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Tremor pathophysiology: lessons from neuroimaging

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Purpose of review
We discuss the latest neuroimaging studies investigating the pathophysiology of Parkinson's tremor, essential tremor, dystonic tremor and Holmes tremor.

Recent findings
Parkinson's tremor is associated with increased activity in the cerebello-thalamo-cortical circuit, with interindividual differences depending on the clinical dopamine response of the tremor. Although dopamine-resistant Parkinson's tremor arises from a larger contribution of the (dopamine-insensitive) cerebellum, dopamine-responsive tremor may be explained by thalamic dopamine depletion. In essential tremor, deep brain stimulation normalizes cerebellar overactivity, which fits with the cerebellar oscillator hypothesis. On the other hand, disconnection of the dentate nucleus and abnormal white matter microstructural integrity support a decoupling of the cerebellum in essential tremor. In dystonic tremor, there is evidence for involvement of both cerebellum and basal ganglia, although this may depend on the clinical phenotype. Finally, in Holmes tremor, different causal lesions map to a common network consisting of the red nucleus, internal globus pallidus, thalamus, cerebellum and pontomedullary junction.

Summary
The pathophysiology of all investigated tremors involves the cerebello-thalamo-cortical pathway, and clinical and pathophysiological features overlap among tremor disorders. We draw the outlines of a hypothetical pathophysiological axis, which may be used besides clinical features and cause in future tremor classifications.

Keywords
dystonia, essential tremor, Holmes tremor, Parkinson, pathophysiology

INTRODUCTION

Tremor is defined as an involuntary, oscillatory movement of one or more body parts. It can occur in combination with other neurological signs and symptoms, for example, in Parkinson's disease, or as an isolated sign, for example, in essential tremor. Currently, tremor is classified along two axes: clinical features (axis 1) and cause (axis 2) [1]. Here we discuss studies from the last 18 months that used neuroimaging to investigate the pathophysiology of tremor. We focused on four clinical tremor syndromes: Parkinson's tremor, essential tremor, dystonic tremor and Holmes tremor. We mainly included MRI and nuclear imaging studies, but also some neurophysiological approaches [electroencephalography (EEG) or direct intracranial recordings]. Based on these findings, we draw the outlines of a hypothetical pathophysiological axis, which may be used besides clinical features and cause in future tremor classifications (Fig. 1, Table 1).

NEUROIMAGING APPROACHES TO TREMOR

Neuroimaging techniques can help identify the pathophysiological mechanisms underlying tremor at the level of structural, neurotransmitter or circuit alterations (Fig. 1, Table 1). A first approach is to detect circuit-level tremor-related activity. Since tremor is usually much faster

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KEY POINTS

- Dopamine-resistant Parkinson's tremor is linked to increased activity in cerebellum (interposed nuclei), dopamine-responsive tremor by thalamo-cortical activity.
- Essential tremor arises from pathological oscillations arising from the cerebellum or because of cerebellar decoupling.
- Dystonic tremor involves both cerebellum and basal ganglia, possibly depending on tremor phenotype.
- Lesions causing Holmes tremor are all linked to a common network including red nucleus, internal globus pallidus, thalamus, cerebellum and pontomedullary junction.
- We present the outline of a hypothetical pathological axis that may be useful in future tremor classifications.

(3–6 Hz) than the sampling rate of standard functional MRI (fMRI) sequences (0.3–2 Hz), fMRI studies have focused on detecting brain activity associated with (much slower) changes in tremor power during scanning [12,13]. This can be done by building a regressor that captures scan-by-scan tremor power, using accelerometry or electromyography (EMG) during scanning, and testing for brain activity associated with this regressor. A second approach is to use structural, nuclear or functional imaging to compare cerebral 'traits' between Participates with and without tremor, such as gray matter volume or network properties. A caveat here is that these traits may be associated with the tremor itself, or with the overall disease phenotype – of which tremor is (only) one aspect [14]. A third approach, lesion mapping, links cause to circuit-level alterations and was recently applied to Holmes tremor [11▪▪]. Here, an fMRI dataset in healthy subjects (human connectome project) is used to identify the cerebral circuit that is connected to all the different brain lesions known to cause tremor. This approach can only be used for tremors that are caused (or removed) by structural brain lesions at various locations. The functional role of this 'lesion network' is not entirely clear, as it does not always overlap with symptom-related activity [15].

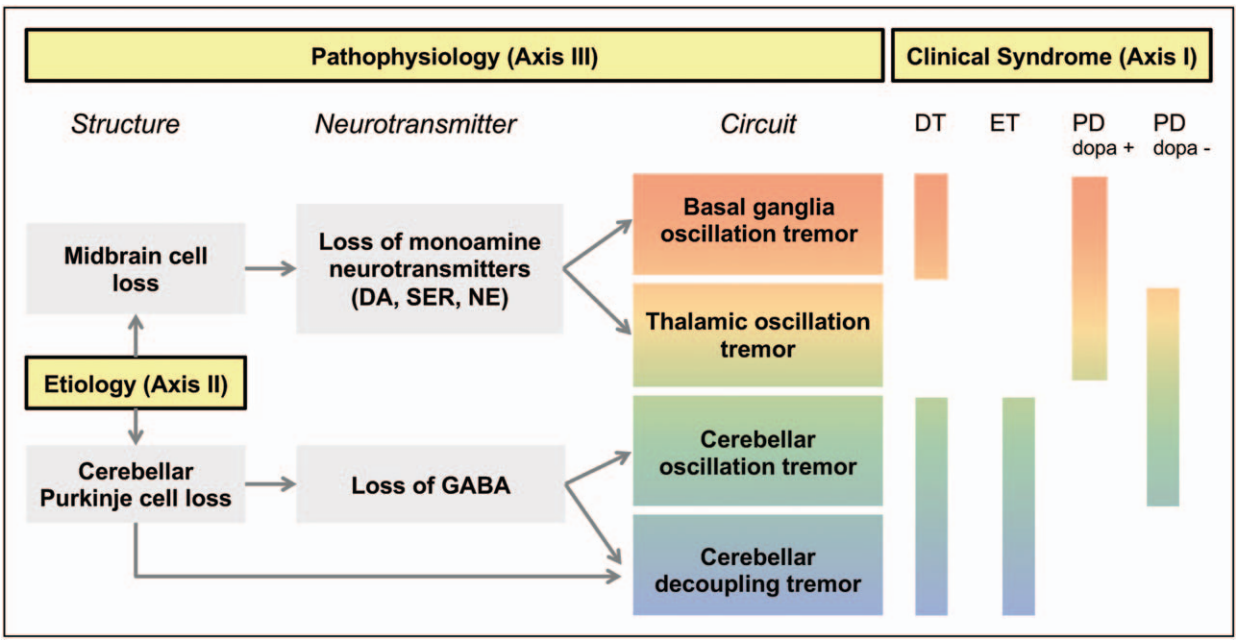

FIGURE 1. Hypothetical framework combining clinical syndrome (axis I), cause (axis II) and pathophysiology (axis III) in tremor disorders. Here, we illustrate how different clinical syndromes share underlying pathophysiological mechanisms, as indicated by the affected circuitry in rainbow colors. Based on recent findings (Table 1), we outline four pathophysiological mechanisms that may play a role in tremor: first, basal ganglia oscillation tremor, in which oscillations in the basal ganglia drive the tremor; second, thalamic oscillation tremor, in which oscillations in the thalamus drive the tremor; third, cerebellar oscillation tremor, in which cerebellar oscillations drive the tremor; fourth, cerebellar decoupling tremor, where a disconnection of the cerebellum from other brain areas causes instabilities in the motor network, resulting in tremor. Multiple mechanisms may play a role in a clinical tremor syndrome. DA, dopamine; DT, dystonic tremor; ET, essential tremor; GABA, γ-aminobutyric acid; NE, norepinephrine; PD dopa −, dopamine resistant Parkinson's tremor; PD dopa +, dopamine responsive Parkinson's tremor; SER, serotonine.

Table 1. Summary of recent neuroimaging findings and their interpretation related to pathophysiology

Clinical syndrome (axis I)	Method	Findings	Pathophysiology (axis III)
Parkinson's tremor	EMG-fMRI: Dopa-resistant versus dopa-responsive tremor; levodopa versus placebo [2▪]	Increased tremor-related activity in cerebellum (interposed nuclei) of dopa-resistant tremor. Dopamine increases thalamic inhibition in dopa-responsive >dopa-resistant tremor	Cerebellar oscillation hypothesis in dopa-resistant PD tremor Thalamic oscillation hypothesis in dopa-resistant + responsive PD tremor
	DTI + DTBZ-PET: Correlation with PD motor symptoms [3▪▪]	Inverse correlation of tremor severity with free water in SNp, but not with striatal DTBZ signal	SNp cell loss, but not striatal dopamine depletion, is involved in PD tremor. Thalamic oscillation hypothesis?
	LFP's in STN in one tremor-dominant patient [4▪]	Transient alpha/low beta power in STN around tremor onset. Beta suppression and increased oscillatory activity at tremor frequency in STN and motor cortex during tremor maintenance	Basal ganglia oscillation hypothesis
Essential tremor	fMRI: Postural task, DBS ON versus OFF [5▪▪]	DBS-ON: decreased primary sensorimotor cortex + cerebellar lobule III activity during postural task; increased SMA and cerebellar lobule V activity during rest	Normalization of cerebellar hyperactivity by treatment: cerebellar oscillation hypothesis
	fMRI: Dentate nucleus seed-based functional connectivity [6▪]	Decreased dentate nucleus functional connectivity with cortical areas (SMA, pre & postcentral gyri, prefrontal cortex), thalamus and cerebellar cortex; correlations with tremor severity, amplitude and disease duration	Functional disconnection of the dentate nucleus: cerebellar decoupling hypothesis
	DTI: White matter microstructure in ET versus PD patients [7▪]	Decreased integrity in all three cerebellar peduncles in ET, carrying afferent and efferent cerebellar projections	A myelin-related process may disrupt cerebellar connectivity: cerebellar decoupling hypothesis
	Translational study (pathology, mouse model, EEG) [8▪▪]	Synaptic pruning deficits of climbing fiber-to-Purkinje cell synapses related to GluRd2 protein insufficiency cause excessive cerebellar oscillations; confirmed with cerebellar EEG in ET patients	Cerebellar oscillation hypothesis
Dystonic tremor	fMRI: Grip force task [9▪]	Similar grip-force-related cerebellar activity in dystonic and essential tremor; reduced grip-force-related functional connectivity in cortical, basal ganglia and cerebellar regions in dystonic tremor	Functional disconnection between cerebellum and other areas: cerebellar decoupling hypothesis
	fMRI: Effective connectivity analysis [10▪]	Decreased self-inhibitory influence in the left inferior parietal cortex, right premotor cortex and left putamen in spasmodic dysphonia patients with versus without voice tremor	Reduced self-inhibition may lead to hyperactivity in basal-ganglia-cortical loop: basal ganglia oscillation hypothesis
Holmes tremor	fMRI: Lesion network mapping [11▪▪]	Lesions causing Holmes tremor map to a network consisting of red nucleus, GPi, thalamus (VOP and pulvinar nucleus), cerebellum (vermis, lateral cerebellar cortex and flocculonodular) and the pontomedullary junction	Involvement of multiple circuits in Holmes tremor

This table refers to a selection of articles discussed in the main text and serves to substantiate the hypothetic framework presented in Fig. 1. DBS, deep brain stimulation; DTBZ-PET, dihydrotetrabenazine positron emission tomography; DTI, diffusion tensor imaging; EEG, electroencephalography; EMG-fMRI, electromyography-functional MRI; ET, essential tremor; GluRd2, glutamate receptor delta 2; GPi, globus pallidus pars interna; LFP, local field potential; SMA, supplementary motor area; SNp, posterior substantia nigra; STN, subthalamic nucleus; VOP, ventralis oralis posterior.

PARKINSON'S TREMOR

Parkinson's resting tremor is associated with increased cerebral activity in the cerebello-thalamo-cortical circuit, as identified using combined EMG-fMRI scanning [16,2▪]. It has been hypothesized that the basal ganglia drive the cerebellar circuit into tremor [17]. This dimmer-switch hypothesis, based on EMG-fMRI data, has been confirmed using local field potentials from the subthalamic nucleus (STN) [4▪] in a single, tremor-dominant Parkinson patient. It was found that alpha/low-beta power in the STN increased transiently around tremor onset, after which persistent beta suppression and increased oscillatory activity at tremor frequency in the STN and motor cortex were associated with tremor maintenance. This suggests that the STN plays a role both in the switch and in the dimmer, given its connections to both basal ganglia and cerebello-thalamo-cortical circuit [18]. The neurochemical changes underlying these effects remain unclear. Given the inconsistent clinical response of Parkinson's tremor to dopaminergic medication [19], and given the lack of a correlation between nigro-striatal dopamine depletion and tremor severity [20,21], the dopaminergic basis of Parkinson's tremor has been questioned [11▪▪]. Several recent neuroimaging studies have approached this question from various angles.

THE DOPAMINERGIC BASIS OF PARKINSON'S TREMOR

Structural imaging studies investigated the integrity of the substantia nigra as a 'trait' of tremor-dominant Parkinson patients, using MRI sequences sensitive to neuromelanin, iron deposition or free water (diffusion-weighted MRI). Yang *et al.* [3▪▪] investigated, in 129 patients with Parkinson's disease, the relationship between clinical disease severity, free water concentration in the substantia nigra (using MRI), and monoaminergic imaging of the striatum [using (11C) dihydrotetrabenazine (DTBZ) PET]. Free water in the substantia nigra has previously been linked to dopaminergic cell loss [22]. As expected, free water concentration in the substantia nigra was inversely related to DTBZ signal in the striatum, and bradykinesia severity was significantly related to both. In contrast, tremor was inversely associated with posterior substantia nigra free water, but not with striatal DTBZ signal. Other studies have shown that abnormal neuromelanin signal [23] and iron deposition in the substantia nigra [24] both distinguish tremor-dominant Parkinson's disease from other tremor pathologies such as essential tremor and dystonic tremor. This may have clinical (diagnostic) value, but the pathophysiological meaning is less clear, given that group differences are not specific to tremor. Finally, a structural MRI study in 392 Parkinson patients reported that striatal gray matter volume was inversely related to the severity of bradykinesia and rigidity, but not tremor [25▪]. Taken together, these studies show that (dopaminergic) cell loss in the substantia nigra may contribute to Parkinson's tremor, but through different mechanisms than striatal dopamine depletion.

Two functional MRI studies investigated the effect of a dopaminergic intervention on brain activity in tremor-dominant Parkinson's disease. Nigro *et al.* tested the effect of apomorphine on brain activity in 16 tremor-dominant Parkinson patients. Tremor-related activity was removed from the data, so the authors focused on 'traits'. Apomorphine led to a clinical reduction in tremor severity, which was associated with reorganization of the modular structure of the basal ganglia and an increase in the centrality (participation coefficient) of motor and premotor cortex [26▪]. Hence, apomorphine may reduce Parkinson's tremor by acting on the motor cortex.

A second fMRI study investigated the dopaminergic basis of Parkinson's tremor by comparing Parkinson patients with dopamine-resistant resting tremor (clinical response $<20\%$ after 200/50 mg levodopa/benserazide; $n=14$) versus patients with a dopamine-responsive resting tremor (clinical response $>60\%$; $n=20$) [2▪]. Tremor-related activity after placebo and after 200/50 mg levodopa/benserazide was measured using combined EMG–fMRI. Patients with dopamine-resistant tremor had increased tremor-related activity in the cerebellum (interposed nuclei), whereas patients with dopamine-responsive tremor had increased activity in the thalamus (ventral intermediate nucleus) and somatosensory cortex, as well as increased functional connectivity between these regions. Furthermore, levodopa increased thalamic inhibition to a larger extent in the dopamine-responsive group, replicating previous work [27]. These data suggest that dopamine-resistant Parkinson's tremor can be explained by a larger contribution of the (dopamine-insensitive) cerebellum, whereas dopamine-responsive tremor may be explained by thalamic dopamine depletion – possibly linked to loss of specific dopaminergic neurons in the mesencephalon.

An MRI spectroscopy study built on this previous study, testing the role of inhibitory, γ-aminobutyric acid (GABA)-ergic mechanisms in the thalamus in Parkinson's tremor [28▪]. Surprisingly, there were no differences in thalamic GABA concentration between Parkinson patients with dopamine-responsive tremor ($n=23$), dopamine-resistant tremor ($n=17$), no tremor ($n=20$) or healthy controls ($n=22$). However,

GABA levels in the motor cortex were inversely correlated with disease severity, especially rigidity and tremor, both ON and OFF dopaminergic medication. These findings raise the interesting possibility that cerebral GABA might have a protective role in Parkinson's disease, independent of dopamine depletion, either at the neuronal level (e.g. by preventing calcium-based neurotoxicity) or at the circuit-level (e.g. by preventing dysfunctional motor hyperactivity).

ESSENTIAL TREMOR: CEREBELLAR OSCILLATOR OR CEREBELLAR DECOUPLING?

Essential tremor is currently understood as a syndrome of bilateral upper limb tremor with many types of 'essential tremor plus' (e.g. with resting tremor, with subtle dystonia, with slight bradykinesia, or another 'symptom of unknown significance'), of which the exact meaning is under debate [1,29,30]. It seems likely that these different subtypes arise from different pathophysiological substrates. Therefore, every study in essential tremor needs to address the issue of variability between essential tremor patients, and reporting the clinical phenotype in imaging studies should become a priority.

Essential tremor is proposed to result from pathological oscillations within the cerebello-thalamocerebral circuit [31]. The question remains where these oscillations originate. Essential tremor may be caused by increased cerebellar drive, in which case the cerebellum can be seen as a driving oscillator (cerebellar oscillator hypothesis), or essential tremor may be caused by cerebellar dysfunction (cerebellar decoupling hypothesis). Several recent studies have addressed this issue using different approaches.

Awad *et al.* [5▪▪] investigated the influence of deep brain stimulation (DBS) in the caudal zona incerta on the cerebello-thalamo-cortical circuit during postural holding and rest, comparing two conditions in the fMRI scanner: DBS-ON versus OFF. This unique ON/OFF paradigm facilitates the investigation of both pathologic activity and its response to treatment. During tremor-inducing postural holding, DBS was associated with decreased cerebral activity in the primary sensorimotor cortex and cerebellar lobule III, and with increased cerebral activity in the supplementary motor area (SMA) and cerebellar lobule V during rest. These effects of DBS onto the cerebellum lie within the sensorimotor cerebellar lobules (IV/V and VIII) in which previous studies have shown increased tremor-related activity [12,32,33]. This can be taken as normalization of cerebellar overactivity through treatment, which would fit the cerebellar oscillator hypothesis. The main effect of DBS, independent of the task that patients performed, was observed as activity increase in the lateral premotor cortex. This task-independent effect may mediate the therapeutic effect of DBS through the facilitation of compensatory premotor control over the sensorimotor circuit, making it less susceptible to tremor entrainment. Moreover, these results indicate that DBS-related changes occur in regions both near and distant to the stimulated area in essential tremor patients, which fits with the findings of Benito-Leon *et al.* [34] who reported widespread functional network disruption by using graph theory analysis in essential tremor.

Tikoo *et al.* [6▪] explored the role of disconnection of the dentate nucleus, the main cerebellar output pathway, by using seed-based functional connectivity in 25 essential tremor patients versus 26 healthy controls. There was significantly decreased dentate nucleus functional connectivity with cortical, subcortical and cerebellar areas in essential tremor patients. More specifically, they found that dentate nucleus functional connectivity with the SMA, pre and postcentral gyri and prefrontal cortex negatively correlated with tremor severity and disease duration. Furthermore, dentate nucleus functional connectivity with the cerebellar cortex correlated positively with tremor amplitude, whereas dentate-thalamus connectivity correlated negatively with tremor amplitude. Overall, this study suggests that a functional disconnection of the dentate nucleus plays a role in the pathophysiology of essential tremor, supporting the cerebellar decoupling hypothesis.

Additional evidence in support of cerebello-thalamo-cortical network disruption in essential tremor comes from a recent white matter microstructural integrity study [7▪]. They investigated a cohort of 57 essential tremor and 99 Parkinson (PD) patients who were sedated for the implantation of DBS devices, indicating that they had clinically severe essential tremor. The greatest distinctions in essential tremor versus PD encompassed decreased integrity in all three cerebellar peduncles, which are densely packed with afferent and efferent cerebellar projections, mediating the dentate-rubro-thalamic and cortico-ponto-cerebellar tracts. The authors hypothesize that a myelin-related process disrupts the cerebello-thalamo-cortical network, ultimately leading to the manifestation of action tremor. This explanation is consistent with the cerebellar decoupling hypothesis. The white matter changes in the cerebellar peduncles were also reported by Pietracupa *et al.* [35] who compared 19 essential tremor patients with 15 healthy subjects, and Tikoo *et al.* (see above) [6▪], who found that functional disconnection of the

dentate nucleus was independent of white matter changes.

Combining the above, recent neuroimaging evidence has emerged both for the cerebellar oscillator hypothesis and the cerebellar decoupling hypothesis. Beyond the field of neuroimaging, a recent carefully conducted translational study by Pan *et al.* [8▪▪] provides support for the cerebellar oscillator hypothesis. They investigated brain tissue from essential tremor patients and mouse models to report that synaptic pruning deficits of climbing fiber-to-Purkinje cell synapses, which are related to glutamate receptor delta 2 protein insufficiency, cause excessive cerebellar oscillations that might cause tremor. Consecutive human validation by cerebellar EEG confirmed that these excessive cerebellar oscillations also exist in patients with essential tremor. It remains to be seen whether the role of the cerebellum in essential tremor (oscillator or decoupling) differs between individuals or between stages of the disease, and whether it predicts the response to treatment. This may be relevant, as tremors associated with cerebellar dysfunction usually have a worse or more transient response to DBS [36].

DYSTONIC TREMOR: THE ROLE OF THE BASAL GANGLIA AND THE CEREBELLUM

The pathophysiology of tremor in dystonia likely involves the cerebello-thalamo-cortical pathway and its connections to basal ganglia [37]. It remains under debate whether the driving pathophysiology has a cerebellar or basal ganglia nature, or whether it involves a combination of both. The clinical overlap between many types of dystonic tremor and essential tremor begs the question to what extent the pathophysiologies of both clinical tremor syndromes overlap. Furthermore, it remains unclear if and how dystonia and dystonic tremor share a common pathophysiological basis. Two recent neuroimaging studies shed light on these questions.

First, DeSimone *et al.* [9▪] showed that during a grip-force-task (sensitive to grip-force tremor) cerebellar activity did not differ between patients with tremor in dystonia and patients with essential tremor. Although cerebral activity in this task is only a proxy of actual tremor related-activity, this finding supports the notion that tremor in dystonia might emerge from similar cerebellar mechanisms as essential tremor. Also, widespread reduced functional connectivity was found in cortical, basal ganglia and cerebellar regions in patients with dystonic tremor compared with essential tremor. It remains unclear whether this is characteristic of dystonia, dystonic tremor or a combination.

Second, Battistella and Simonyan [10▪] reported that spasmodic dysphonia patients with and without voice tremor both show reduced functional connectivity in left inferior parietal cortex, putamen and bilateral premotor cortices compared with healthy controls. This finding was thus not tremor-specific, but rather characteristic of dystonia. Significantly, in the subsequent effective connectivity analysis, patients with tremor showed decreased self-inhibitory influences in the left inferior parietal cortex, right premotor cortex and the left putamen compared with patients without tremor. This tremor-specific finding argues for involvement of a basal-ganglia-cortical loop in voice tremor.

These two recent neuroimaging studies suggest both cerebellar and basal ganglia contributions to tremor in dystonia. Two other recent studies support a prominent role of the cerebellum. DBS of the cerebellar thalamus (VIM) had long lasting beneficial effects on dystonic tremor [38], and patients with cervical dystonia with head tremor had more signs of ataxia, a purely cerebellar symptom, than cervical dystonia patients without head tremor [39]. Finally, pallidal single-neuron recordings during DBS showed that pure dystonia and dystonia with jerky tremor differ from dystonia with sinusoidal tremor in terms of pallidal physiology [40]. This yields the interesting hypotheses that the pathophysiology of dystonic symptoms and jerky tremor is based on basal-ganglia alterations, whereas sinusoidal (essential tremor-like) tremor in dystonia is on the basis of cerebellar alterations. Future studies should further explore the relative contributions of the basal ganglia and cerebellum in dystonic tremor. In such studies, clinical characteristics such as jerkiness of tremor could be considered.

HOLMES TREMOR

Given the rarity of the disorder, inferences on the pathophysiological mechanisms underlying Holmes tremor largely depend on case studies. However, Joutsa *et al.* [11▪▪] implemented an interesting technique called 'lesion network mapping' to combine information from individual lesions (see 'Neuroimaging approaches to tremor' paragraph). They showed that all lesions causing Holmes tremor map to a network consisting of red nucleus, globus pallidus pars interna (GPi), thalamus [ventralis oralis posterior (VOP) and pulvinar nucleus], cerebellum (vermis, lateral cerebellar cortex and flocculonodular) and the pontomedullary junction. It remains unknown how this network relates to actual tremor-related cerebral activity. Significantly, the authors argue that most successful DBS targets to alleviate Holmes tremor lie in or adjacent to this network.

Thus, GPi or VOP might provide better DBS targets than commonly used VIM or STN.

CONCLUSION

The pathophysiological substrates of Parkinson's tremor, essential tremor, dystonic tremor and Holmes tremor all involve the cerebello-thalamo-cortical circuit and interconnected brain regions. Some tremor disorders share pathophysiological mechanisms, such as the involvement of the cerebellum in dopamine-resistant Parkinson's tremor, dystonic tremor and essential tremor. This mirrors the clinical overlap that also exists between several tremor disorders: the boundaries between essential tremor, essential tremor plus and dystonic tremor are highly debated [27,28▪,41]. Based on recent neuroimaging findings, we distinguish distinct pathophysiological mechanisms that may play a role in tremor: basal ganglia oscillation, thalamic oscillation, cerebellar oscillation and cerebellar decoupling (Fig. 1, Table 1). The degree to which one or more of these mechanisms plays a role in a particular tremor may serve as a third 'pathophysiological axis', besides clinical features (axis 1) and cause (axis 2), when classifying tremor [1]. However, before this is feasible, reliable biomarkers are needed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Bhatia KP, Bain P, Bajaj N, *et al.* Consensus statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord 2018; 33:75–87.
2. ▪ Dirkx MF, Zach H, van Nuland A, *et al.* Cerebral differences between dopamine-resistant and dopamine-responsive Parkinson's tremor. Brain 2019; 142:3144–3157.

The current study compared tremor-related activity (using electromyography-functional MRI) between Parkinson patients with dopamine-resistant versus dopamine-respnsive tremor, as identified using a clinical levodopa challenge, during two sessions: placebo versus levodopa-benserazide (200/50 mg). Group-differences point to the cerebellum (resistant group) and the thalamus + somatosensory cortex (responsive group), irrespectve of medication.

3. ▪▪ Yang J, Archer DB, Burciu RG, *et al.* Multimodal dopaminergic and free-water imaging in Parkinson's disease. Parkinsonism Relat Disord 2019; 62:10–15.

The current study investigated, in a large group of 129 Parkinson's disease patients, disease severity, free water concentration in the substantia nigra (as a marker for dopaminergic cell loss) and monoaminergic imaging of the striatum. Bradykinesia was related to both changes in nigral free water and striatal monoamine, whereas tremor was only inversely associated with nigral free water. Thus, (dopaminergic) cell loss in the substantia nigra may contribute to Parkinson's tremor, but through another mechanism than striatal dopaminergic depletion.

4. ▪ Hirschmann J, Abbasi O, Storzer L, *et al.* Longitudinal recordings reveal transient increase of alpha/low-beta power in the subthalamic nucleus associated with the onset of parkinsonian rest tremor. Front Neurol 2019; 10:145.

In this study, local field potentials were recorded from the subthalamic nucleus (STN) in one tremor-dominant Parkinson patient. Alpha/low-beta power in the STN increased transiently around tremor onset, after which persistent beta suppression and increased oscillatory activity at tremor frequency in the STN and motor cortex were associated with tremor maintenance, indicating that the STN plays a double role in the dimmer-switch hypothesis of Parkinson's tremor.

5. ▪▪ Awad A, Blomstedt P, Westling G, Eriksson J. Deep brain stimulation in the caudal zona incerta modulates the sensorimotor cerebello-cerebral circuit in essential tremor. Neuroimage 2020; 209:116511.

This is the first study to investigate essential tremor patients with DBS ON versus OFF during scanning, making it possible to investigate the effect of this treatment directly. DBS ON resulted in normalised brain activity in sensorimotor cerebellar lobules during a tremor-inducing task, fitting with the cerebellar oscillator hypothesis, whereas the overall effect of DBS was that of increased compensatory premotor control.

6. ▪ Tikoo S, Pietracupa S, Tommasin S, *et al.* Functional disconnection of the dentate nucleus in essential tremor. J Neurol 2020; 267:1358–1367.

The seed-based functional connectivity study suggests that a functional disconnection of the dentate nucleus plays a role in essential tremor pathophysiology, supporting the cerebellar decoupling hypothesis.

7. ▪ Juttukonda MR, Franco G, Englot DJ, *et al.* White matter differences between essential tremor and Parkinson disease. Neurology 2019; 92:e30–e39.

In this large cohort of sedated patients, decreased integrity was found in all three cerebellar peduncles in essential tremor versus PD patients, which may lead to a disruption of the cerebell-thalamo-cortical network, which would fit the cerebellar decoupling hypothesis.

8. ▪▪ Pan MK, Li YS, Wong SB, *et al.* Cerebellar oscillations driven by synaptic pruning deficits of cerebellar climbing fibers contribute to tremor pathophysiology. Sci Transl Med 2020; 12:eaay1769.

The translational study used brain tissue from essential tremor patients and mouse models to establish that synaptic pruning deficits of climbing fiber-to-Purkinje cell synapses (related to glutamate receptor delta 2 protein insufficiency) cause excessive cerebellar oscillations which appear cause tremor. Subsequent human validation by means of cerebellar electroencephalography confirmed the existence of these excessive cerebellar oscillations in essential tremor patients. These findings are indicative of a cerebellar oscillator in essential tremor. The combination of different kind of data is impressive.

9. ▪ DeSimone JC, Archer DB, Vaillancourt DE, Wagle Shukla A. Network-level connectivity is a critical feature distinguishing dystonic tremor and essential tremor. Brain 2019; 142:1644–1659.

Dystonic tremor patients showed no differences in cerebellar activity during a tremor-inducing grip-force task compared with essential tremor patients, suggesting a similar cerebellar mechanism. Functional connectivity was widely reduced in dystonic tremor patients including in the basal ganglia, which points towards a second pathophysiological mechanism involving the basal ganglia.

10. ▪ Battistella G, Simonyan K. Top-down alteration of functional connectivity within the sensorimotor network in focal dystonia. Neurology 2019; 92:e1843–e1851.

In this study, spasmodic dysphonia patients with voice tremor showed decreased self-inhibitory influences in the left inferior parietal cortex, right premotor cortex and the left putamen compared with patients without tremor. This suggests involvement of the basal ganglia-cortical circuit in voice tremor.

11. ▪▪ Joutsa J, Shih LC, Fox MD. Mapping Holmes tremor circuit using the human brain connectome. Ann Neurol 2019; 86:812–820.

The technique of 'lesion network mapping' is employed in this study, to reveal that all lesions causing Holmes tremor map to a network that contains the red nucleus, internal globus pallidus, thalamus, cerebellum and pontomedullary junction. The authors suggest that the internal globus pallidus or ventralis oralis posterior of the thalamus may be promising deep brain stimulation (DBS) targets.

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