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ORIGINAL PAPER

# Characteristics of Tremor Induced by Lesions of the Cerebellum

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## Abstract

It is a clinical experience that acute lesions of the cerebellum induce pathological tremor, which tends to improve. However, quantitative characteristics, imaging correlates, and recovery of cerebellar tremor have not been systematically investigated. We studied the prevalence, quantitative parameters measured with biaxial accelerometry, and recovery of pathological tremor in 68 patients with lesions affecting the cerebellum. We also investigated the correlation between the occurrence and characteristics of tremor and lesion localization using 3D T1-weighted MRI images which were normalized and segmented according to a spatially unbiased atlas template for the cerebellum. Visual assessment detected pathological tremor in 19% while accelerometry in 47% of the patients. Tremor was present both in postural and intentional positions, but never at rest. Two types of pathological tremor were distinguished: (1) low-frequency tremor in 36.76% of patients (center frequency 2.66 ± 1.17 Hz) and (2) normal frequency–high-intensity tremor in 10.29% (center frequency 8.79 ± 1.43 Hz). The size of the lesion did not correlate with the presence or severity of tremor. Involvement of the anterior lobe and lobule VI was related to high tremor intensity. In all followed up patients with acute cerebellar ischemia, the tremor completely recovered within 8 weeks. Our results indicate that cerebellar lesions might induce pathological postural and intentional tremor of 2–3 Hz frequency. Due to its low frequency and low amplitude, quantitative tremorometry is neccessary to properly identify it. There is no tight correlation between lesion localization and quantitative characteristics of cerebellar tremor.

**Keywords** Tremor · Cerebellum · Recovery · Frequency · Accelerometry

## Introduction

The mechanism and nature of tremor in focal cerebellar lesions are poorely understood, and there are only a few quantitative data on tremor in focal cerebellar lesions. Both the 1998 and the 2018 consensus statements on tremor of the Movement Disorder Society define cerebellar tremor as mostly intention tremor with less than 5 Hz frequency; however, no quantitative studies are referred to [1, 2].

## Pathophysiology and Neurophysiological Characteristics of Cerebellar Tremor

Animal experiments showed that lesioning various cerebellar structures or cooling of the dentate nuclei might induce behavioral changes, impaired arm movement, and tremor, ipsilaterally to the side of the lesion [3–5]. In these experiments, various frequency values were detected at the elbow of monkey, ranging from 3–5 Hz [5] to 5–8 Hz [4]. Tremor frequency of 3–5 Hz in isotonic conditions decreased to 1.7–2.5 Hz in isometric conditions [5]. These findings led to the hypothesis that multiple mechanisms underlie cerebellar tremor and the central oscillator activity might be modulated by peripheral mechanisms. Other studies showed that sustained postural tremor could be detected only after harmaline injection even if the dentate nuclei were cooled [6, 7]. This suggested that

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concomitant involvement of upper brainstem monoaminergic pathways, which effect is multiplied by harmaline potentiating Cav3.1 channels' responsiveness, or the inferior olive might also be needed for sustained tremor [8].

Only a few human studies on tremor induced by lesions of cerebellar pathways have been published. Holmes made the first observations by investigating patients with isolated cerebellar damage [9]. He identified three types of tremor, each with different underlying pathomechanisms: static tremor (postural), kinetic tremor (intention) and a third type involving both the trunk and the head. He considered hypotonia and muscular asthenia the main causes of tremor. He also noted the absence of physiologic tremor in the affected limb [9].

In humans, frequency of cerebellar tremor was seldom measured quantitatively [10]. Cole and his colleagues described a 5–7-Hz tremor in patients with cerebellar damage using a strain gauge–based equipment [11]. Milanov, using EMG, reported a cerebellar tremor of 8–12 Hz, a frequency very similar to physiologic tremor [12]. In the literature we have encountered only one human quantitative study reporting EMG and accelerometry data on cerebellar tremor with less than 5 Hz in the so-called delayed onset cerebellar syndrome with a tremor of 1.5–4 Hz [13].

It is accepted that disruption of the dentato-rubro-thalamic tract (DRT) is the main cause of cerebellar tremor [14]. Cerebellar tremor might develop even without cerebellar lesion, if the DRT is damaged [15]. The DRT is involved in all tremor syndromes, which makes it an ideal deep brain stimulation-target [16]. It has not been disclosed yet why some patients with cerebellar lesion exhibit pathological tremor and others do not. Current imaging techniques provide deeper insight into the correlation between lesion anatomy and functional alterations [17]. Atlases showing the human cerebellum in a proportional stereotactic space are available [18–20]. Diffusion tensor imaging (DTI) studies precisely display cerebellar white matter stuctures [21]. Lesion–symptom studies demonstrated that both the anterior (especially lobule V) and posterior lobes (especially lobule VIII) contain a somatotopic representation of sensorimotor functions, including upper limb movements [22, 23]. Lobules VI–VII were connected to cognitive tasks [23], such as attentional focus during complex movements of the upper limbs [24]. To the best of our knowledge, quantitative parameters of tremor caused by focal cerebellar lesions have not yet been correlated with detailed cerebellar imaging.

### Recovery of Cerebellar Tremor

It is a clinical evidence that tremor due to acute cerebellar lesion regresses; however, there has been no objective follow-up study conducted. By investigating the amelioration of ataxia and bradykinesia after cerebellar stroke, it has been demonstrated that most of the improvement occurred in the first 2 weeks [25]. In neurodegenerative diseases involving the cerebellum and its connections, cerebellar symptoms do not recover; on the contrary, they progressively deteriorate.

### The Cerebellum in the Tremor Network

The cerebellum is "exclusively sensitive to all deviations of the intended movement" [14]. It is part of a complex tremor generator network and is involved in all tremor syndromes [14]. It works in close structural and functional relationships with the brainstem [14, 26] due to their abundant white matter connections and common blood supply. Moreover, it also influences the activity of basal ganglia [27]. Functional connectivity analyses in PD patients with rest tremor proposed that activity of the cerebello-thalamic circuit correlates with tremor amplitude, while basal ganglia set the onset and offset of tremor episodes [28]. The cerebellum has been connected to essential tremor (ET) [29–35] and to other degenerative diseases which might manifest with tremor, like multiple system atrophy type-C [36], spinocerebellar ataxias [37], and fragile X-associated tremor–ataxia syndrome [38]. All these disorders progressively worsen over time [39].

The objective of our study was to explore the prevalence, quantitative parameters, and recovery of pathological tremor in patients with focal lesions affecting the cerebellum. We studied the correlation between the occurrence and characteristics of tremor and lesion localization.

## Materials and Methods

### Patients

We examined 90 patients with focal lesions affecting the cerebellum and/or its pathways who were treated between 2014 and 2017 in the National Institute of Clinical Neurosciences, Budapest, Hungary, and 30 age-matched right-handed healthy controls. We involved 68 patients in the study. Exclusion criteria were the following: any type of cerebellar degeneration, diseases which may manifest with tremor (essential tremor, Parkinson's disease, Parkinsonian syndrome, hepatic encephalopathy, etc.), drugs which may cause tremor and/or Parkinsonian syndrome (alcohol, valproic acid, carbamazepine, lamotrigine, lithium, selective serotonine-reuptake inhibitors, haloperidol, benzodiazepins, barbiturates, etc.), patients with tremor with a center frequency which decreased more than 1 Hz after weight load [40], upper limb paresis, patients with severe vibratory sense deficit in the upper limbs ($\leq$ 5/8 on an arbitrary scale from 0 (no sensation) to 8 (normal sensation) of a Rydel–Seiffer 64-Hz tuning fork), insufficient cooperation, and multiple lesions in the CNS (multiple metastases, multiple vascular lesions). Patients with multiple sclerosis (MS) were not included, except one patient, who

developed tumefactive MS with only one brainstem and one parietal lesion.

We collected the following clinical data: age at symptom onset, sex, handedness, and time elapsed from symptom onset until the first tremor recording in case of patients with acute conditions and clinical symptoms at time of tremor recording. The 11 tumor patients were grouped in three subgroups according to histological findings (Supplementary Table 1). Patients were treated with antihypertensive drugs (ACE inhibitors, calcium channel blockers), cardio-selective beta-blockers, short-term osmotherapy when needed (mannitol, methyl-prednisolone), low-molecular-weight heparin in prophylactic or therapeutic dosage, antiplatelet drugs, proton pump inhibtors, statins, insulin, and antibiotics when needed. None of the patients received antipsychotics, antiepileptics, antidepressants, or propranolol. Details are presented in Supplementary Table 1.

The study was approved by the local ethical committee of the Institute. Subjects' informed consent was obtained according to the Declaration of Helsinki.

Controls were healthy individuals who had no history of neurological diseases and whose quantitative tremor analysis did not show pathological results.

## Experimental Design

### Clinical Examination

Patients underwent a detailed neurological examination. The presence of cerebellar nystagmus and truncal ataxia was accounted as vestibulo-cerebellar signs. Gait ataxia, which depends both on archi- and neocerebellar functions, could not be tested in many cases because of the patients' poor clinical condition; therefore, it was not included in clinical characterization. Hypotonia, limb ataxia, and postural/intentional tremor were accounted as motor cerebellar signs. Hypotonia was examined by passive joint movements and by Holmes-rebound test. Finger-to-nose test was used to detect upper limb intention tremor. For clinimetric tremor rating, we used the Fahn–Tolosa–Marin scale part A because the use of this scale is recommended by the Movement Disorders Society, and it is suitable for both postural and kinetic/intentional positions [41].

### Tremor Recording

Tremor parameters were measured using a computerized test system (CATSYS 2000, Danish Product Development Ltd., Snekkersten, Denmark). Patients were seated comfortably. Measurements were carried out on the right and left hand simultaneously. Tremor was recorded for 20 s in six different positions: (1) at rest (RT): the forearm and the hand were fully supported on a table; (2) in postural position with eyes open (PTeo): the arm and hand were held against gravity in an outstretched, horizontal, prone position with eyes open; (3) in postural position with closed eyes (PTec): the arm and hand were held against gravity in an outstretched, horizontal, prone position with eyes closed; (4) in postural position with weight load (PTwl): the arm and hand were held against gravity in an outstretched, horizontal, prone position with eyes closed and with a load of 200 g which was secured at the level of the metacarpophalangeal joints of the hand; (5) in a kinetic precision task (kinetic tremor; KT): on a 14.1-in. screen the patient with his index finger followed the tip of an arrow moving with a uniform rectilinear motion with a speed of 0.015 m/s; (6) in a static precision task (intention tremor; IT): the patient with his index finger pointed to the tip of an arrow, stable on the screen. Patients in poor clinical condition were not assessed in PTwl and/or in KT and/or in IT positions.

Tremor was registered using a biaxial micro-accelerometer (weight 10.5 g, sensitivity > 0.3 $m/s^2$), fixed between the second and the third metacarpal bone, 2 cm proximal to the metacarpophalangeal joint as it has been described previously [42]. Accelerometry signals of the two axes were digitized at 128 Hz. Data between 0.9 and 25 Hz were analyzed. Tremor parameters were derived from fast-Fourier power spectra. The following parameters described in previous studies [42, 43] were automatically calculated by the built-in software of our CATSYS tremor recording system: (1) *Tremor intensity* (TI, $m/s^2$), which is related to tremor amplitude, was calculated as the root-mean square of acceleration. (2) *Frequency dispersion* (FD, Hz) which reflects the regularity of tremor was defined as the half width of the frequency band centered on the peak frequency containing 68% of the total power. The frequency dispersion of physiologic tremor is broad (3–4 Hz), while it is reduced (0.5–1 Hz) in pathological tremors like parkinsonian or essential tremor [42]. (3) *Center frequency* (CF, Hz) is the frequency below which lies 50% of the power in the spectrum. CATSYS provides this parameter, because, as it has been discussed by Edwards and Beuter [44], a computer-based system must use a clearly defined algorithm for calculation of tremor frequency characteristics in all subjects. However, when there is no apparent peak frequency, or the spectrum is bi- or trimodal, the calculated CF may lie at a frequency without much power, unrelated to any oscillatory component of the signal [45]. In our study, since we have not filtered out the low-frequency components, patients with physiologic tremor and controls had bimodal spectra: one in the low-frequency range related to the eigenfrequency of physiologic shoulder oscillation [46] and one in the higher frequency range representing the true frequency of tremor. Patients with pathological tremor always had unimodal spectra; the center and peak frequencies were in the low-frequency range, due to the increased relative power of low-frequency pathologic tremor components. The relation between center and peak frequency is presented in Supplementary Fig. 1. To

determine the impact of low-frequency components on center frequency, we introduced a new measure, the (4) *proportional power of 0.9–3 Hz frequency range* (PP 0.9–3 Hz, %), which quantifies the contribution of the low-frequency range to the total power in percentage. The proportional power of 0.9–3 Hz range is expected to increase in pathological low-frequency tremors.

In case of patients with acute stroke, tremor recordings were carried out as early as possible, but no longer than 10 days after symptom onset. Consecutive measurements were perfomed to determine the changes of tremor paramaters during clinical recovery.

For the 30 age-matched right-handed healthy controls, we used the same tremor measurement protocol that was used for patients. For normal values of children, we used the database of Després et al. [47], who have defined tremor parameters only in postural position.

Pathological values in adult patients were defined as outliers from the control group, according to the following formula: values $< q25 - (q75 - q25) \times 1.5$ and values $> q75 + (q75 - q25) \times 1.5$ where q75 represents the upper quartile, q25 the lower quartile, and $q75 - q25$ the interquartile range. Pathological values in children were defined as lower or higher values than the mean ± 2SD (as data for computing q25 and q75 were not available). Normal values for both children and adults are presented in Supplementary Table 2.

Tremor was considered pathological if center frequency was lower than 5.2 Hz in postural and 4.81 Hz in intentional position. Frequency dispersion lower than 3 Hz in postural and 2.33 Hz in intentional position was another sign of pathology. Tremor intensity elevated on both sides without alteration of frequency or frequency dispersion was not used as an indicator of pathological tremor since it characterizes enhanced physiologic tremor. However, tremor intensity in postural position higher than 0.3 $m/s^2$ ipsilaterally to the side of the lesion was considered pathological and it delineated a distinct group of patients.

### Neuroimaging

**MRI Measurement** All patients underwent skull MRI examination. In case of 34 patients, high-resolution 3D T1-weighted structural image series were acquired on a 3T Magnetom Verio MRI scanner (Siemens, Erlangen, Germany) using a magnetization prepared rapid gradient echo (MPRAGE) sequence (TR = 2300 ms; TE = 3.94 ms; TI = 1100 ms; flip angle = 12°; spatial resolution 1 × 1 × 1 mm). Standard Siemens 12-channel head coil was applied. All data were acquired at the National Institute of Clinical Neurosciences, Budapest, Hungary. In case of the other 34 patients, MPRAGE images were not available, since MRI scans were obtained in other institutions, using different protocols.

**Image Preprocessing** We used the SPM12-toolbox (Wellcome Trust Centre for Neuroimaging, University College, UK) and custom MATLAB (The Mathworks) codes for preprocessing. The images were reoriented with the horizontal line defined by the anterior and posterior commissures (ACPC orientation) and the sagittal planes parallel to the midline. Every lesion was defined manually with MRIcron (https://www.nitrc.org/projects/mricron) and saved as region of interest (ROI) files. The spatially unbiased infratemporal template (SUIT) of the cerebellum toolbox 3.2 was used for normalization, cerebellar lobule segmentation, and cerebellar lesion detection [19, 20, 48, 49]. SUIT was designed for cerebellar lobule segmentation and cerebellar lesion detection. It can show if the brainstem is affected, but it is not able to distinguish brainstem nuclei. Therefore, the affected brainstem regions could not be precisely determined. We used the SUIT built-in functions to define the size of each ROIs and to determine what regions/cerebellar lobules were affected. Figures presenting overlapping or adjacent lesions were prepared with MRIcron.

### Statistical Analysis

Statistical analysis was performed using the Statistica software package (Statsoft Inc., 8.0 version, Tulsa, OK, USA). Due to small sample size, the distribution of data was controlled using Shapiro–Wilks test. Parametric and non-parametric tests were used. To compare tremor parameters in various recording positions, *t* test or Wilcoxon's signed rank test was applied. To compare tremor parameters in patients with low-frequency tremor, physiologic tremor, and controls, we applied one-way ANOVA or Kruskal–Wallis test; for post-hoc comparisonwe used Scheffé test or Dunn's test. To investigate if there is any correlation between lesion size and tremor parameters, we used Pearson correlation or Spearman correlation test. To compare tremor parameters between patients with lesions affecting the cerebellum and the brainstem together and those with lesions affecting the cerebellum only, furthermore, in patients with involvement of various cerebellar lobules and those without, we applied independent sample *t* test or Mann–Whitney test. The alpha level to determine significance was set to 0.05.

## Results

### Patients and Clinical Data

We investigated 90 patients with cerebellar lesion and included 68 in the study (Supplementary Table 1). We excluded five patients because of residual upper limb paresis due to earlier strokes, four due to multiple CNS lesions, three because their medication (phenytoin, valproic acid, antidepressants) might have influenced the results, five patients because of cerebellar

atrophy of unknown origin, three due to concomitant essential tremor, and two patients due to Parkinson's disease.

Most of the patients were right-handed (91.18%), middle-aged adults, with acute stroke (28 patients (41.17%), symptom onset less than 1 week) or tumor (29 patients, 42.64%). Six patients (8.82%) had stroke with a symptom onset longer than 3 weeks. One patient had tumefactive demyelination, two had abscess, and two other patients had cavernoma. Patients with tumor were investigated before surgical intervention. Acute stroke patients were assessed in the first 10 days after symptom onset (6.57 ± 4.1 days). Six patients (8.82%) were children (mean age 7.5 ± 2.42 years); all of them had CNS-tumors.

Cerebellar motor syndrome developed in 48 patients (70.58%): hypotonia was found in 11 (16.17%), and limb ataxia was present in 30 patients (44.11%). We have not found rest tremor in any patient. Intentional and/or postural tremor was visible at routin clinical examination in only 13 patients (19.11%). Tremor severity in these patients assessed by the Fahn–Tolosa–Marin scale did not exceed 1 point. Twenty-five (36.76%) patients presented with vestibulo-cerebellar syndrome. Brainstem signs were seen in 14 (20.58%) patients (Supplementary Table 1).

## Tremor Data

### Neurophysiological Characteristics

Rest tremor parameters of patients did not differ from that of controls. Parameters of PTeo did not differ from PTec. Parameters of KT did not differ from IT. Therefore, PTeo and KT data are not presented in the text, only in Table 1 and in Supplementary Table 3. Characteristics of PTec (referred to as PT) and IT are described in details in the following sections. (For all tremor parameters, see Supplementary Table 3.)

Based on quantitative measures, we identified three tremor patterns in our patients: (A) *low frequency pathological tremor* (LFT) with CF lower than or equal to the lower limits (as defined in "Materials and Methods" and presented in Supplementary Table 2), in at least two recording positions (e.g., ≤ 5.2 Hz in PT and ≤ 4.81 Hz in IT); (B) *physiologic tremor* (PHT); and (C) *high-intensity–normal frequency pathological tremor* (HINFT), where TI was higher than or equal to the upper limit (as defined in "Materials and Methods" and presented in Supplementary Table 2) only ipsilaterally to the lesion, in at least two recording positions (e.g., ≥ 0.3 m/s$^2$ in PT or ≥ 0.33 m/s$^2$ in IT). CF was in the normal range. Tremor time series and corresponding power spectra of the various tremor types are presented in Fig. 1. Mean and standard deviation of tremor parameters of different tremor groups and controls are shown in Table 1.

(A) *Low frequency pathological tremor* was found in 36.76% of the patients ($n$ = 25/68). It was characterized by a low CF, low FD, and high PP of 0.9–3 Hz frequency range. CF of PT and IT was 2.38 ± 0.88 Hz and 2.91 ± 0.95 respectively. CF of PT and PTwl was not significantly different. FD of PT and IT was 1.50 ± 1.17 Hz and 1.70 ± 1.47 Hz respectively. PP of 0.9–3 Hz range was around 50% for all positions, twice as high as in the two other groups. TI was higher than normal in 7/25 patients only (28%). Mean values were 0.25 ± 0.17 m/s$^2$ in PT and 0.34 ± 0.19 m/s$^2$ in IT.

(B) In the *physiologic tremor* group ($n$ = 36/68, 52.94%), CF of PT and IT was 7.81 ± 1.29 Hz and 7.12 ± 1.40 Hz respectively. In PTwl, CF was significantly lower compared to PT (6.35 ± 1.40 Hz, $t = -4.83$, df = 23, $p < 0.001$). FD of PT and IT was 4.55 ± 1.07 Hz and 4.26 ± 1.33 Hz respectively. PP of 0.9–3 Hz range was 22.83 ± 7.02% in PT and 19.86 ± 7.60% in IT.

(C) The *high-intensity–normal frequency pathological tremor* group ($n$ = 7/68, 10.29%) included four adults and three children. These patients showed normal or slightly, but not significantly elevated CF. (Note that reference range for adults and children differ. Results were compared to the appropriate reference range shown in Supplementary Table 2. For children, results of PT are presented.) Mean CF was normal for both PT and IT (8.66 ± 1.67 Hz and 8.9 ± 1.3 Hz, respectively). Mean FD of PT was normal (4.33 ± 1.39 Hz) but decreased in IT (2.79 ± 1.14 Hz). TI was elevated only ipsilateral to the lesion. Mean TI for adults was 0.35 ± 0.17 m/s$^2$ in PT and 0.51 ± 0.13 m/s$^2$ in IT. Children showed normal average CF (4.51 ± 2.98 Hz in postural position), a decreased average FD (2.36 ± 1.56 Hz), and a considerably elevated average TI of 0.90 ± 0.30 m/s$^2$.

Statistics showed that there was a significant difference of CF, FD, and PP of 0.9–3 Hz range between the LFT, PHT, and control groups. Significant group effect on CF was observed in PT ($H(83) = 47.92$, $p < 0.001$) and in IT ($H(72) = 40.19$, $p < 0.001$) as well as on FD in PT ($H(82) = 42.94$, $p < 0.001$) and in IT ($H(75) = 31.98$, $p < 0.001$). Similarly, significant group effect on PP of 0.9–3 Hz range was demonstrated in PT ($F(79) = 119.02$, $p < 0.001$) and in IT ($F(66) = 88.86$, $p < 0.001$). The group effect on TI reached level of significance only in IT ($H(73) = 6.26$, $p = 0.04$). However, post-hoc tests revealed that patients with PHT did not differ from controls. In contrast, patients with LFT had significantly lower FD and CF and signicantly higher PP of 0.9–3 Hz range than patients with PHT and controls (Supplementary Table 4).

**Table 1** Mean and standard deviation of tremor parameters of different tremor type groups

| Parameters | Low-frequency tremor ($n = 25$) | | Physiologic tremor ($n = 36$) | | Adult controls ($n = 30$) | | High-intensity tremor (n=4) | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Tremor intensity | | | | | | | | |
| RT TI | 0.06 | 0.02 | 0.07 | 0.03 | 0.06 | 0.01 | 0.06 | 0.02 |
| PTeo TI | 0.23 | 0.11 | 0.18 | 0.04 | 0.19 | 0.04 | 0.35 | 0.26 |
| PTec TI | 0.25 | 0.17 | 0.19 | 0.05 | 0.19 | 0.04 | 0.35 | 0.17 |
| PTwl TI | 0.21 | 0.11 | 0.20 | 0.06 | 0.18 | 0.04 | | |
| KT TI | 0.29 | 0.08 | 0.24 | 0.06 | 0.24 | 0.06 | | |
| IT TI | *0.34* | 0.19 | 0.25 | 0.07 | 0.22 | 0.05 | 0.51 | 0.13 |
| Center frequency | | | | | | | | |
| RT | 12.82 | 1.24 | 13.33 | 1.55 | 14.13 | 1.30 | 13.26 | 1.30 |
| PTeo | *2.92* | 1.60 | 7.55 | 1.21 | 7.77 | 0.93 | 8.82 | 1.32 |
| PTec | *2.38* | 0.88 | 7.81 | 1.29 | 7.87 | 0.98 | 8.66 | 1.67 |
| PTwl | *2.50* | 0.69 | 6.39 | 1.40 | 6.54 | 1.14 | | |
| KT | *2.59* | 1.77 | 7.01 | 1.67 | 8.09 | 1.13 | | |
| IT | *2.91* | 0.95 | 7.12 | 1.40 | 8.04 | 1.06 | 8.9 | 1.3 |
| Frequency dispersion | | | | | | | | |
| RT | 7.18 | 0.53 | 7.15 | 0.61 | 6.91 | 0.86 | 7.05 | 0.52 |
| PTeo | *1.83* | 1.51 | 4.49 | 1.01 | 4.69 | 0.76 | 4.55 | 1.14 |
| PTec | *1.50* | 1.17 | 4.55 | 1.07 | 4.66 | 0.64 | 4.33 | 1.49 |
| PTwl | *1.57* | 1.10 | 4.02 | 0.85 | 4.03 | 0.93 | | |
| KT | *1.27* | 0.74 | 4.18 | 1.47 | 4.71 | 0.93 | | |
| IT | *1.70* | 1.47 | 4.26 | 1.33 | 4.75 | 0.91 | 2.79 | 1.14 |
| Proportional power of 0.9–3 Hz | | | | | | | | |
| RT | 6.69 | 2.50 | 6.93 | 1.85 | 6.67 | 1.87 | 6.67 | 0.78 |
| PTeo | *55.05* | 15.40 | 24.25 | 8.20 | 19.30 | 4.84 | 20.16 | 9.68 |
| PTec | *56.93* | 14.08 | 22.83 | 7.02 | 20.68 | 5.86 | 18.16 | 9.68 |
| PTwl | *56.88* | 12.42 | 29.13 | 7.59 | 25.59 | 7.94 | | |
| KT | *46.98* | 18.20 | 17.83 | 6.16 | 16.59 | 4.15 | | |
| IT | *54.43* | 15.84 | 19.86 | 7.60 | 17.49 | 4.83 | 13.19 | 10.80 |

Numbers in italics identify values significantly different compared to the two other groups

*RT* rest tremor, *PTeo* postural tremor with eyes open, *PTec* postural tremor with eyes closed, *PTwl* postural tremor with weight load, *KT* kinetic tremor, *IT* intention tremor

Due to the normal range difference between children and adults, the HINFT group should have been divided into two subgroups; however, the small sample sizes ($n = 4$ adults and $n = 3$ children) did not allow further meaningful statistical analysis.

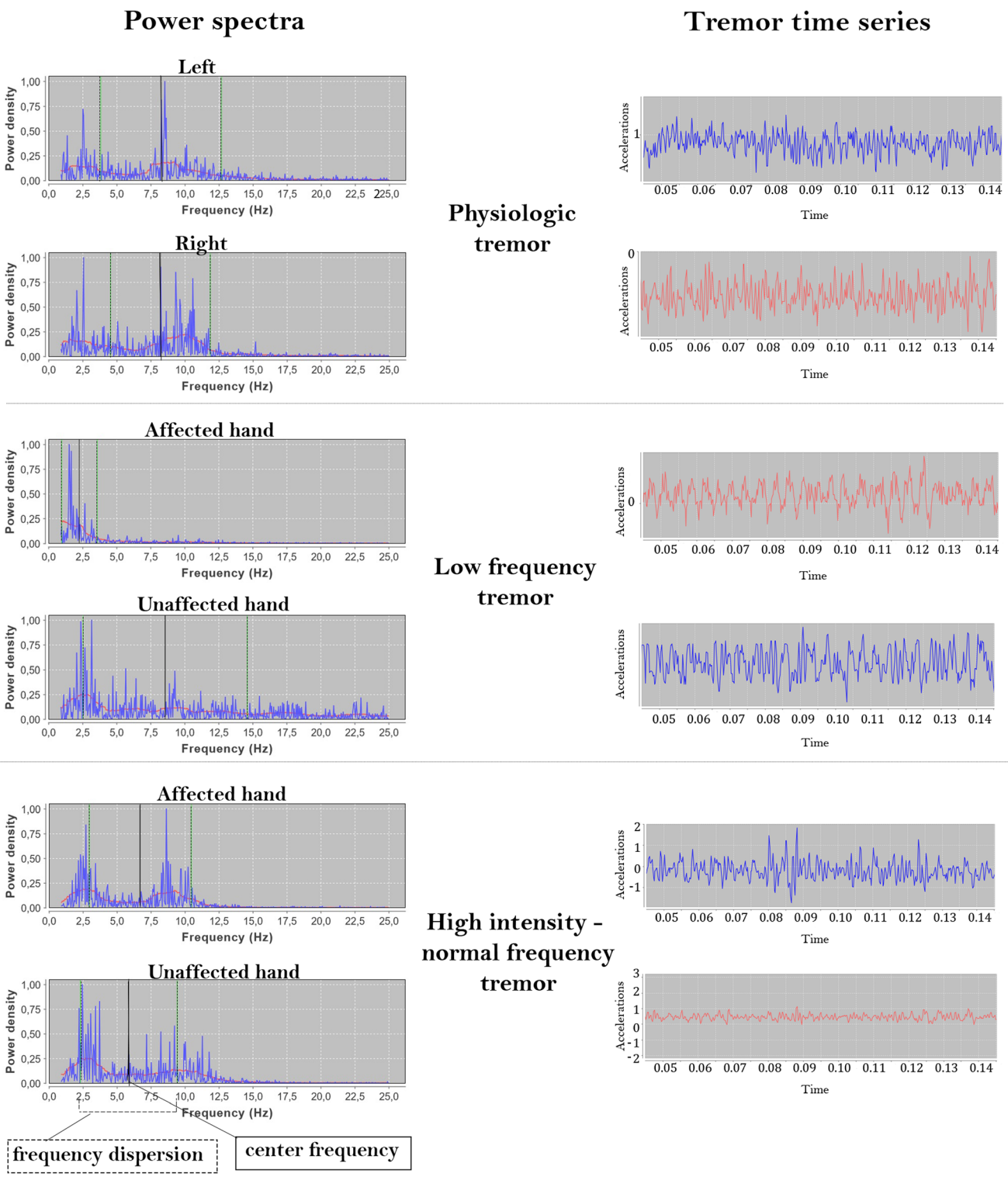
## Prevalence of Pathological Tremor in Patients with Cerebellar Lesion

Quantitative tremor measurements proved pathological tremor in 32 out of 68 cases (47.05%), while the rest of the patients had PHT.

Among patients with pathological tremor, LFT developed in 25 (78.12%), while HINFT in 7 (21.87%, three of these were children).

Lesions of various origins were associated with different tremor patterns. LFT was found in acute stroke, in metastases, and in malignant primary CNS tumors in adults. HINFT was rare in adults but frequent in children. PHT was found in chronic stroke lesions and meningeomas (Table 2).

**Fig. 1** The three different tremor types caused by cerebellar lesions. ▶ Curves on the right show the digital accelerometric tremor time series. Curves on the left are the corresponding power spectra plots. Continuous black lines indicate center frequency. Dashed lines delineate the band width of frequency dispersion. The plots showing physiologic tremor were recorded from patient "10FSz" who had a cerebellar metastasis, involving lobules I–IX and all cerebellar deep nuclei, bilaterally. Each tremor parameter was in the normal range: TI was 0.14 m/s$^2$ (left) and 0.2 m/s$^2$ (right); CF was 8.2 Hz both sides; FD was 4.43 Hz (left) and 3.66 Hz (right); PP of 0.9–3 Hz range was 20.2% (left) and 19.7% (right). The plots showing low-frequency tremor were recorded from patient "1ADV" who had a tumefactive MS lesion involving lobules I–V, IX–X, and the dentate nucleus, unilaterally. Tremor on the affected side had normal TI (0.15 m/s$^2$), decreased CF (2.25 Hz), low FD (1.3 Hz), and increased PP of 0.9–3 Hz range (59.95%). The unaffected side had normal TI (0.16 m/s$^2$), normal CF (8.55 Hz), normal FD (6.02 Hz), and normal PP of 0.9–3 Hz (20.92%). The plots showing high-intensity tremor were recorded from patient "8DE" who had a tumor (with unidentified histology) involving the upper brainstem and lobules I–V, IX, and the dentate and fastigial nucleus, unilaterally. Tremor on the affected side had three times higher TI (0.58 m/s$^2$) compared to the unaffected side (0.25 m/s$^2$). CF was normal on both sides (6.7 Hz—affected, 5.85 Hz—unaffected), and FD was normal on both sides (3.75 Hz—affected, 3.56 Hz—unaffected). PP of 0.9–3 Hz range was also normal on both sides (25.94%—affected, 24.91—unaffected)




Pathological tremor developed in both postural and intentional position in 20 patients out of 32 (62.5%). Three patients (9.37%) had intention tremor only and another three (9.37%) developed postural tremor only. (Tremor recordings in intentional position could not be carried out in six cases.) Rest tremor was not observed in any cases.

## MRI Data

MPRAGE images were available for 34 patients. The affected cerebellar structures in these patients are presented in Supplementary Table 5. Clinical and tremor data for these patients are summarized in Supplementary

**Table 2** Prevalence of pathological tremor in cerebellar lesions of various origins

| Cause of the lesion | | Number of patients | Number of patients with low-frequency tremor (%) | Number of patients with high-intensity tremor (%) | Number of patients with physiologic tremor (%) |
|---|---|---|---|---|---|
| Acute stroke | | 28 | 17 (60.71) | 1 (3.57) | 10 (35.71) |
| Chronic stroke | | 6 | 0 (0) | 0 (0) | 6 (100) |
| Malignant primary CNS tumors | Adults | 3 | 2 (66.66) | 1 (33.33) | 0 (0) |
| | Children | 6 | 0 (0) | 3 (50) | 3 (50) |
| Metastases | | 11 | 5 (45.45) | 0 (0) | 6 (54.54) |
| Meningioma | | 9 | 0 (0) | 1 (11.11) | 8 (88.88) |
| Others (MS, abs, cav) | | 5 | 1 (MS) (20) | 1 (abs) (20) | 3 (60) |

*MS* multiple sclerosis, *abs* abscess, *cav* cavernoma

Table 6. The estimation of affected brainstem and white matter structures are presented in Supplementary Table 7.

Both cerebellar hemispheres were affected in 15/34 patients (44.11%). In most tumor or ischaemia cases, the lesion was unilateral, but the perifocal oedema involved the opposite side as well. These cases were considered bilateral. Prevalence of involvement of various cerebellar structures is presented in Table 3. The mean lesion size was 2829.677 ± 3456.57 voxels.

The brainstem was affected in 11 of 34 patients (32.35%): the medulla oblongata in 6 (17.64%), the pons in 7 (20.58%), and the midbrain in 3 (8.82%). Two patients had isolated brainstem lesion affecting the pons (5.88%).

## Correlation Between Tremor Parameters and MRI Data

There was no correlation between any tremor parameter and the size of the lesion (correlation coefficient varied between 5 and 32% among various tremor parameters).

Lesions grouped according to LFT, PHT, and HINFT types are presented in Fig. 2. LFT was induced by a variety of lesions involving the midline structures, the anterior lobe and the posterior lobe of the cerebellar hemispheres (Fig.2a, b). Lesions which affected the anterior lobe with or without the midbrain structures caused tremor with low CF and high TI (Fig. 2c). The midbrain was affected in both of those patients who presented with HINFT (Fig. 2d).

**Table 3** Percentage of patients with pathological tremor parameters according to the affected cerebellar lobules/deep nuclei and brainstem

| Localisation of the lesion | Number of patients with that lobulus/nucleus affected | Number of patients with pathologic tremor parameters | Percentage of patients with pathologic tremor parameters |
|---|---|---|---|
| I–IV | 11 | 7 | 63.63 |
| V | 15 | 8 | 53.33 |
| Anterior lobe only | 5 | 3 | 60.00 |
| VI | 14 | 7 | 50.00 |
| Crus I | 15 | 8 | 53.33 |
| Crus II–VIIB | 17 | 9 | 52.94 |
| VIII | 19 | 9 | 47.36 |
| IX | 21 | 12 | 57.14 |
| Posterior lobe only | 10 | 6 | 60.00 |
| X | 12 | 8 | 66.66 |
| Vermis | 13 | 7 | 53.84 |
| Whole cerebellum | 5 | 3 | 60.00 |
| Dentate nucleus | 20 | 11 | 55.00 |
| Interposed nucleus | 13 | 6 | 46.15 |
| Fastigial nucleus | 8 | 5 | 62.50 |
| Brainstem | 11 | 9 | 81.81 |

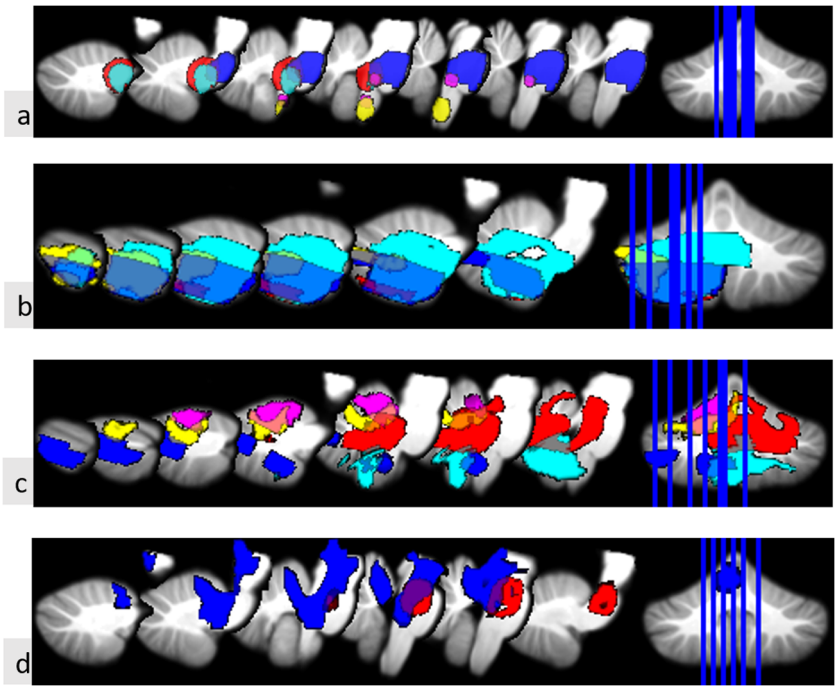



**Fig. 2** Lesions in patient groups with different tremor characteristics. **a** Lesions of five different patients with low-frequency, normal intensity tremor (1ADV in red, 15HK in dark blue, 17KT in light blue, 20KK in purple, 29SJ in yellow). **b** Lesions of four different patients with low-frequency, normal intensity tremor (19KJ in dark blue, 27NKE in red, 23MS in yellow, 3BA in light blue). **c** Lesions in patients with low-frequency, high-intensity tremor (4BI in red, 24MJ in dark blue, 25MP in light blue, 33TGy in purple, 34VM in yellow). **d** Lesions in patients with high-intensity–normal-frequency tremor (2BJ in red, 8DE in blue). Different colors depict different patients in each part of the figure

Interestingly, lesions in the same brain regions of different patients resulted in different tremor parameters (Fig. 3). Figure 3a shows two patients (34VM in red, 18KL in blue), both of them had acute ischaemia in the territory of the superior cerebellar artery. Patient 34VM developed LFT (CF = 2 Hz, FD = 0.7 Hz), while patient 18KL had PHT (CF = 8.75 Hz, FD = 4.29 Hz). Lesions in both patients involved lobules I–VI but that of 34VM affected the vermis, Crus II, and lobulus VIIB, as well. Lesion size of the non-tremorous patient was twice as big as the lesion of the tremorous patient.

Figure 3b (patient 9EE in dark blue, 24MJ in yellow, and 27NKE in red) and Fig. 3c (patient 25MP in red, 26MGy in dark blue and 22MZ in light blue) show six patients with acute ischaemia in the territory of the posterior inferior cerebellar artery (PICA). All lesions affected the posterior lobe to various extents. Three patients (24MJ, 27NKE, and 25MP) developed pathological tremor (CF below 2 Hz, FD below 1 Hz). Two of them (24MJ and 25MP) had lesions in both cerebellar hemispheres and in the connected brainstem sructures as well, and these had elevated TI (higher than 0.62 m/s$^2$). The TI of patient 27NKE was normal (0.1 m/s$^2$). The three other patients had physiologic tremor. The affected cerebellar lobules and nuclei of the tremorous and non-tremorous patients were overlapping, with minor differences. The non-tremorous patient shown on Fig. 3b had the most extensive lesion. All PICA lesions involving the brainstem resulted in pathological tremor.

Figure 3d shows three overlapping lesions, all affecting mainly the anterior lobe. However, the lesions of the two patients who developed pathological tremor (patient 1ADV in red: CF = 2.45 Hz, FD = 1.2 Hz and patient 17KT in yellow: CF = 2.1 Hz, FD = 1.25 Hz) affected both lobules IX and X, whereas the lesion of the non-tremorous patient affected only the anterior lobe (patient 5BI in blue, CF = 6.2 Hz, FD = 3.8 Hz).

Lesions affected both cerebellar hemispheres in 15 patients out of those 34 who had MPRAGE images (44.11%). None of these patients developed bilateral pathological tremor. Pathological tremor was present in 8 out of 15 (53.33%) always ipsilaterally to the hemisphere with the more extensive lesion. Tremor parameters did not significantly differ between patients with uni- and bilateral cerebellar involvement. Lesions affecting the deep cerebellar nuclei did not produce tremor more frequently and were not associated with statistically lower FD, CF, or higher TI than lesions with intact deep nuclei. Tremor characteristics and tremor occurrence were not statistically different in patients with uni- or bilateral deep nuclei involvement.

The prevalence of pathological tremor was between 45 and 65% in case of any cerebellar lobulus or deep nucleus lesion (Table 3). Patients with anterior lobe and those with posterior lobe involvement developed tremor with 60% prevalence. If the anterior lobe and lobules V–VI or VIII were affected, the occurrence of pathological tremor was 47–63%. Even in cases when all cerebellar lobules and the vermis were affected, only 60% of patients developed pathological tremor. In patients with brainstem involvement (with or without affected cerebellum), the prevalence of pathological tremor was much higher (81.81%) than in those with cerebellar involvement only.

When comparing patients with involvement of lobules I–IV, V, and VI to those whose corresponding lobules were not affected, significant differences were found. Patients with

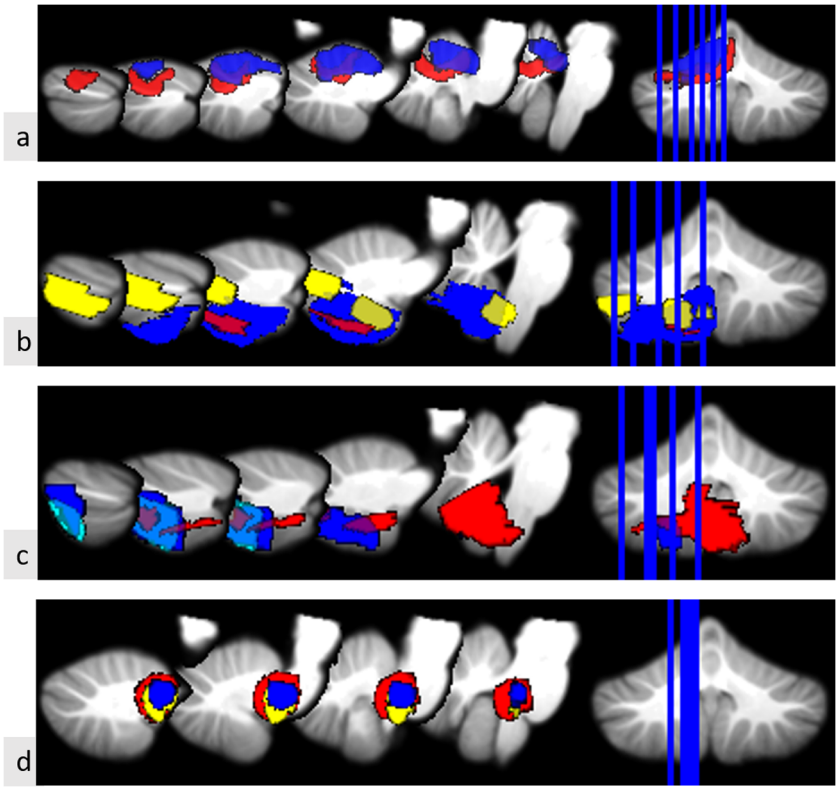



**Fig. 3** Lesions in the same brain regions result in different types of tremor. Lesions with red and yellow were associated with low-frequency tremor. Lesions with dark or light blue were associated with physiologic tremor. (Violet represents the overlap of red and blue.) **a** Patient 34VM in red and 18KL in blue with ischaemia in the territory of the superior cerebellar artery. Patient 34VM developed low-frequency pathological tremor, while patient 18KL had physiologic tremor. Note that the lesion size of the non-tremorous patient is twice as big. **b**, **c** Six patients with acute ischaemia in the territory of posterior inferior cerebellar artery (In **b**: 27NKE in red, 24MJ in yellow, 9EE in dark blue, and in **c**: 25MP in red, 26MGy in dark blue and 22MZ in light blue). All lesions affected the posterior lobe to various extent. Three patients (24MJ, 27NKE, and 25MP) developed pathologic tremor. Two of them (24MJ and 25MP) had brainstem lesion, and both cerebellar hemispheres were affected. The two patients with brainstem lesion had elevated TI, whereas 27NKE had normal TI. The three other patients had physiological tremor. The affected cerebellar lobules and nuclei were overlapping, with minor differences. The non-tremorous patient on **b** had the most extensive lesion. **d** Three overlapping lesions, all affecting mainly the anterior lobe. Patient 1ADV in red and patient 17KT in yellow had low-frequency tremor while patient 5BI in blue did not have pathologic tremor

affected I–IV lobules had significantly higher tremor intensity in all positions than those without: in PTeo ($U = 65$, $Z = 1.97$, $p = 0.04$), in PTec ($U = 48$, $Z = 3$, $p = 0.002$), in PTwl ($t(20) = 2.21$, $p = 0.03$), in KT ($t(28) = 2.21$, $p = 0.03$), and in IT ($t(24) = 4.19$, $p < 0.001$). Patients with affected lobulus V had significantly higher TI than patients with intact lobulus V in PTec ($U = 64$, $Z = 2.21$, $p = 0.02$) and in IT ($t(24) = 3.21$, $p = 0.003$). Patients with affected lobulus VI had significantly higher TI in KT ($t(19) = 2.26$, $p = 0.03$) and in IT ($t(24) = 2.19$, $p = 0.03$). Schematic overview of the contribution of cerebellar lobes to change in tremor intensity is presented in Fig. 4.

We have created three groups according to the involved cerebellar lobe(s): (1) the anterior lobe only, (2) the posterior lobe only, and (3) both lobes are affected. Tremor parameters did not significantly differ among these groups.

Lesions affecting the brainstem and affecting both the cerebellum and brainstem evoked the same LFT and HINFT types as lesions affecting the cerebellum only. Patients with brainstem involvement showed significantly higher TI in postural position than those without ($t(13) = -2.69$, $p = 0.01$). The difference of TI in intentional position did not reach the level of significance. In patients with brainstem involvement, CF and FD were significantly lower in intentional position only compared to patients with lesions affecting the cerebellum only (CF of IT ($t(11) = 2.41$, $p = 0.03$) and FD of IT ($t(12) = 2.32$, $p = 0.03$)). PP of 0.9–3 Hz range was significantly higher in patients with brainstem lesion in IT ($t(12) = -2.21$, $p = 0.04$).

## Temporal Characteristics of Cerebellar Tremor Recovery

Ten patients with acute stroke that caused pathological tremor (35.71% of all patients with acute stroke and 31.25% of all patients with pathological tremor) were followed up until their tremor became physiologic. Increase of center frequency and frequency dispersion of intentional tremor was used as main indicator of tremor recovery. Power spectra presenting the

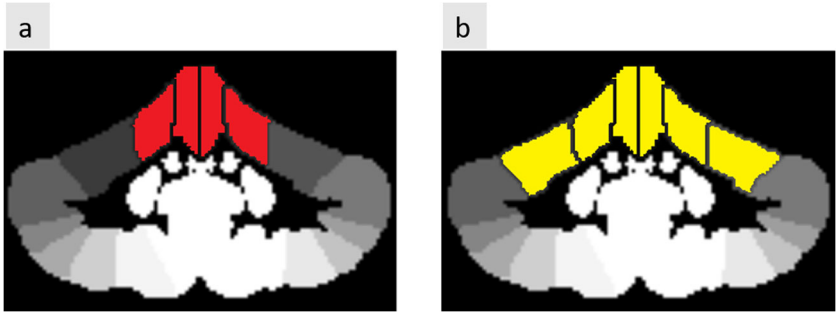



**Fig. 4** Lesion–symptom map of increased tremor intensity of postural and intentional tremor caused by cerebellar lesions. Cerebellar lobules I–X and cerebellar deep nuclei are presented according to SUIT atlas in different shades of gray. **a** In red, lobules I–IV and lobule V are shown bilaterally, which were statistically associated with higher tremor intensity in postural position. **b** In yellow, lobules I–IV and lobules V and VI are shown bilaterally, which were statistically associated with higher tremor intensity in intentional position. Lobule VI was involved only in pathological intentional tremor

gradual increase of CF and FD as sign of tremor recovery in one of our acute ischemic cerebellar stroke patient are presented in Supplementary Fig. 2. The speed of recovery was different (minimum 1, maximum 8 weeks), but the pathological tremor ceased within 3.65 ± 2.66 weeks in all followed acute stroke patients (Fig. 5). There was no correlation between any parameter of tremor and duration of recovery or localisation of the lesion.

## Discussion

In our paper, we present the results of the first systematic study on quantitative parameters of tremor related to focal cerebellar lesions localized by high-resolution MRI scans.

Postural tremor as a consequence of cerebellar lesion has already been mentioned by Holmes in 1922, who named it as "static tremor" [9]. Our quantitative data show that cerebellar lesions cause pathological tremor both in postural and intentional position, but not in rest. In our patients, the quantitative characteristics and recovery profile of postural and intentional tremor were similar.

Postural tremor in cerebellar lesion is considered a frequent clinical finding. However, in our 68 patients with cerebellar lesion, neurological bedside examination detected tremor in only 20%, while quantitative accelerometry revealed pathological tremor in 50% of the cases. Clinical assessment could not identify 30% of patients with pathological tremor. This shows the importance of objective quantitative tremor registration which is inevitable not only for the appropriate diagnosis but also for pathophysiological considerations.

In our study, we used accelerometry without parallel EMG recording. Accelerometry is a simple and reliable technique for tremor analysis [47–49]. Both linear (root-mean square,

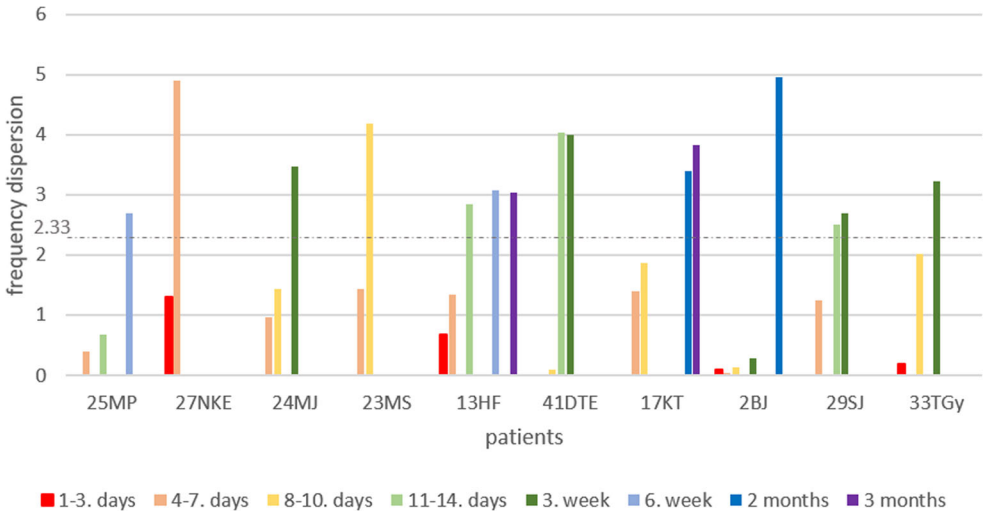



**Fig. 5** Recovery of intention tremor in 10 acute stroke patients. Intention tremor in cerebellar lesions recovers in 1–8 weeks. Recovery of intention tremor was demonstrated by the increase of frequency dispersion during follow-up. Serial tremor registrations were carried out in 10 patients with acute stroke. Increase of frequency dispersion was used as indicator of tremor reduction. The dashed line shows the lower limit of normal frequency dispersion in this position (2.33 Hz). Different colors indicate various time points of tremor recordings after symptom onset. Postural tremor showed similar improvement (data are not presented)

frequency parameters) and non-linear (fractal analysis, approximate entropy) analysis procedures have been successfully applied to accelerometry [50, 51]. Recent studies, introducing a new tremor parameter, the tremor stability index, found accelerometry more suitable than EMG as it is able to capture the temporal variability of tremor, whereas EMG is focused on the possible variability driven by the sampled muscles [52]. Results of accelerometry recordings are in strong correlation with clinical tremor ratings both in ET [53] and PD [54].

To identify the quantitative characteristics of cerebellar tremor, we measured those parameters (intensity, peak frequency, center frequency, frequency dispersion) which have already been determined in classical tremor syndromes like Parkinson's disease and essential tremor [45, 55].

In most previous accelerometric and EMG studies, tremor recordings were high-pass filtered at 2 Hz to avoid low-frequency artifacts due to physiologic shoulder oscillation with an eigenfrequency of about 2–3 Hz [47, 56–59]. This method prevented the registration of tremor frequencies lower than 2 Hz both in physiologic and pathologic conditions. Since we did not use high-pass filter, we detected peak frequencies below 3 Hz both in controls with physiologic tremor and in patients with cerebellar lesion. However, in patients with pathological cerebellar tremor, the proportion of the power in the low-frequency range (below 3 Hz) increased significantly compared to our subjects with physiologic tremor (both controls and patients). Due to this, the center frequency of cerebellar tremor shifted towards the low frequencies resulting in the overlap of center frequency and peak frequency. This overlap was a new sign of tremor pathology in our patients, which might be used in the future to differentiate pathologic versus physiologic tremor.

The above observation underlines the importance of determining the relative power of the low (0.9–3 Hz) frequency range, a parameter we have introduced. We found that in physiologic tremor, the relative power of low frequencies is less than 20%, while in cerebellar tremor, it is higher than 55%. As a result of this, frequency dispersion in physiologic tremor was higher than 4 Hz, while it was less than 2 Hz in cerebellar tremor. It is known that frequency dispersion is low in pathological tremors like Parkinsonian tremor or essential tremor [42, 56]; however, frequency dispersion data on cerebellar tremor have not been published yet. Our study demonstrated that a frequency dispersion less than 2 Hz is a clear sign of pathology in cerebellar tremor. The validity and clinical usefulness of the above findings are supported by our observation on the recovery of cerebellar tremor. We found that during recovery after acute ischemic cerebellar lesion, the center frequency gradually shifted to the normal range (above 6 Hz), and the frequency dispersion became normal (above 2.33 Hz).

For the first time, we determined the frequency of cerebellar tremor in humans using quantitative methods in a series of patients with morphologically identified cerebellar lesions. We found that cerebellar tremor had a frequency below 3 Hz ($2.38 \pm 0.88$ Hz in postural and $2.91 \pm 0.95$ Hz in intentional position) in 78% and had high intensity but normal frequency ($8.66 \pm 1.67$ Hz in postural and $8.9 \pm 1.3$ Hz in intentional position) in 22% of our patients. HINFT was considered pathological tremor since tremor intensity was higher only ipsilaterally to the lesion. Higher than 5 Hz center frequency cerebellar tremor has already been described in previous quantitative studies by Cole et al. (5–7 Hz) and by Milanov (8–12 Hz). Although two of our patients with HINFT had a lesion in the mesencephalon, this tremor type could not be associated with any specific lesion site. Further conclusions are limited by the fact that MPRAGE images were available in 34 patients only.

We assume that the LFT and HINFT types are most probably different entities, with possibly different mechanisms. The LFT type is more likely a result of silencing higher frequencies; therefore, the relative power of low frequencies can be very high, without increased tremor intensity. The center frequency of LFT (2–3 Hz) is similar to the eigenfrequency of shoulder in humans [46]. Distal joints have much higher eigenfrequency (17–20 Hz in the fingers [46]). In our power spectra, high-frequency tremor of the distal joints was not present, suggesting the suppression of distal joints' physiologic tremor. Holmes described a similar phenomenon [9]. The high-intensity–normal-frequency tremor type is more likely a result of associated midbrain lesions. We cannot provide strong evidence to support this hypothesis because of our small sample size.

Our investigation provides the first systematic analysis of cerebellar lesion-tremor mapping. We found no correlation between localization and/or size of the lesion and presence of tremor. Bilateral lesions did not cause higher intensity or lower frequency dispersion than unilateral ones. As tremor in focal cerebellar lesions has always been considered a result of damage of the dentato-rubro-thalamic tract, we expected that the involvement of dentate and interposed nuclei had a significant effect on tremor parameters. However, our statistical analysis found no difference in quantitative tremor characteristics between patients with affected or non-affected deep cerebellar nuclei. The lesion–symptom study on ataxia caused by cerebellar lesions showed similar results [57].

Tremor intensity was consistently increased when lesions affected lobules I–V, V, and VI of the cerebellum. These results support previous data from lesion–symptom mapping studies on arm and finger movements suggesting that the anterior lobe together with lobule VI are linked to upper limb motor functions [23, 24, 58]. The involvement of lobule VI resulted in significant increase of tremor intensity only in intentional position. This might be explained by the fact that lobule VI is responsible for cognitive tasks [24] and, through its connections with the frontal cortex, it increases attentional focus needed to maintain the intentional position.

We found that involvement of the brainstem was the only morphological factor which had a consistent effect on frequency parameters (CF and FD decreased, PP of 0.9–3 Hz increased in 14 patients). Since we used the SUIT atlas which is optimalized for the morphological assessment of cerebellar structures, we were not able to differentiate various brainstem regions. However, the visual analysis of images by expert neuroradiologist (N.P.) suggests that LFT might be associated with lower brainstem (including the inferior olive), while HINFT with upper brainstem (including the red nucleus) lesions. The role of the brainstem in tremorgenesis is still a very much debated topic [59]. One of the limitations of our study is that although the SUIT atlas can identify if a lesion extends to the brainstem, it is not able to differentiate the various brainstem structures. Therefore, we could not determine the correlation between the recorded tremor and the affected brainstem regions. Future studies using DTI methods are necessary to define the role of cerebellar peduncles and various brainstem structures in the generation of pathological tremor.

The interconnection between the cerebellum and the basal ganglia is involved in various aspects of tremor genesis [60, 61]. The involvement of the cerebellum in neurodegenerative diseases, which are classically associated with the basal ganglia (like Parkinson's disease), has been raised [62]. It has also been hypothesized that increased cerebellar activity in Parkinson's disease might be a compensatory phenomenon of decreased basal ganglia function [63]. Disorders of timing, and tremor might be considered a symptom of timing disorder, involve the basal ganglia as well. The influence of basal ganglia in predictive timing in patients with neurodegenerative diseases of the cerebellum (like spinocerebellar ataxia) has also been demonstrated [64, 65].

Our quantitative data suggest that tremor due to cerebellar lesion is most probably generated by a network rather than a single structure. The fact that tremor parameters were significantly affected when the brainstem was involved suggests that cerebellar connections with the subthalamic nucleus, the thalamus, and its pathways are important elements of the tremor generating network. Although, we could not investigate the structural bases for the interplay between the cerebellum and brainstem or basal ganglia in tremor genesis, this seems to be a very important field for further research in elucidating the complexity of tremor generators.

As we do not have fMRI data, functional alteration in the basal ganglia-cerebral cortex loop is not known in our patients. However, we cannot exclude a possible compensatory activity of basal ganglia which might support tremor recovery in patients with focal cerebellar lesions.

We demonstrated for the first time using quantitative follow-up measurements that cerebellar tremor evoked by acute ischemic lesion recovers spontaneously within 8 weeks (mean 3.65 ± 2.66 Hz). We assume that in those patients who had chronic ischemic lesion, this might be one possibility why we could not detect pathological tremor. The temporal characteristics of restitution are similar to those reported previously for cerebellar ataxia [25]. The mechanism of recovery is unknown. A case report using DTI analysis showed that white matter structures might completely recover after surgical intervention [66]. New theories like cerebellar redundancy and cerebellar reserve might also be reasonable explanations, but they need further elucidation [67].

It is a clinical evidence that tremor in neurodegenerative diseases involving the cerebellum, like essential tremor or tremor in cerebellar type multisystem atrophy (MSA-C), steadily progresses [68, 69], in contrast to the tremor caused by acute ischemic lesion of the cerebellum. There are further significant differences, like essential tremor is a bilateral action tremor [2] with a peak frequency of 5–9 Hz [70, 71], while acute cerebellar tremor is present only ipsilaterally to the lesion and it has lower peak frequency (below 3 Hz). Tremor in MSA-C is bilateral and has an irregular, jerky character. It is present mostly in action, but in one third of the patients, it can be detected at rest as well [69, 72]. In our study, acute cerebellar lesion did not cause tremor at rest in any patient. These differences might suggest that the mechanism of pathological tremor caused by acute ischemic cerebellar lesion is fundamentally different than the tremor caused by cerebellar neurodegenerative diseases and might represent the lack of network plasticity in the latter conditions.

## Conclusions

Our research shows that focal lesions in the cerebellum and the connected brainstem structures cause pathological postural and intentional tremor in about 50% of the patients, and none of them develop tremor at rest. Cerebellar tremor has low frequency (lower than 3 Hz) and usually low amplitude; therefore, bedside clinical examination reveals it only in about 20% of the cases. To reliably detect cerebellar tremor quantitative registration, including the measurement of frequency components below 3 Hz, is essential. Increased proportional power (higher than 25%) in the low-frequency range (0.9–3 Hz) together with narrow frequency dispersion (less than 2–3 Hz) strongly suggest cerebellar tremor. Our data show that cerebellar tremor intensity is significantly higher in intentional compared to postural position: the observation of this phenomenon might help the diagnosis of cerebellar tremor in clinical settings.

We have shown that there is no statistically significant correlation between the cerebellar lesion localization and the occurrence or type of pathological tremor. Lesions in the same cerebellar site might result in different tremor types. However, the involvement of the brainstem is associated with higher prevalence of pathological tremor than lesions affecting the cerebellum only. This suggests that both the cerebellum and

the brainstem are parts of a complex tremor generator network, and they cooperate in the regulation of tremor frequency and intensity.

We have demonstrated that tremor induced by acute focal cerebellar lesion recovers spontaneously in 8 weeks. The improvement of center frequency and frequency dispersion might be assessed by quantitative tremor recordings. The objective demonstration of functional recovery after cerebellar damage might provide help in determining patients' prognosis.

As it has been demonstrated by several preclinical and clinical studies, the cerebellum plays a complex and diverse role both in motor and cognitive functions. Lesion–symptom studies in humans provide an excellent method to determine the complex and widespread network of cerebellar connections that enable normal functions or in case of pathology causes specific symptoms.

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## Compliance with Ethical Standards

The study was approved by the local ethical committee of the Institute. Subjects' informed consent was obtained according to the Declaration of Helsinki.

**Conflict of Interest** The authors declare that they have no conflict of interest.

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