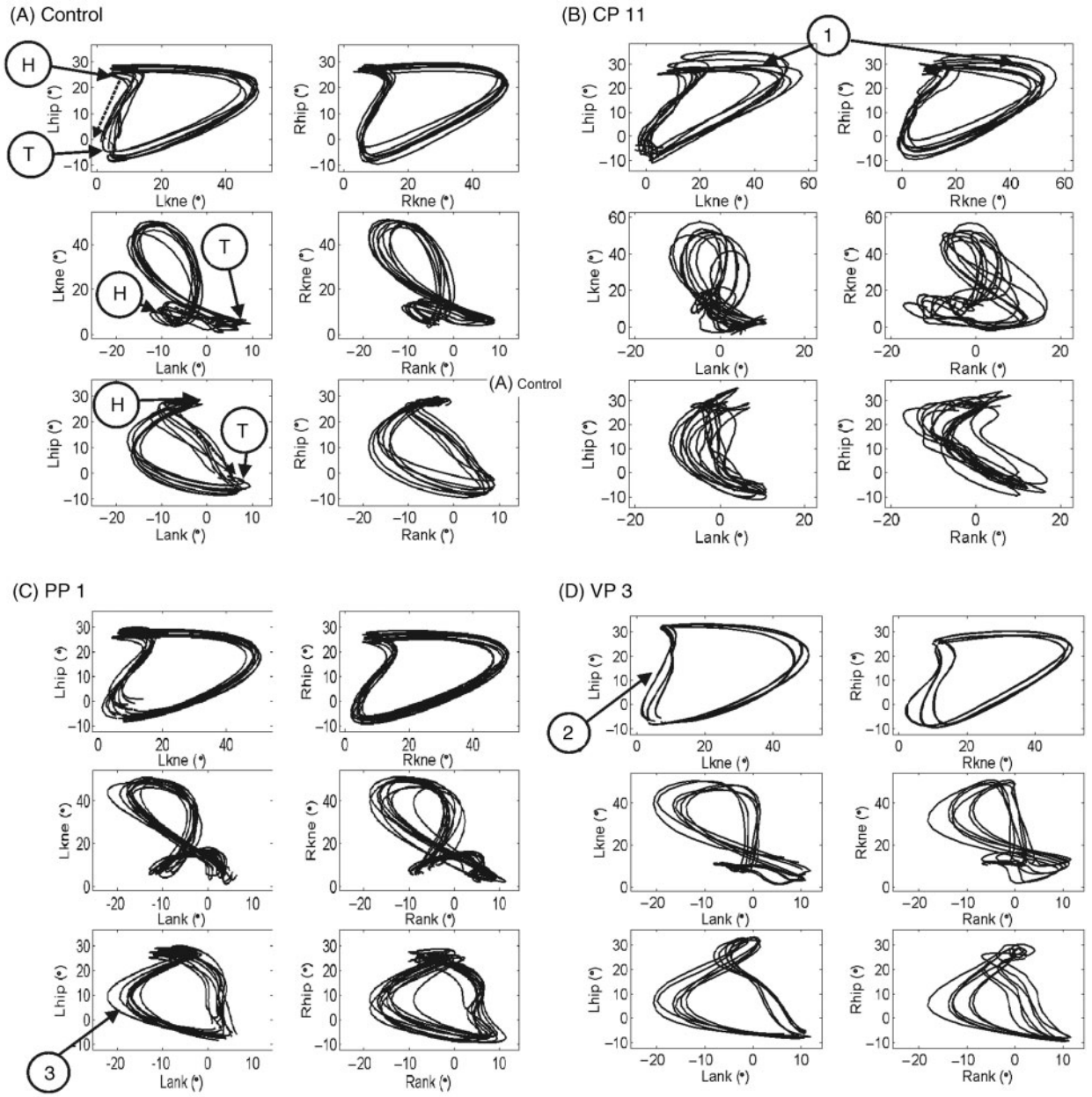

Fig. 3 Angle–angle plots illustrating the joint coordination patterns for right and left leg. (**A**) Normal control subject, (**B**) patient CPII with pancerebellar atrophy, (**C**) patient PPI with idiopathic Parkinson's disease, (**D**) patient VP3 with unilateral vestibulopathy. Labels (H) indicate the heel strike at the beginning of stance phase, and labels (T) the toe-off event at the beginning of swing phase. The dotted arrows indicate the stance phase. In each panel, the upper row indicates the phase plots for hip and knee angles, the middle row the plots for the knee and ankle angles, and the lower row the plots for the hip and ankle angles. CPII shows specific abnormalities in intra-limb coordination (label 1). The increased variability for PPI and VP3 seems to reflect predominantly changes of the joint angle amplitudes (labels 2 + 3).

Summarizing, this variability analysis supports the main hypothesis of our study that increased temporal variability of intra-limb coordination represents a deficit that is related to voluntary limb control, while spatial variability that reflects changes of the angle amplitudes is much less specific.

Another set of statistical analyses rules out that the observed variability changes reflect general confounding parameters, like age or gait velocity. Previous studies indicate that gait variability depends on age (Gabell and Nayak, 1984; Menz *et al.*, 2003; Owings and Grabiner, 2004) and gait velocity (Winter, 1983; Borghese *et al.*, 1996). A potential confounding influence of these two parameters is ruled out by the fact that the correlations between the temporal variability measure var_τ and age ($r < 0.33$, $P > 0.26$) and gait velocity ($r < 0.23$, $P > 0.45$) were

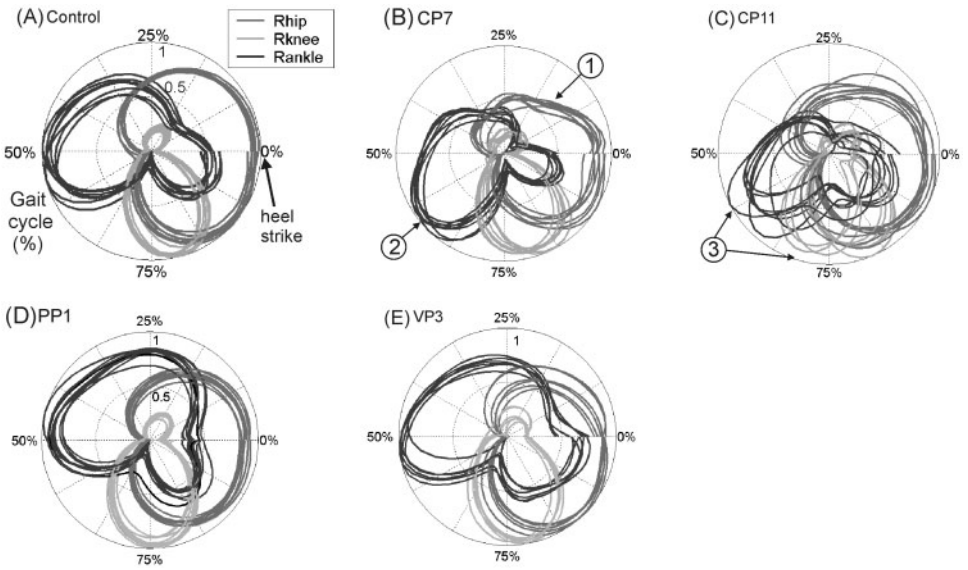

Fig. 4 Polar plots for the illustration of abnormalities of the joint coordination patterns of the right leg. Shown are angles of the right hip, right knee and right ankle. Angles are normalized to the interval [0, 1]. The polar angle indicates the relative time over the gait cycle, and the radius the normalized joint angles. Maximum flexion corresponds to radius 1, and minimum flexion (respectively maximum extension) to the radius zero. The gait cycle begins with heel strike of the right leg (0%). Panel **A** shows the diagram from a control subject (54 years, female). Panels **B** and **C** show two cerebellar patients with a balance-dominated and a limb kinetics-dominated impairment. Panel **D** shows the polar plot for a patient with Parkinson's disease, and panel **E** for a patient with unilateral vestibular failure (see text for further details).

Table 4 Correlations for the temporal variability measure var_τ and the clinical ataxia scale ICARS for 13 patients

Correlation coefficients *r*	ICARS	ICARS posture	ICARS kinetics
Joint angle combinations			
L-HK	0.58*	0.38	0.69*
L-HA	0.52	0.44	0.59*
L-KA	0.58*	0.33	0.76**
L-HKA	0.46	0.28	0.6*
R-HK	0.39	0.17	0.52
R-HA	0.32	0.02	0.54
R-KA	0.40	0.12	0.62*
R-HKA	0.40	0.09	0.58*

Second column indicates the total ICARS scores, and the last columns the subscales for posture and kinetic deficits. Significances were assessed using the Spearman's rank correlation coefficients. Significance levels are indicated by asterisks (*$P<0.05$ for single pairwise correlation; **$P<0.05$ with Bonferroni correction for the eight joint angle combinations, corresponding to the uncorrected level $P<00625$). The letter combinations along encode different joint angle combinations: L, left leg; R, right leg; H, hip; K, knee; A, ankle. Example: L-HKA is the combination of the flexion angles of the hip, knee and ankle of the left leg.

non-significant for all tested joint angle combinations. In addition, the temporal variability of joint coordination var_τ did not correlate significantly with the intra-subject variability of walking speed (step cycle by step cycle) ($r<0.26$, $P>0.39$). This implies that the observed temporal variability is not just a side effect of variations in gait speed over different step cycles.

Furthermore, we failed to find significant correlations between important balance-related parameters, like step width and lateral body sway, and the variability measure var_τ ($r<0.45$, $P<0.12$). In addition, we computed the partial correlations between var_τ and the ICARS kinetic subscore, treating gait velocity and step width as additional confounding predictors. The correlation between var_τ and the kinetic subscore remains significant, even if the influence of gait velocity or step width is eliminated (e.g. for feature set L-HK, velocity $r=0.69$, $P=0.006$, step width $r=0.62$, $P=0.03$). This makes it highly unlikely that the correlation between temporal variability and kinetic subscore just reflects confounding biomechanical factors.

Temporal variability as specific characteristics of cerebellar dysfunction

To examine whether increased temporal variability is a specific consequence of cerebellar dysfunction or a side–effect of more general factors, like balance impairments which are also caused by other movement disorders, we examined the joint coordination patterns of the two other patient groups applying the same type of analysis. As discussed before, the analysis of the standard gait parameters shows that for balance-related parameters cerebellar and vestibular patients were comparable, and that all three patients groups show comparable values in step length variability. Consistent with these results, also the spatial variability of the joint coordination patterns,

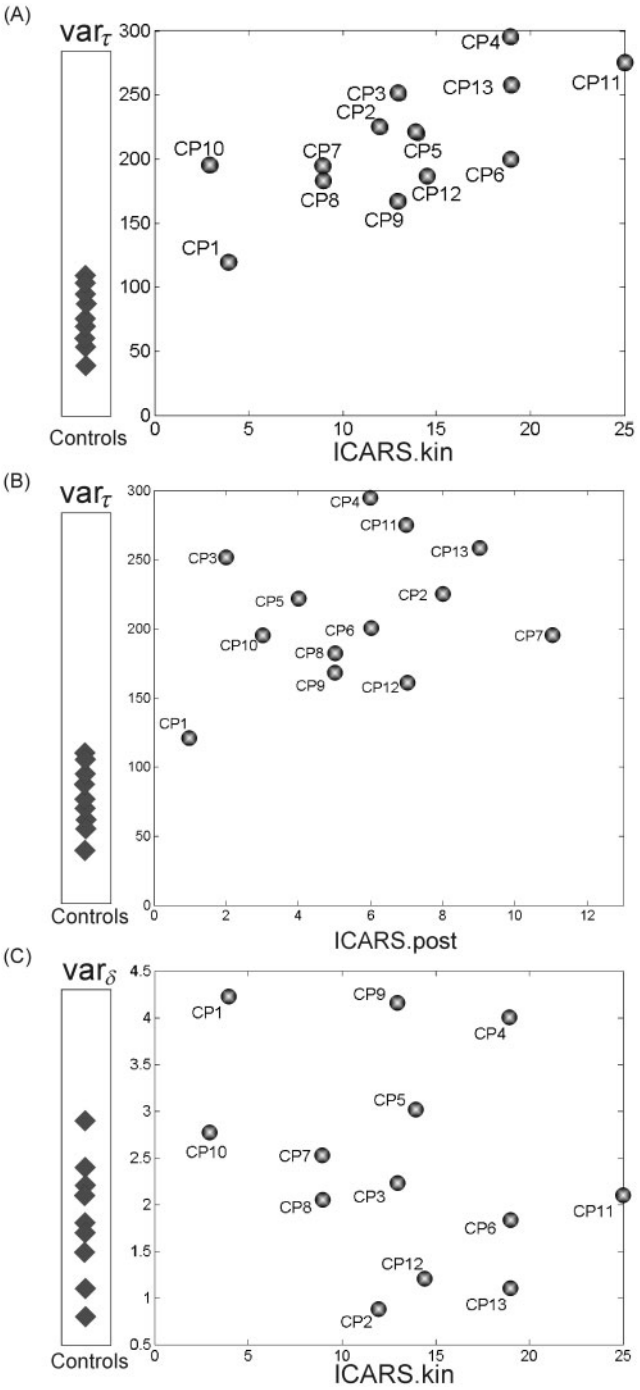

Fig. 5 Temporal variability measure var_τ plotted against the kinetic subscore (**A**) and the posture subscore (**B**) of the ICARS scale for 13 cerebellar patients and nine control subjects. (**C**) Spatial variability measure var_δ (see 'Methods') plotted against the kinetic subscore. The variability measures were determined for one exemplary set of joints, including flexion angles of the left hip and the left knee (L-HK).

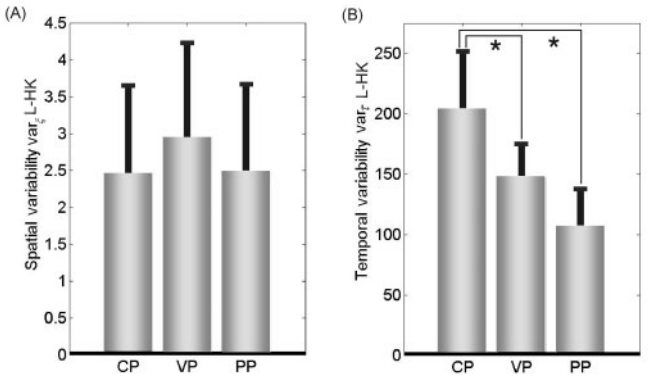

Fig. 6 Comparison of the spatial variability measure var_ξ (panel A) and temporal variability measure var_τ (panel B) between cerebellar patients (CP), vestibular patients (VP) and Parkinson patients (PP). The exemplary joint angle set includes the flexion angles of the left hip and the left knee (L-HK). Significant pairwise group differences are indicated for $*P < 0.05$. The spatial variability var_ξ shows no significant difference between the patient groups. In contrast, the temporal variability measure var_τ is significantly higher for the cerebellar group than for the vestibular and Parkinson group.

measured by the variability measure var_ξ did not differ significantly between the three patient groups [$F(2,25) = 0.38$, $P = 0.68$] (Fig. 6A). However, we found that the temporal variability var_τ was significantly higher for the cerebellar patients than for all other patient groups ($t > 2.74$; $P < 0.01$) (Fig. 6B).

These results further confirm the central hypothesis that increased temporal variability of intra-limb coordination patterns is specific for cerebellar dysfunction, and not an indirect consequence of balance problems.

Discussion

This study investigates quantitatively the influence of different types of cerebellar dysfunction on ataxic gait. Specifically, it addresses the question whether ataxic gait is influenced by deficits related to intra-limb coordination, and whether the observed changes are specific for cerebellar disorders.

Consistent with the previous literature (Palliyath *et al.*, 1998; Stolze *et al.*, 2002; Morton and Bastian, 2003), we found high correlations between balance-related gait parameters and posture and balance deficits, as measured by a subscore of the ICARS clinical scale. Also, these gait measures were significantly different between patients and normal controls. This confirms the relevance of the cerebellum for balance control in gait.

The novel measure for the temporal variability of multi-joint coordination patterns was highly correlated with deficits of voluntary limb control, as measured by the ICARS subscale for kinetic deficits. This provides support for an influence of common cerebellar structures on intra-limb coordination in gait and voluntary limb control.

The comparison of the different gait measures between cerebellar patients, Parkinson patients and patients with peripheral vestibular failure showed that increased timing variability is a specific indicator of cerebellar dysfunction,

and does not arise for other movement disorders, even in presence of similar spatial gait variability and balance deficits. This implies in particular that the observed timing variability was not caused by balance problems, but very likely is a cerebellar-induced signature of impaired limb coordination. Opposed to cerebellar patients, Parkinson patients showed almost normal temporal variability, but very high spatial variability. This variability might reflect fluctuations in force exertion (Kunesch *et al.*, 1995; Vieregge *et al.*, 1997). The previous results imply that temporal variability might represent a specific clinical indicator for the presence of cerebellar-induced coordination deficits.

Influence of cerebellar deficits on intra-limb coordination in gait

The influence of cerebellar deficits on the control of limb dynamics and multi-joint coordination in ataxic gait might be mediated by several factors.

(i) Such impairments might reflect the inadequate modulation of rhythmical activation patterns of the lower limb muscles during walking. Several studies with cats suggest that the intermediate cerebellum and interpositus nuclei are important for the control of limb dynamics and the modulation of rhythmic movements (Schwartz *et al.*, 1987; Pardoe *et al.*, 2004), potentially by a compensation of inter-joint interactions (Apps and Garwicz, 2005). This interpretation is also supported by studies showing that lesions of these areas cause significant hypermetria in ipsilateral joints (Chambers and Sprague, 1955*a*, *b*; Yu and Eidelberg, 1983), impairments of timing of the touch-down and lift-off events (Udo *et al.*, 1980) and dragging during walking on flat surfaces (Bracha *et al.*, 1999).

(ii) Mechanisms related to voluntary limb control might be important for the compensation of gait perturbations by the modulation and the integration of reflex patterns into locomotion. Deficits of the scaling of reflex patterns and postural responses, resulting in hypermetria, have been shown in numerous studies with cerebellar patients, e.g. during surface displacements (Horak and Diener, 1994) and stepping (Hudson and Krebs, 2000). The same mechanism might also contribute to other deficits, like impaired obstacle avoidance during walking or stepping (Morton *et al.*, 2004), perturbations of gait initiation (Timmann and Horak, 1998) and perturbed treadmill locomotion (Rand *et al.*, 1998). This interpretation seems also compatible with physiological studies showing that the interposite nuclei are involved in the compensation of gait perturbations (Schwartz *et al.*, 1987).

(iii) For patients with severe gait ataxia, mechanisms of voluntary limb control might become more important during walking. Since these patients walk highly insecurely and have to concentrate on each step, their locomotion potentially 'degenerates' towards a visually guided placement of each single step. This behaviour is likely more dependent on neural structures for voluntary and visually guided leg control than normal walking. The lateral zone of the cerebellum is suggested to be relevant for this function. Lesions in this region cause impairments of foot placement, movement planning and adjustment of treadmill locomotion after perturbations (Schwartz *et al.*, 1987; Thach *et al.*, 1992; Armstrong *et al.*, 1997; Marple-Horvat *et al.*, 1998; Marple-Horvat and Criado, 1999; Cerminara *et al.*, 2005). Since our analysis demonstrated that the increase of temporal variability is not a side effect of slow walking, this suggests a specific influence on visually guided leg placement in severe ataxia.

Since our study was based on patients with pancerebellar atrophy, we are not able to make strong claims about relevant anatomical structures. But summarizing the previous discussion, it seems plausible that the increased temporal variability of joint coordination patterns might be related to dysfunctions to the intermediate zone of the cerebellum. This hypothesis would explain the correlation with deficits for goal-directed movements (as measured by the ICARS). In addition, it is consistent with the clinical observation that focal lesions of the intermediate part of the anterior lobe can cause abnormalities in gait and stance, and prominent ataxia of the lower limbs (Dichgans and Diener, 1984). Future experiments involving patients with focal lesions and the quantification of coordination deficits for other types of lower limb movements, such as goal-directed stepping (Morton and Bastian, 2003), might help to clarify such questions.

Supplementary material

Supplementary data are available at *Brain* Online.

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