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Intact serotonergic and dopaminergic systems in two cases of orthostatic tremor

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Orthostatic tremor (OT) is a rare neurological syndrome of unknown aetiology defined as high frequency tremor (13–18 Hz) of the leg muscles while standing. This movement disorder, first described in 1984 by Heilman [1], causes disabling unsteadiness and instability that is relieved when the patients walk, sit or lay down.

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A previous single-photon emission computed tomography (SPECT) study demonstrated striatal dopamine transporter (DAT) deficits in OT [2] but also patients with normal presynaptic nigrostriatal pathway have been reported [3]. OT has been suggested to arise from a central oscillator involving the brainstem or cerebellum [4–7]. Interestingly, neuropathological changes in essential tremor have also been found in brainstem and cerebellar structures [8]. An association between the severity of parkinsonian rest tremor and the reduction of serotonin receptor ($5\text{-}HT_{1A}$) binding potential in the midbrain raphe has been shown in a positron emission tomography (PET) study which might indicate a role of the serotonergic system in the generation of tremor [9, 10]. Although imaging of presynaptic pathways by measuring the serotonin transporter (SERT) availability has been performed in different neuropsychiatric disorders including Parkinson's disease [11, 12] where in advanced patients a regionally widespread loss of brain serotonergic innervation was found [13], studies of the serotonergic system in OT do not exist. Here, we report for the first time two cases of OT with normal SERT availability and intact nigrostriatal dopaminergic pathways suggesting a normal function of these monaminergic neurotransmitter systems.

Two patients (A: 61 years, male, B: 61 years, female) presented to our neurologic department with a 5 (A) and 10 (B) year history of progressive instability when standing. Their past medical histories were unremarkable except hypertension that was treated adequately. The family history of patient A remained uninformative, the father of patient B had suffered from Parkinson's disease. On neurological examination both patients displayed marked instability during stance that was abolished by sitting down, the gait of patient B was disturbed mildly by a feeling of unsteadiness, otherwise the clinical investigation including mini-mental status test and Hamilton depression scale was normal. In contrast to lying or sitting positions a 16–18 Hz tremor activity was recorded by electromyography (EMG) in antagonistic leg muscles of both patients after standing up (Fig. 1 a) leading to the diagnosis of OT. Administration of gabapentin (increased gradually up to 2000 mg/d) that was found to improve postural stability and quality of life in OT [14] and clonazepam (1 mg/d, only patient B) resulted in symptomatic benefit.

The 3 Tesla magnetic resonance imaging (MRI) of patient A showed two small unspecific lesions in the right frontal white matter, while patient B displayed a single lesion in the right cerebellar white matter next to the vermis (Fig. 1 b). Symptomatic OT in patient B caused by a small unilateral cerebellar lesion seems unlikely although cerebellar dysfunction and pontine lesions have been described [4, 5]. In both patients the imaging of striatal DAT ($[^{123}I]$FP-CIT-SPECT) and dopamine D_2/D_3 receptors ($[^{123}I]$IBZM-SPECT), performed as described previously [15], showed ratios for specific uptake well within the range of healthy subjects indicating normal function of nigrostriatal dopaminergic systems. Also, PET imaging using the SERT-selective radioligand $[^{11}C]$DASB displayed a normal availability of brain SERT (Fig. 1 c–d) suggesting intact presynaptic serotonergic pathways in these cases. However, in some OT patients the dysfunction of modulatory control of a higher motor centre (basal ganglia) associated with reduced striatal DAT availability could play a part in the pathophysi-

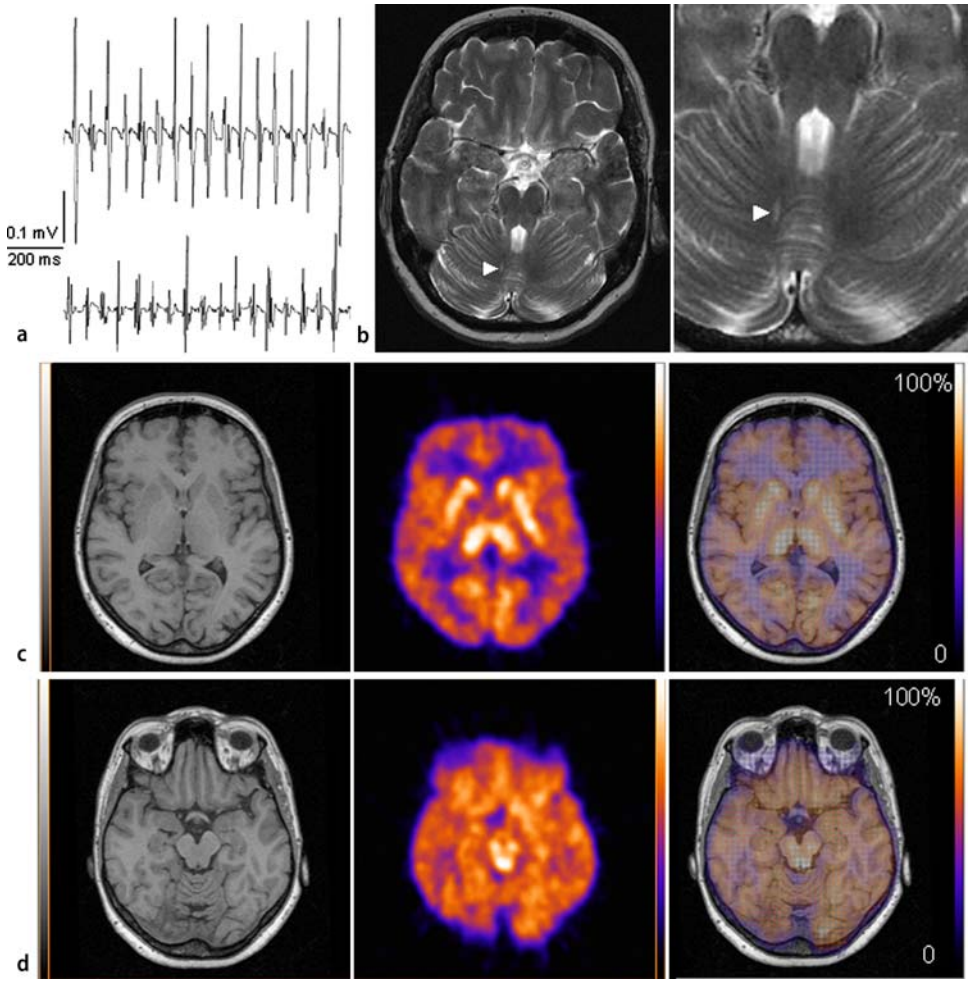

Fig. 1 **a** Electromyographical analysis of orthostatic tremor. Recordings obtained from unilateral Musculus rectus femoris (upper trace) and Musculus semitendinonus (lower trace) show typical high frequency (17 Hz) tremor profiles induced by standing while tremor was absent in lying and sitting positions. **b** Transverse 3 Tesla T2w magnetic resonance image (MRI, magnified on the right) of patient B with orthostatic tremor displays a single lesion (4 x 1.5 mm, arrowhead) in the cerebellar white matter next to the vermis. **c, d** Transverse MRI (left), positron emission tomography (PET) images of [^{11}C]DASB distribution (summed slices, middle), and overlaid MRI-PET images (right) at striatal/thalamus (**c**) and midbrain (**d**) levels of patient B. Distribution volume ratios are 1.94 for the right, 1.88 for the left striatum, 2.19 for the right, 2.24 for the left thalamus, and 2.52 for the midbrain which are within the range of our normal controls (1.94 ± 0.14, 1.92 ± 0.01, 2.21 ± 0.20, 2.15 ± 0.21, and 2.30 ± 0.16, respectively)

ology [2]. Whether in such OT cases the SERT function is also abnormal has to be investigated in further studies. While the role of dopaminergic dysfunction in the pathophysiology of OT remains controversial [2, 3, 7], our data suggest that the integrity of the serotonergic innervation is not affected in OT.

Conflict of interest The authors declare no conflict of interest.

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