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ORIGINAL COMMUNICATION

Morphological differences in Parkinson's disease with and without rest tremor

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Abstract *Background* Rest tremor is a hallmark of Parkinson's disease (PD), but its pathogenesis remains incompletely understood. Nigro-striatal dopamine deficiency correlates best with bradykinesia, but not with tremor. Oscillating neurons in one or multiple localizations within the basal ganglia-thalamo-cortical loop may cause rest tremor, and an active contribution of the cerebellum and the cerebello-thalamo-cortical projections has been postulated. *Objective* To compare the pattern of grey matter volume in PD patients with and without tremor to identify structural correlates of rest tremor. *Methods* Voxel-based morphometry (VBM) of a high-resolution 3 Tesla, T1-weighted MR images, pre-processed according to an optimized protocol using SPM2, was performed in 24 patients with mild to moderate PD comparing local grey matter volume in patients with (n = 14) and without rest tremor (n = 10). *Results* Grey matter volume is decreased in the right quadrangular lobe and declive of the cerebellum in PD with tremor compared to those without ($P_{FDR} < 0.05$). *Conclusions* These results demonstrate for the first time morphological changes in the cerebellum in PD patients with rest tremor and highlight the involvement of the cerebellum and cerebello-thalamo-cortical circuit in the pathogenesis of parkinsonian rest tremor.

Key words Parkinson's disease · voxel-based morphometry · tremor akinetic-rigid syndrome

Introduction

Rest tremor is a hallmark of Parkinson's disease (PD), yet its pathogenesis is incompletely understood. A specific pattern of neuronal loss in the substantia nigra in PD patients with tremor has been described [38–40, 53], but does not translate into a different pattern of striatal dopamine deficiency or postsynaptic dopamine receptor density compared to akinetic-rigid PD [19, 25, 51]. Nigro-striatal dopamine deficiency correlates best with bradykinesia, but not with tremor [65]. Oscillating neurons in one or multiple localizations within the basal ganglia-thalamo-cortical loop may cause rest tremor, and an active contribution of the cerebellum and the cerebello-thalamo-cortical projections has been postulated [16, 42, 61].

Clinical manifestation and disease progression are variable and highlight the heterogeneity of PD. The clinical heterogeneity reflects the extent and topography of the pathological process and may indicate different causes of PD as also suggested by specific phenotypic

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presentations of patients with defined genetic forms of PD. Approaches to classify PD into subgroups have principally been based on the clinical phenomenology, in particular, discriminating tremor-dominant, akinetorigid and also "mixed" PD. Clinical evidence suggests that the motor phenotype may be predictive of clinical course and prognosis [21]. Compared to patients with tremor-dominant PD, "akinetic-rigid" patients show a more rapid clinical progression and have an increased risk to develop disability [27, 30, 31, 33, 35, 48] and dementia [1].

Brain imaging may allow identification of anatomical correlates of phenotypic differences such as a distinct pattern of grey matter loss in PD patients with and without tremor. MRI-based voxel-based morphometry (VBM) offers an operator-independent, unbiased and comprehensive morphological analysis of the brain. VBM has shown more widespread loss of grey matter in PD with dementia (PDD) [8, 9, 50, 56, 62]. VBM may also allow to distinguish PD from atypical Parkinsonian disorders [7, 55].

We intended to study the differences in the pattern of grey matter volume in PD patients with and without tremor to identify possible structural correlates of rest tremor, and also to test the hypothesis of a more advanced cortical grey matter loss in PD patients without tremor.

Methodology

Study population

Patients with idiopathic PD were prospectively recruited in the Department of Neurology, University Hospital of Zurich, Switzerland. Inclusion criteria were mild to moderate PD corresponding to Hoehn and Yahr stages (HY) 2–3 [33]. Diagnosis of PD was based on UK PD Brain Bank criteria [26] with a minimum disease duration of three years. We chose to investigate only men of a certain age span of 55–70 years due to sex and age differences in brain size [13, 29]. Exclusion criteria were advanced PD stages equivalent to HY 4–5, secondary parkinsonism, atypical parkinsonian diseases and other concomitant neurodegenerative diseases, tremor of non-parkinsonian origin, dementia as defined by a score < 24 in the Mini-Mental State Examination [20], any structural pathology in brain MR and CT imaging except for mild vascular changes within age norms, previous stereotactic surgery, and medical or psychiatric conditions precluding study participation and/or performance of MRI. Patients were dichotomized in a group with and without tremor. Patients with tremor were required to have classical parkinsonian rest tremor with or without postural or action tremor of similar frequency, and in PD patients without tremor, rest as well as postural or action tremor must have been excluded, also by meticulous review of all medical documents.

All patients gave written informed consent and the local ethics committee had approved the study.

Study protocol

All patients underwent a detailed clinical assessment including history, physical and neurological examination, and neuropsychological and -psychiatric evaluation to control for any differences between PD patients with and those without tremor which could confound morphological analysis. We presumed that a distinct pattern of grey matter volume distribution related to tremor would show up when comparing patient groups with similar clinical deficits except for tremor as their corresponding grey matter volume changes would match. For this reason, a comparison of PD patients with healthy controls would have been confounded and was, therefore, not performed.

All patients were examined on medication and in the "off" condition when medication effect was wearing off or during an (unpredictable) "off". A practically "defined off" condition, which would have required a temporary withdrawal of dopaminergic and also anti-cholinergic medication was not undertaken. To assess the severity of rest tremor with and without postural or action tremor more accurately considering its variability, an additional composite tremor score was based on clinical and historical data of the last 6 months using a similar scale as in UPDRS (0 = *absent*; 1 = *mild* and infrequent, not bothersome; 2 = *moderate* and bothersome; 3 = *severe* and interfering with many activities and 4 = *marked* and interfering with most activities).

Detailed neuropsychological evaluation included Mini-Mental State Examination [20], verbal and figural (five-point test) fluency, Rey Auditory Verbal Learning Test (RAVLT), Visual Design Learning Test (RVDLT) and Complex Figure Test, Stroop Interference Test [60], Goldenberg Association Learning [28] and screening for other cognitive deficits such as apraxia, aphasia and agnosia. A handedness questionnaire [12] was applied. Patients were also screened for hallucinations, delusions and other psychiatric disorders, and evaluated by a psychiatrist if deemed necessary. Depression was considered present if either one or both cut-offs of 14/15 [66] and 12/13 [17] in the Beck Depression Inventory (BDI) [4] and the Hamilton Depression Rating Scale (HAMD) [32], respectively, was/were exceeded.

Medical records including history and examination, and anatomical and, if performed nuclear brain imaging were reviewed.

Statistical analysis

Statistical analysis of clinical data was carried out with SPSS Version 12.0.1 for Windows. Normality of distribution was checked with skewness and kurtosis tests. Unpaired t-tests were used to compare parametric data between groups, and Mann-Whitney U test for non-parametric data. Chi-square tests or Fisher exact test were used to compare nominal data.

Brain MR scanning procedure

MR imaging using a standard head coil was performed at a 3T MR-scanner (PHILIPS, Achieva). For T1-weighted high resolution structural MRI, a T1-weighted, 3D-MP-RAGE sequence technique (TR = 8.7 ms, TE 2.3 ms, flip angle 8.0°, voxel-size 0.86 × 0.86 × 1.0 mm, axial slice orientation, matrix size 256 × 256) covering the anterior and posterior commissure within the same trans-axial plane was acquired in each patient. Images were reviewed for motion artifacts before pre-processing and redone if deemed necessary.

Voxel-based morphometry

Image pre-processing followed the optimized protocol as described by Good et al. [29] using SPM2 (http://www.fil.ion.ucl.ac.uk/spm): first an automatic segmentation was performed using age-matched template and priors (mean age: 56.6 ± 18.6), second the deformation field was determined by normalization of the segmented gray and white matter image using the respective prior, third the initial image was normalized using the determined deformation field followed by an automatic segmentation of the normalized image again using age-matched template and priors. Finally, in order to preserve the total amount of brain tissue, grey and white matter voxel values were multiplied by the Jacobian determinants derived from the spatial normalization step, respectively [29].

For comparison of the two groups of patients with and without tremor, a voxel-wise ANCOVA of these maps was performed. To compensate for effects resulting from general brain atrophy, a measure for the relative total brain volume $V_{brain} = (V_{grey\ matter} + V_{white\ matter})/V_{liquor}$ was included as nuisance variable into the statistical model. Two orthogonal contrasts: *patients with versus without tremor* and *patients without versus with tremor* were calculated ($p_{uncorrected} < 0.001$) to test for regions of lower amount of grey matter volume within the non tremor group ($C_{T\text{-}NT}$) and tremor group ($C_{NT\text{-}T}$) group, respectively.

Additional voxel-wise ANCOVAs were performed to test for effects of impaired balance and fluctuations, respectively, by comparing groups of patients with and without impaired balance and groups of patients with and without fluctuations as well as a regression analysis using the UPDRS III Balance and Gait score as explanatory variable to exclude possible confounding effects of clinical differences between patients with and those without tremor.

Based on current understanding of tremor pathogenesis [16, 42, 61], we predicted structural changes in the basal ganglia, the thalamus, the brainstem and/or the cerebellum ($R_{BG\text{-}thalamus\text{-}brainstem\text{-}cerebellum}$), and, therefore, restricted the statistical analysis to these regions applying a mask of these regions to the grey matter volume distribution maps prior to statistical analysis.

To control for additional differences outside these regions, a second statistical analysis was performed restricted to the cerebral cortex ($R_{Cerebrum}$). Data were corrected for multiple comparisons across the respective region using the false-discovery rate (FDR) method [24].

Results

All patients with PD seen in the Department of Neurology in the years 2002–2004 were screened, and 24 of 27 men who qualified for the study could be included. Two had declined participation and one could not be included due to MR-incompatibility (pacemaker). Fourteen of the 24 (58 %) had classical parkinsonian rest tremor including four who fulfilled criteria of tremor-dominant PD [36, 67] and ten who could be considered "mixed" PD. In the ten remaining PD patients without tremor, rest tremor as well as postural and/or action tremor was firmly excluded. PD diagnosis was confirmed and ET excluded in all patients in a follow-up assessment > 2 years (in 2007) after enrollment in this study.

Demographic and clinical characteristics are shown in Table 1. Motor complications and impaired balance were more prevalent in patients without tremor, who had a higher score of balance and gait (UPDRS items 27–30). No other differences were found, neither in scores of bradykinesia (items 18–19, 23–26, 31), rigidity (items 22), single and combined UPDRS parts (I, II, III on and IV; sparse III "off" data precluded comparison), nor in regard to the degree of asymmetry and to the laterality of disease preponderance.

Rest tremor was bilateral in ten and unilateral in four patients (right, n = 3; UPDRS item 20 on, median 2, range 0–10). Ten of those fourteen had an additional postural and/or action tremor at a similar frequency range as the ipsilateral rest tremor (bilateral, n = 8; unilateral right, n = 2; UPDRS item 21 on, median 1.5, range 0–3), which lessened transiently during action and re-emerged during posture after a delay of some seconds corresponding

Table 1 Demographic and clinical findings of patients with Parkinson's disease with and without tremor

	Tremor (n = 14)	No tremor (n = 10)	P
Age [years; mean ± SD]	61.5 ± 3.5	62.3 ± 5.1	ns[a]
Age at onset [years; mean ± SD]	53.1 ± 6	55 ± 7.6	ns[b]
Hoehn-Yahr stages [median (range)]	2.3 (2–3)	2.5 (2.5–3)	ns[b]
Disease duration [years; median (range)]	6 (3–20)	7.5 (3–18.5)	ns[b]
Duration of therapy [years; median (range)]	6 (3–18)	6 (2.3–18.5)	ns[b]
LED [mg; median (range)]	980 (150–1790)	1140 (100–1540)	ns[b]
Motor score (UPDRS III) [score; median (range)]	25 (12–35)	28 (12–35)	ns[b]
Impaired balance (HY ≥ 2.5)[c] [% (n)]	50 % (7)	100 % (10)	0.008[d]
Balance and Gait (UPDRS items 27–30)	3.4 ± 1.5	4.5 ± 0.9	0.041[b]
Motor complications[e] [% (n)]	21.4 % (3)	80 % (8)	0.005[d]
MMSE [score; mean ± SD]	28.6 ± 1.2	28.0 ± 0.8	ns[a]
PDQ39 [score; median (range)]	35 (9–86)	53 (9–90)	ns[b]
Depression (Beck/Hamilton) [% (n)]	42.9 % (6)	40 % (4)	ns[d]

LED Levodopa equivalent dosage; *ns* statistically non-significant; *PDQ 39* Parkinson's Disease Questionnaire (39 items); *SD* standard deviation; *UPDRS III* Unified Parkinson's Disease Rating Scale, part III (motor score)
[a] independent t-Test; [b] Mann-Whitney U-Test; [c] Patients with impaired balance have an increased prevalence of motor fluctuations (64.7 % vs 0 %, p = 0.004) and decreased prevalence of tremor (35.3 % vs 100 %, p = 0.004); [d] Pearson χ^2-Test; [e] Patients with motor complications have a longer duration of disease (median 108, 60–240 months vs 60, 36–156 months; p = 0.005) and of dopaminergic therapy (median 104, 58–222 months vs 60, 27–144 months; p = 0.015) with higher LED (median 1355, 570–1540 mg vs 900, 100–1790 mg; p = 0.01) and younger age at onset (50.3 ± 5.9 vs 56.9 ± 5.7 years, p = 0.011)

to postural and action tremor related to PD [37]. Postural and/or action tremor was milder and less persistent than rest tremor in all patients and none had an isolated postural and/or action tremor. Concomitant essential tremor was excluded in all. Composite rest ± postural and/or action tremor scores were similar in most patients when off medication (moderate, n = 6; severe, n = 7; marked, n = 1). The response of rest tremor and also of postural and/or action tremor to dopaminergic (in all) and anti-cholinergic (n = 3) medication was moderate to good. Rest with and without action and/or postural tremor in the best "on" condition was either mild (n = 7) or even absent (n = 4), but remained moderate and bothersome in three without interfering in daily activities. Neurological examination was otherwise normal in all patients.

Compared to age- and sex-matched healthy controls (unpublished data), neuropsychological assessment of the patients yielded mild impairments in executive functions (figural fluency, and concept learning and shifting) and in memory (verbal and figural learning and recall). No significant differences in the neuropsychological test results were found when comparing patients with and those without tremor. Depression was prevalent in both groups, but a short neuro-psychiatric screening did not identify significant psychiatric comorbidities requiring further evaluation or therapeutic intervention. Four (two with tremor) reported single episodes of visual hallucinations, but no confusion or delusions. All patients were right-handed.

Voxel-based morphometry

Within the region $R_{BG\text{-}thalamus\text{-}brainstem\text{-}cerebellum}$ at a level of statistical significant $p_{uncorrected} < 0.001$, the contrast $C_{TN\text{-}T}$ revealed a lower amount of grey matter volume for the tremor group in the posterior part of the cerebellar quadrangular lobe mainly right, but also paramedian on the left side, and in the declive of the vermis (Table 2). The contrast $C_{T\text{-}NT}$ revealed a small cluster of lower amount of grey matter volume for the non-tremor group along the lateral border of the right thalamus (Table 2).

Within the region $R_{Cerebrum}$, four clusters of higher amount of grey matter volume were found for the contrast $C_{T\text{-}NT}$ (Table 2) located in the medial anterior temporal lobes (right: Brodmann area [BA] 38, 34 and 28; left: BA 28), the left middle frontal gyrus and the right inferior frontal gyrus (BA 9). The contrast $C_{TN\text{-}T}$ revealed in total three small clusters of reduced grey matter volume, located in the right frontal and parietal lobe (Table 2).

At statistical significance level $p_{FDR} < 0.05$, only the cluster within the posterior part of the right quadrangular lobe and the declive of the cerebellum was significant (Fig. 1).

No significant clusters of grey matter volume changes ($p_{FDR} < 0.05$) were found neither for the region *BG-thalamus-brainstem-cerebellum* nor the region *Cerebrum* in the additional analysis of the groups with and without impaired balance, the groups with and without fluctuations and the regression analysis of the UPDRS III Balance and Gait score.

Table 2 Clusters of different grey matter volume for the two brain regions and the two different contrasts at a significance level $p_{uncorrected} < 0.001$ and in **bold** at a significance level $p_{FDR} < 0.05$ corrected for false positive clusters due to multiple testing. Anatomical structure, size of the cluster and coordinates of local maxima of significance are given

Clusters of different grey matter volume within $R_{BG\text{-}thalamus\text{-}brainstem\text{-}cerebellum}$								
Contrast $C_{T\text{-}NT}$					Contrast $C_{NT\text{-}T}$			
Anatomical structure	N_{voxel}	Local maxima of significance (Tal. coord.)			Anatomical structure	N_{voxel}	Local maxima of significance (Tal. coord.)	
		x	y	z			x	y	z
lateral border of right thalamus	110	25	−24	9	**Right and left posterior part of the quadrangular lobe and declive**	3529	25 21 −4	−67 −64 −65	−22 −19 −19
Clusters of different grey matter volume within $R_{Cerebrum}$								
Contrast $C_{T\text{-}NT}$					Contrast $C_{NT\text{-}T}$			
Anatomical structure	N_{voxel}	Local maxima of significance (Tal. coord.)			Anatomical structure	N_{voxel}	Local maxima of significance (Tal. coord.)	
		x	y	z			x	y	z
Right medial anterior temporal lobe (BA 28, 34 and 38)	3375	28 23 23 14 34	13 2 4 1 16	−38 −26 −41 −19 −39	Right parietal lobe (BA 39)	324	48	−65	27
Left medial anterior temporal lobe (BA 28)	304	−19	1	−24	Right middle frontal gyrus (BA 10)	222	50	−51	29
Left middle frontal gyrus (BA 5)	565	−21	−12	42	Right postcentral gyrus (BA 1)	548	55	−18	50
Right inferior frontal gyrus (BA 8)	273	37	5	26					

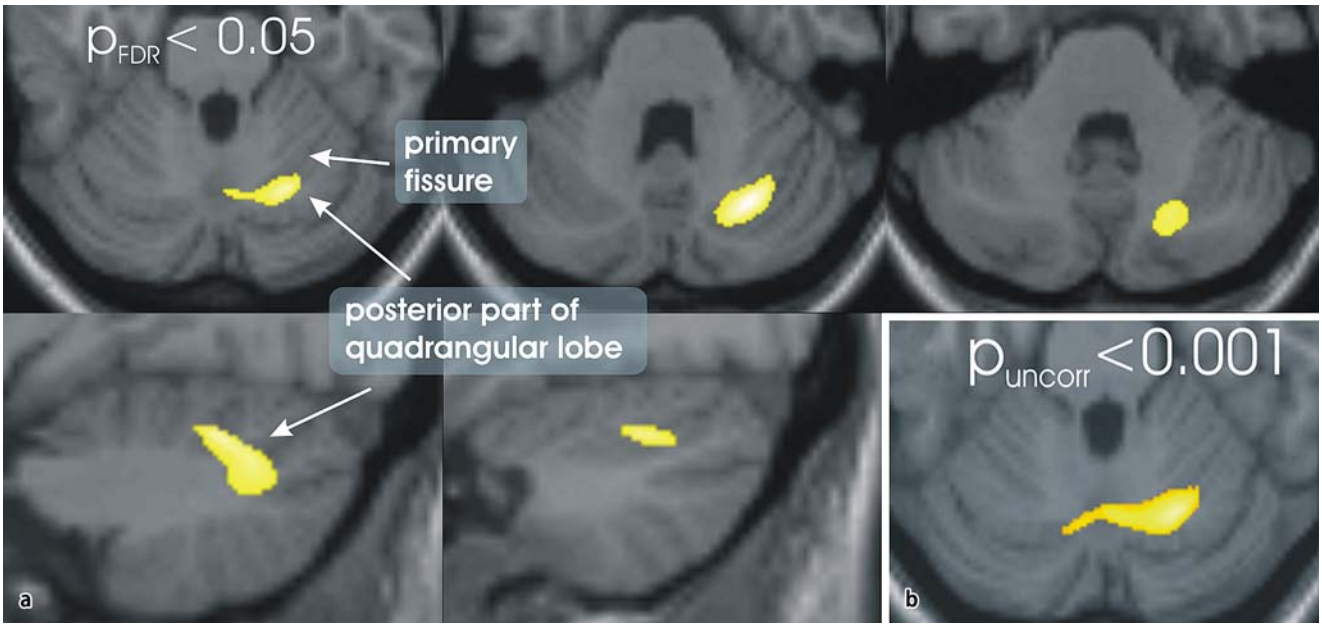

Fig. 1 The cerebellar region of lower amount of grey matter for the tremor group in comparison to the non-tremor group is shown. At a significance level corrected for false positive clusters due to multiple testing $P_{FDR} < 0.05$, this region is located in the posterior part of the right quadrangular lobe and the declive (**A**). Without this correction at $p_{uncorrected} < 0.001$, this region extends over the midline to a small part in the contralateral left quadrangular lobe (**B**)

Discussion

The principal finding of this study is a reduction of the grey matter volume in the right quadrangular lobe and declive of the cerebellum in PD patients with rest tremor compared to PD patients without tremor. This prospective study using high-resolution MRI VBM to compare brain morphology of the different motor phenotypes of PD demonstrates for the first time a structural abnormality in the cerebellum in PD with rest tremor and highlights the postulated cerebellar involvement in the pathogenesis of rest tremor [16, 42, 61]. Rest tremor has been shown to correlate with increased metabolic [3, 15, 22] and oscillatory activity [64] in the cerebellum, thalamus and motor cortex. Those structures are connected by somatotopically organized cerebello-thalamo-cortical projections, and the posterior quadrangular lobule (lobule VI) of the cerebellar cortex has been shown to be linked with the hand area of the motor cortex [43]. This finding underscores previously reported grey matter volume changes in the ventral intermediate nucleus (Vim) in the lateral thalamus which relays the cerebellum with the motor cortex [42]. The grey matter volume change in our study bordering the lateral thalamus lacked statistical significance and also its small size precludes further interpretation.

A strong argument in favor of a contribution of the cerebellum and its projections to the thalamus in the pathogenesis of rest tremor comes from experience with stereotactic surgery. The thalamic targets, Vim [5, 10, 44, 46, 47] and the cerebello-thalamic projections [11], have proven efficacious in the suppression of rest tremor and Vim was even postulated to a better target than the ventro-oralis posterior nucleus (Vop) receiving pallidal afferents [61]. The fact that Vim receives cerebellar afferents, but none from the basal ganglia [34], implies that rest tremor originates from either a cerebellar generator [61] or an interaction of the basal ganglia- and cerebello-thalamo-cortical circuits in the cerebral cortex, where those segregated circuits converge [16].

In monkeys, ablation of the interpositus nucleus manifests with tremor during reaching movements [63]. This nucleus receives projections from the intermediate zone of the cerebellum where the decrease of grey matter volume is mainly found in our patients with tremor. The intermediate zone and its output via the interpositus nucleus have been postulated to modulate the activity of agonist and antagonist muscles during movements [63], and also to control whether the muscle activity pattern is reciprocal or a co-contraction [58].

A possible explanation for the preponderance of the findings in the right cerebellum may be the disparity of tremor manifestation. All patients with tremor but one had tremor on the right, while three had no tremor on the left. Brain asymmetry due to lateralization [2, 23] and consistent right-handedness of all patients may have also contributed to the asymmetry of findings. A structural asymmetry of the cerebellar hemispheres in association with handedness has been described, and seems to be more marked in right-handers [59]. On the contrary, the equal-handedness may have minimized a confounding effect of brain asymmetry.

These grey matter volume changes in VBM raise questions about their nature. In PD, α-synuclein aggregates in cerebellar glia [54] and Purkinje cells [49] have been shown, but their appearance in regard to disease stage and clinical correlate remain yet to be identified. The decrease of grey matter volume may reflect a loss of neurons and/or glial cells, but also changes on the synaptic or cellular level [18].

Also, large clusters of decreased grey matter volume are found in the right medial anterior temporal lobe and to a lesser degree in left homologous counterpart in patients without tremor. These are the cortical regions which become earliest affected in the disease process after the brainstem nuclei [6], which is in line with the notion that "akinetic-rigid" patients without tremor experience a more rapid clinical progression to disability [27, 30, 31, 33, 35, 48] and dementia [1]. However, clusters in these regions have not reached significance after correction. A longitudinal analysis may provide more evidence to this preliminary observation.

Shortcomings of this study may be the available spatial resolution of MRI precluding the differentiation of small neuronal structures, particularly in the brainstem and thalamus. Changes in thalamic grey matter may have been missed, but the other VBM study had compared PD patients with unilateral rest tremor with healthy subjects [42]. Confounding factors had been minimized by exclusion of advanced PD, dementia and other co-morbidities. Both groups had a similar demographic, clinical and neuropsychological profile, except for more prevalent balance impairment, and motor fluctuations and dyskinesias in the patients without tremor. These differences are not expected to have confounded our findings since no morphological correlates of either balance impairment or motor fluctuations and dyskinesias were identified in additional VBM analyses, motor fluctuations and dyskinesias presumably originate from long-lasting functional alterations without known structural abnormality, and impaired balance and eventually loss of postural stability in PD is primarily caused by degeneration of brainstem nuclei such as the tegmental pedunculopontine nucleus [45, 52, 57]. Essential tremor which could be a confounding factor, even though a recent VBM study had failed to detect cerebellar changes in essential tremor [14], was clinically excluded. Postural and action tremor related to PD differs from essential tremor and is considered a continuation of rest tremor during action and posture presumably originating from the same tremor generator [37].

For the study objectives, we dichotomized patients

based on the presence of tremor alone ensuring that all patients with tremor and, therefore, a presumed underlying tremor generator were included. The deviating tremor-dominant PD criteria [36, 67] may allow the identification of a subgroup of patients with a comparatively benign disease course [27, 30, 31, 33, 35, 41, 48], but the small number of tremor-dominant PD patients in this collective precludes a separate VBM analysis of this subgroup.

In line with physiological and functional imaging studies, this study provides good evidence of a structural substrate for the involvement of the cerebellum in the pathogenesis of rest tremor.

Conflict of interest The authors declare no conflict of interest.

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References

1. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P (2003) Prevalence and characteristics of dementia in Parkinson disease – An 8-year prospective study. Arch Neurol 60: 387–392
2. Amunts K, Schlaug G, Schleicher A, Steinmetz H, Dabringhaus A, Roland PE, Zilles K (1996) Asymmetry in the human motor cortex and handedness. Neuroimage 3:216–222
3. Antonini A, Moeller JR, Nakamura T, Spetsieris P, Dhawan V, Eidelberg D (1998) The metabolic anatomy of tremor in Parkinson's disease. Neurology 51:803–810
4. Beck AT, Ward CH, Mendelsohn M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571
5. Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, Derougemont J (1991) Long-Term Suppression of Tremor by Chronic Stimulation of the Ventral Intermediate Thalamic Nucleus. Lancet 337:403–406
6. Braak H, Del Tredici K, Rub U, De Vos RAI, Steur ENHJ, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197–211
7. Brenneis C, Seppi K, Schocke MF, Muller J, Luginger E, Bosch S, Loscher WN, Buchel C, Poewe W, Wenning GK (2003) Voxel-based morphometry detects cortical atrophy in the Parkinson variant of multiple system atrophy. Mov Disord 18:1132–1138
8. Burton EJ, McKeith IG, Burn DJ, O'Brien JT (2005) Brain atrophy rates in Parkinson's disease with and without dementia using serial magnetic resonance imaging. Mov Disord 20: 1571–1576
9. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT (2004) Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 127:791–800
10. Caparros-Lefebvre D, Blond S, Vermersch P, Pecheux N, Guieu JD, Petit H (1993) Chronic Thalamic-Stimulation Improves Tremor and Levodopa Induced Dyskinesias in Parkinson Disease. J Neurol Neurosurg Psychiatry 56:268–273
11. Caparros-Lefebvre D, Ruchoux MM, Blond S, Petit H, Percheron G (1994) Long-Term Thalamic-Stimulation in Parkinsons-Disease – Postmortem Anatomoclinical Study. Neurology 44:1856–1860
12. Chapman LJ, Chapman JP (1987) The Measurement of Handedness. Brain and Cognition 6:175–183
13. Coffey CE, Lucke JF, Saxton JA, Ratcliff G, Unitas LJ, Billig B, Bryan RN (1998) Sex differences in brain aging – A quantitative magnetic resonance imaging study. Arch Neurol 55:169–179
14. Daniels C, Peller M, Wolff S, Alfke K, Witt K, Gaser C, Jansen O, Siebner HR, Deuschl G (2006) Voxel-based morphometry shows no decreases in cerebellar gray matter volume in essential tremor. Neurology 67:1452–1456
15. Deiber MP, Pollak P, Passingham R, Landais P, Gervason C, Cinotti L, Friston K, Frackowiak R, Mauguiere F, Benabid AL (1993) Thalamic-Stimulation and Suppression of Parkinsonian Tremor – Evidence of A Cerebellar Deactivation Using Positron Emission Tomography. Brain 116:267–279
16. Deuschl G, Raethjen J, Baron R, Lindemann M, Wilms H, Krack P (2000) The pathophysiology of parkinsonian tremor: a review. J Neurol 247:33–48
17. Dissanayaka NN, Sellbach A, Matheson S, Marsh R, Silburn PA, O'Sullivan JD, Byrne GJ, Mellick GD (2007) Validity of Hamilton Depression Inventory in Parkinson's disease. Mov Disord 22: 399–403
18. Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A (2004) Neuroplasticity: Changes in grey matter induced by training. Nature 427: 311–312
19. Eidelberg D, Moeller JR, Dhawan V, Sidtis JJ, Ginos JZ, Strother SC, Cedarbaum J, Greene P, Fahn S, Rottenberg DA (1990) The Metabolic Anatomy of Parkinsons-Disease – Complementary [F-18] Fluorodeoxyglucose and [F-18] Fluorodopa Positron Emission Tomographic Studies. Mov Disord 5:203–213
20. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12(3):189–198
21. Foltynie T, Brayne C, Barker RA (2002) The heterogeneity of idiopathic Parkinson's disease. J Neurol 249:138–145
22. Fukuda M, Barnes A, Simon ES, Holmes A, Dhawan V, Giladi N, Fodstad H, Ma YL, Eidelberg D (2004) Thalamic stimulation for parkinsonian tremor: correlation between regional cerebral blood flow and physiological tremor characteristics. NeuroImage 21:608–615
23. Galaburda AM, LeMay M, Kemper TL, Geschwind N (1978) Right-left asymmetrics in the brain. Science 199:852–856
24. Genovese CR, Lazar NA, Nichols T (2002) Thresholding of Statistical Maps in Functional Neuroimaging Using the False Discovery Rate. NeuroImage 15:870–878
25. Ghaemi M, Raethjen J, Hilker R, Rudolf J, Sobesky J, Deuschl G, Heiss WD (2002) Monosymptomatic resting tremor and Parkinson's disease: A multitracer positron emission tomographic study. Mov Disord 17:782–788
26. Gibb WR, Lees AJ (1988) The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 51: 745–752
27. Goetz CG, Tanner CM, Stebbins GT, Buchman AS (1988) Risk-Factors for Progression in Parkinsons-Disease. Neurology 38:1841–1844

28. Goldenberg G, Podreka I, Müller C, Deecke L (1989) The relationship between cognitive deficits and frontal lobe function in patients with Parkinson's disease. Behav Neurol 2:79–87
29. Good CD, Johnsrude IS, Ashburner J, Henson RNA, Friston KJ, Frackowiak RSJ (2001) A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage 14:21–36
30. Guillard A, Chastang C (1978) Long-Term Prognostic Factors in Parkinsons-Disease. Rev Neurol 134:341–354
31. Guillard A, Chastang C, Fenelon G (1986) Parkinsons-Disease – A Long-Term Study of 416 Patients – Prognostic Factors and Implications for Treatment. Rev Neurol 142:207–214
32. Hamilton M (1960) A Rating Scale for Depression. J Neurol Neurosurg Psychiatry 23:56–62
33. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17(5):427–442
34. Inase M, Tanji J (1995) Thalamic Distribution of Projection Neurons to the Primary Motor Cortex Relative to Afferent Terminal Fields from the Globus-Pallidus in the Macaque Monkey. J Comp Neurol 353:415–426
35. Jankovic J, Kapadia AS (2001) Functional decline in Parkinson disease. Arch Neurol 58:1611–1615
36. Jankovic J, Mcdermott M, Carter J, Gauthier S, Goetz C, Golbe L, Huber S, Koller W, Olanow C, Shoulson I, Stern M, Tanner C, Weiner W (1990) Variable Expression of Parkinsons-Disease – A Base-Line Analysis of the Datatop Cohort. Neurology 40:1529–1534
37. Jankovic J, Schwartz KS, Ondo W (1999) Re-emergent tremor of Parkinson's disease. J Neurol Neurosurg Psychiatry 67:646–650
38. Jellinger KA (1999) Post mortem studies in Parkinson's disease – is it possible to detect brain areas for specific symptoms? J Neural Transm (Supplement):1–29
39. Jellinger KA (2002) Recent developments in the pathology of Parkinson's disease. J Neural Transm (Supplement):347–376
40. Jellinger KA, Paulus W (1992) Clinicopathological correlations in Parkinsons-dtsease. Clin Neurol Neurosurg 94:S86–S88
41. Josephs KA, Matsumoto JY, Ahlskog JE (2006) Benign Tremulous parkinsonism. Arch Neurol 63:354–357
42. Kassubek J, Juengling FD, Hellwig B, Spreer J, Lucking CH (2002) Thalamic gray matter changes in unilateral Parkinsonian resting tremor: a voxel-based morphometric analysis of 3-dimensional magnetic resonance imaging. Neurosci Lett 323:29–32
43. Kelly RM, Strick PL (2003) Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosci 23:8432–8444
44. Koller W, Pahwa R, Busenbark K, Hubble J, Wilkinson S, Lang A, Tuite P, Sime E, Lazano A, Hauser R, Malapira T, Smith D, Tarsy D, Miyawaki E, Norregaard T, Kormos T, Olanow CW (1997) High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Ann Neurol 42:292–299
45. Lee MS, Rinne JO, Marsden CD (2000) The pedunculopontine nucleus: Its role in the genesis of movement disorders. Yonsei Med J 41:167–184
46. Lenz FA, Kwan HC, Martin RL, Tasker RR, Dostrovsky JO, Lenz YE (1994) Single-unit analysis of the human ventral thalamic nuclear group – Tremor-related activity in functionally identified cells. Brain 117:531–543
47. Limousin P, Speelman JD, Gielen F, Janssens M, study c (1999) Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 66:289–296
48. Marras C, Rochon P, Lang AE (2002) Predicting motor decline and disability in Parkinson disease – A systematic review. Arch Neurol 59:1724–1728
49. Mori F, Piao YS, Hayashi S, Fujiwara H, Hasegawa M, Yoshimoto M, Iwatsubo T, Takahashi H, Wakabayashi K (2003) alpha-Synuclein accumulates in Purkinje cells in Lewy body disease but not in multiple system atrophy. J Neuropathol Exp Neurol 62:812–819
50. Nagano-Saito A, Washimi Y, Arahata Y, Kachi T, Lerch JP, Evans AC, Dagher A, Ito K (2005) Cerebral atrophy and its relation to cognitive impairment in Parkinson disease. Neurology 64: 224–229
51. Otsuka M, Ichiya Y, Kuwabara Y, Hosokawa S, Sasaki M, Yoshida T, Fukumura T, Masuda K, Kato M (1996) Differences in the reduced F-18-Dopa uptakes of the caudate and the putamen in Parkinson's disease: Correlations with the three main symptoms. J Neurol Sci 136:169–173
52. Pahapill PA, Lozano AM (2000) The pedunculopontine nucleus and Parkinson's disease. Brain 123:1767–1783
53. Paulus W, Jellinger K (1991) The Neuropathologic Basis of Different Clinical Subgroups of Parkinsons-Disease. J Neuropathol Exp Neurol 50:743–755
54. Piao YS, Mori F, Hayashi S, Tanji K, Yoshimoto M, Kakita A, Wakabayashi K, Takahashi H (2003) alpha-synuclein pathology affecting Bergmann glia of the cerebellum in patients with alpha-synucleinopathies. Acta Neuropathol 105:403–409
55. Price S, Paviour D, Scahill R, Stevens J, Rossor M, Lees A, Fox N (2004) Voxel-based morphometry detects patterns of atrophy that help differentiate progressive supranuclear palsy and Parkinson's disease. NeuroImage 23: 663–669
56. Ramirez-Ruiz B, Marti MJ, Tolosa E, Bartres-Faz D, Summerfield C, Salgado-Pineda P, Gomez-Anson B, Junque C (2005) Longitudinal evaluation of cerebral morphological changes in Parkinson's disease with and without dementia. J Neurol 252: 1345–1352
57. Rye DB (1997) Contributions of the pedunculopontine region to normal and altered REM sleep. Sleep 20(9): 757–788
58. Smith AM, Bourbonnais D (1981) Neuronal-Activity in Cerebellar Cortex Related to Control of Prehensile Force. J Neurophysiol 45:286–303
59. Snyder PJ, Bilder RM, Wu HW, Bogerts B, Lieberman JA (1995) Cerebellar volume asymmetries are related to handedness: a quantitative MRI study. Neuropsychologia 33:407–419
60. Spreen O, Strauss E (1998) A compendium of neuropsychological tests. Oxford: University Press
61. Stein JF, Aziz TZ (1999) Does imbalance between basal ganglia and cerebellar outputs cause movement disorders? Curr Opin Neurol 12:667–669
62. Summerfield C, Junque C, Tolosa E, Salgado-Pineda P, Gomez-Anson B, Marti M, Ramirez-Ruiz B, Mercader J (2005) Structural brain changes in Parkinson disease with dementia. Arch Neurol 62:281–285
63. Thach WT, Goodkin HP, Keating JG (1992) The cerebellum and the adaptive coordination of movement. Annu Rev Neurosci 15:403–442
64. Timmermann L, Gross J, Dirks M, Volkmann J, Freund HJ, Schnitzler A (2003) The cerebral oscillatory network of parkinsonian resting tremor. Brain 126:199–212
65. Vingerhoets FJ, Schulzer M, Calne DB, Snow BJ (1997) Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? Ann Neurol 41: 58–64
66. Visser M, Leentjens AFG, Marinus J, Stiggelbout AM, van Hilten JJ (2006) Reliability and validity of the Beck Depression Inventory in patients with Parkinson's disease. Mov Disord 21: 668–672
67. Zetusky WJ, Jankovic J, Pirozzolo FJ (1985) The heterogeneity of Parkinsons-disease – Clinical and prognostic implications. Neurology 35:522–526