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Tremor and Other Hyperkinetic Movements

Reviews

Animal Models of Tremor: Relevance to Human Tremor Disorders

Ming-Kai Pan[1], Chun-Lun Ni[2], Yeuh-Chi Wu[2], Yong-Shi Li[2] & Sheng-Han Kuo[2]*

[1] Department of Medical Research, National Taiwan University, Taipei, TW, [2] Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Abstract

Background: Tremor is the most common movement disorder; however, the pathophysiology of tremor remains elusive. While several neuropathological alterations in tremor disorders have been observed in post-mortem studies of human brains, a full understanding of the relationship between brain circuitry alterations and tremor requires testing in animal models. Additionally, tremor animal models are critical for our understanding of tremor pathophysiology, and/or to serve as a platform for therapy development.

Methods: A PubMed search was conducted in May 2018 to identify published papers for review.

Results: The methodology used in most studies on animal models of tremor lacks standardized measurement of tremor frequency and amplitude; instead, these studies are based on the visual inspection of phenotypes, which may fail to delineate tremor from other movement disorders such as ataxia. Of the animal models with extensive tremor characterization, harmaline-induced rodent tremor models provide an important framework showing that rhythmic and synchronous neuronal activities within the olivocerebellar circuit can drive action tremor. In addition, dopamine-depleted monkey and mouse models may develop rest tremor, highlighting the role of dopamine in rest tremor generation. Finally, other animal models of tremor have involvement of the cerebellar circuitry, leading to altered Purkinje cell physiology.

Discussion: Both the cerebellum and the basal ganglia are likely to play a role in tremor generation. While the cerebellar circuitry can generate rhythmic movements, the nigrostriatal system is likely to modulate the tremor circuit. Tremor disorders are heterogeneous in nature. Therefore, each animal model may represent a subset of tremor disorders, which collectively can advance our understanding of tremor.

Keywords: Essential tremor, Parkinson's disease, dystonia, cerebellum, tremor, climbing fiber, Purkinje cells

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*To whom correspondence should be addressed. E-mail: sk3295@cumc.columbia.edu

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Introduction

Tremor is the most common movement disorder phenomenology. Tremor disorders are classified based on the predominant tremor characteristics. Essential tremor (ET) is characterized by action tremor in the upper extremities, whereas Parkinson's disease (PD) tremor classically presents as tremor at rest. Dystonic tremor (DT) is less rhythmic and is usually associated with sustained muscle twisting.[1,2] Other tremor disorders, including cerebellar outflow tremor, Holmes tremor, and orthostatic tremor, are relatively rare. Despite some clinical heterogeneity, one of the important aspects of tremor disorders is the overlapping clinical features. For example, severe ET patients can develop rest tremor, and severe PD patients can have action tremor.[3] Many ET cases also have a dystonic component.[4] While tremor disorders are likely to be heterogeneous groups of diseases with phenotypical overlaps, the brain circuitry preferentially involved in the generation of a specific type of tremor (action vs. rest vs. dystonic) is

likely to share some commonalities with additional modulatory components. Therefore, studies of animal models with different types of tremor will likely lead to a comprehensive understanding of the mechanism of diverse yet overlapping clinical features of tremor.

Based on neuroimaging studies[5–7] and pathological studies[8,9] in patients, the cerebellum is involved in tremor generation. In addition, magnetoencephalography and high-density electroencephalography have shown that brain areas interconnected with the cerebellum or further downstream regions, including the thalamus, motor and premotor cortex, and part of the brainstem, may affect tremor expression.[6,10] However, the mechanism by which structural alterations within the brain circuit generate tremor remains unclear. Similarly, the oscillatory neuronal activities are thought to be the physiological correlates for tremor.[11,12] Yet, it is unclear how the brain circuitry alterations generate these rhythmic neuronal activities to drive tremor. Thus, animal models are a useful tool to assess the relationship between structural brain alterations, altered neuronal physiology, and tremor. In addition, animal models of tremor may be a platform for therapy development. Note that tremor is a terminology for movement disorder that describes involuntary, rhythmic movements; therefore, tremor is a symptom, rather than a disease. Thus, animal models of tremor capture the symptoms of a disease, rather than reflect the biological processes underlying the disease.

The present paper will first review the validated tremor animal models with detailed clinical features (action tremor vs. rest tremor) and the pharmacological responses of tremor in these models using frequency-based measurement rather than merely visual observation. We will also briefly review other animal models of tremor with varied results. We will discuss how the pathophysiology learned from animal models of tremor can help us to understand the controversies of phenotypical overlaps of tremor disorders. Finally, we will attempt to apply the knowledge of tremor pathophysiology learned from animal models to explain some of the controversies in the tremor research field.

Methods

A PubMed search was conducted in May 2018 using the term "tremor" in combination with the following search terms: "animal models", "mouse", "rat", "monkey". In the initial screening, we identified 1,171 articles; of these, 64 and 1,039 articles that were not written in English and/or were irrelevant to the topic of this review, respectively, were disregarded. Therefore, we selected 68 of the remaining articles for this review. An additional five articles were included based on the references. Thus, a total of 73 articles were selected for this review (Table 1, Figure 1).

Based on the search results, we will first discuss the most widely studied animal models for action tremor (harmaline-induced rodent models) and rest tremor (dopamine-depleted monkey models) with defined tremor frequency and characteristic measurement. We will next discuss the animal models of tremor with frequency measurement but no detailed action vs. rest tremor description. We will also review the current literature for animal models of tremor without objective tremor measurement; therefore, whether there is true tremor present in these animal models will require further investigation. We will also review the tremor pathophysiology in these animal models and how this knowledge should advance our understanding of human tremor disorders.

Results

Animal models of action tremor

The classical animal model of action tremor is the harmaline-induced model.[13] A single dose of harmaline can induce action tremor by enhancing the coupling between the inferior olivary (IO) neurons.[14–17] The IO neurons have intrinsic subthreshold membrane potential oscillations at 1–10 Hz, and harmaline exposure can result in enhanced communications between IO neurons, which entrain the downstream Purkinje cells (PCs) to fire synchronously and rhythmically at around 10–16 Hz via axons of the IO neurons called climbing fibers (CFs).[14,15] Animals exposed to harmaline develop tremor at the same frequency.[16,17]

Table 1. **Search Strategy**

Key Words and Combination	**Number of Publications**		
Tremor AND Animal models	Total	Included	Excluded
Tremor AND mouse	194	12	182 (not in English, 9; not relevant, 173)
Tremor AND rat	413	37	376 (not in English, 15; not relevant, 361)
Tremor AND monkey	470	15	455 (not in English, 31; not relevant, 424)
Total number of articles included for review	94	4	90 (not in English, 9; not relevant, 81)
Total number of articles included from the references of the including articles		68	
Final number of articles included for review		5	
		73	

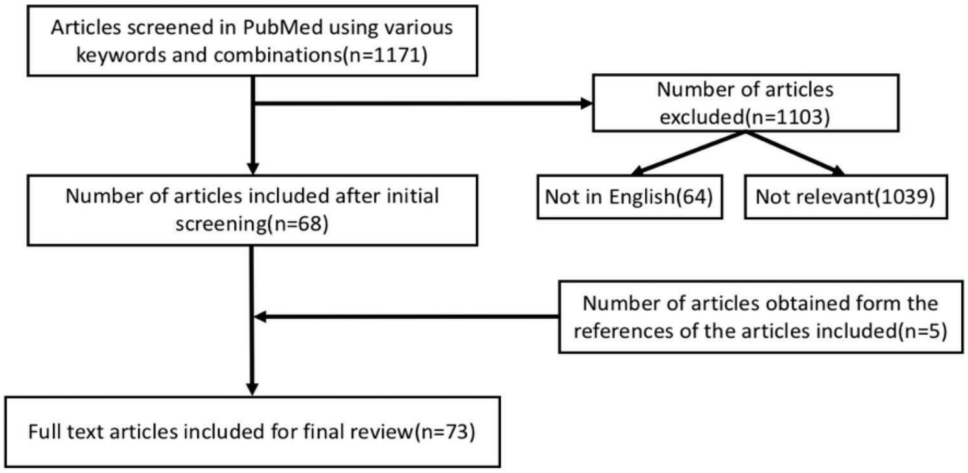

Figure 1. **Search Strategy.** Flow diagram for the literature search results.

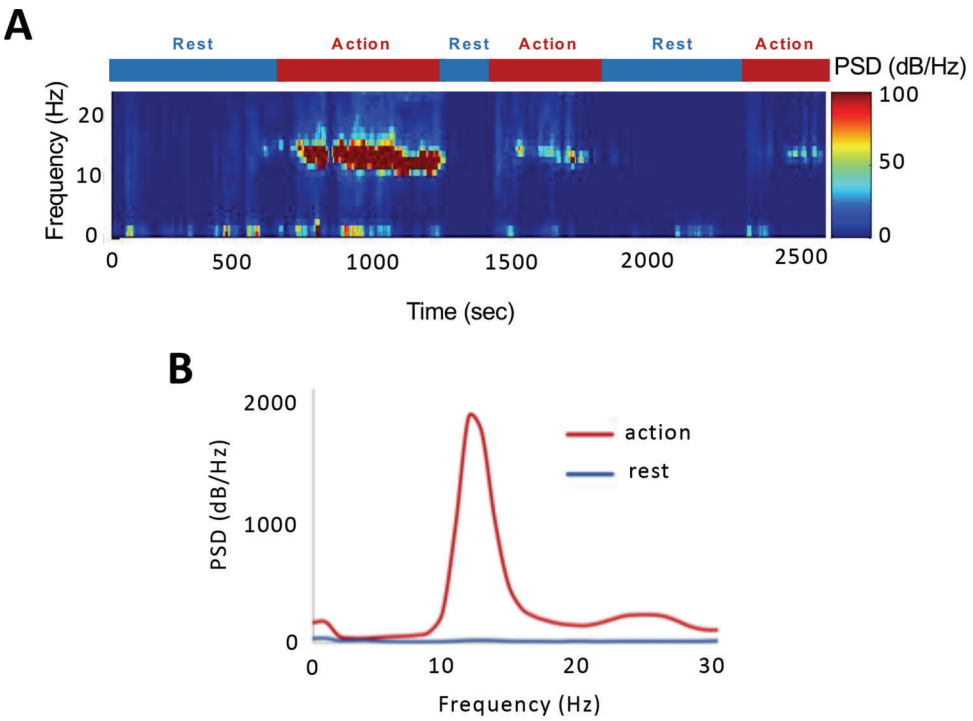

Figure 2. **Characteristics of Harmaline-Induced Tremor in Mice.** (A) A representative time-frequency plot of harmaline-induced mouse tremor, which shows that harmaline can induce action tremor at the peak frequency around 13–15 Hz. The tremor was induced by a single intraperitoneal injection of harmaline hydrochloride (Sigma) at 5 mg/kg into a *WT* C57BL/6J mouse, and the mouse tremor was measured using Convuls-1 sensing platform (Columbus Instruments), co-registered with a video-based motion detection (NeuroMotive, BlackRock microsystem) to separate action vs. rest tremor. (B) The quantification of movement intensity at different frequency, showing that tremor occurs at action but minimal at rest in harmaline-induced tremor mouse model.

During the tremor state, PCs fire rhythmic complex spikes, which originate from CF excitatory synaptic transmission onto PCs with a dramatic suppression of simple spikes.[15,18] Therefore, harmaline is thought to enhance the CF–PC synaptic transmission, which is intrinsically oscillatory, to drive tremor.

Harmaline-induced tremor is predominantly action tremor[13] (Figure 2) that responds to propranolol, primidone, and alcohol.[19] Therefore, harmaline-induced tremor has long been postulated to be an animal model of ET. Harmaline belongs to a group of naturally occurring compounds, called β-alkaloids. In ET patient blood and brain, increased harmaline-related β-alkaloids, such as harmane, have been observed,[20,21] suggesting that environmental factors may contribute to oscillatory activities in the olivocerebellar system in ET patients.

Under the conceptual framework of oscillatory neuronal activities in tremor, several modulatory agents that can influence the olivocerebellum have been tested in this harmaline-induced tremor model as pre-clinical studies for ET. For example, a gap junction blocker, carbenoxolone, has been shown to effectively suppress harmaline-induced tremor[22] and T-type calcium channels that are important for PC complex spikes can also suppress harmaline-induced tremor.[23] Currently, a phase II randomized placebo-controlled clinical trial for a T-type calcium channel blocker is underway for ET (clinicaltrials.gov: NCT03101241), partly based on the understanding of the cerebellar circuitry in harmaline-induced tremor.

While harmaline-induced tremor indicates the importance of the connections between the IO neurons and PCs (Figure 3), animal model studies suggest that other parts of the cerebellar system can also drive oscillatory neuronal activities. For example, the gamma-aminobutyric acid (GABA)-ergic deep cerebellar nuclei (DCN) send axons to IO neurons, which may control the coupling between IO neurons. Loss of this nucleo-olivary GABAergic control may result in enhanced electrotonic coupling between IO neurons, leading to synchronized PC complex spikes.[24] Additionally, IO neurons also receive glutamatergic inputs, which may modulate the synchronization of PC firing.[25] These regulatory components of the olivo-cerebellar system are likely to determine the frequency and the strength of neuronal synchrony, and potentially influence the presentation of tremor. In a post-mortem study of ET patients, there was no evidence of IO neuronal loss,[26] which might have allowed the olivocerebellum system to generate rhythmic and synchronized neuronal activities, under the regulation of the above-mentioned nucleo-olivary control, to drive tremor. Whether ET patients exhibit alterations of these synaptic structures in IOs requires further investigation.

Harmaline has been shown to induce action tremor in a wide variety of animals, including mice,[19,22,27] rats,[19] cats,[15] monkeys,[28] and pigs,[29] suggesting an evolutionarily conserved olivocerebellar circuit for tremor generation. However, different species may have different frequencies in harmaline-induced tremor (mice, 10–16 Hz; rats, 8–12 Hz; pigs, 8–12 Hz).[19] Note that ET patients have tremor at 4–12 Hz.[11] Interestingly, the chronic responses to harmaline also differ among species. Repeated exposures to harmaline will induce "tolerance" in rats and pigs, where the tremor decreases with repeat exposure. This phenomenon presents an exception in mouse models, which tend to develop robust tremor even with repeated harmaline injections.[29,30] Neuropathological assessment between rats and mice with repeated harmaline exposures showed that rats have extensive PC loss,[31] which may be due to excitotoxicity from overstimulation of CF synaptic transmission onto PCs,[31] whereas PCs in mice are relatively preserved.[30] These results might indicate that preserved PCs may be required for the continuous harmaline-induced tremor, which is thought to generate from CF-driven synaptic activities. In ET patients, moderate PC loss has also been identified.[8,32] Whether the PC loss in ET is due to the longstanding, abnormal excitatory synaptic transmission or is a primary PC degenerative process requires further investigation.

While harmaline-induced action tremor models present similarities to ET, this model remains controversial. First, agents that can worsen ET, such as valproate and lithium, tend to suppress harmaline-induced action tremor;[33] however, these tremor-suppressing effects might be due to the non-specific reduction of motor activities because harmaline induces predominantly action tremor. Further studies are required. Second, harmaline is a toxin model and, as such, tremor amplitude may be dose-dependent and further influenced by the timing of tremor

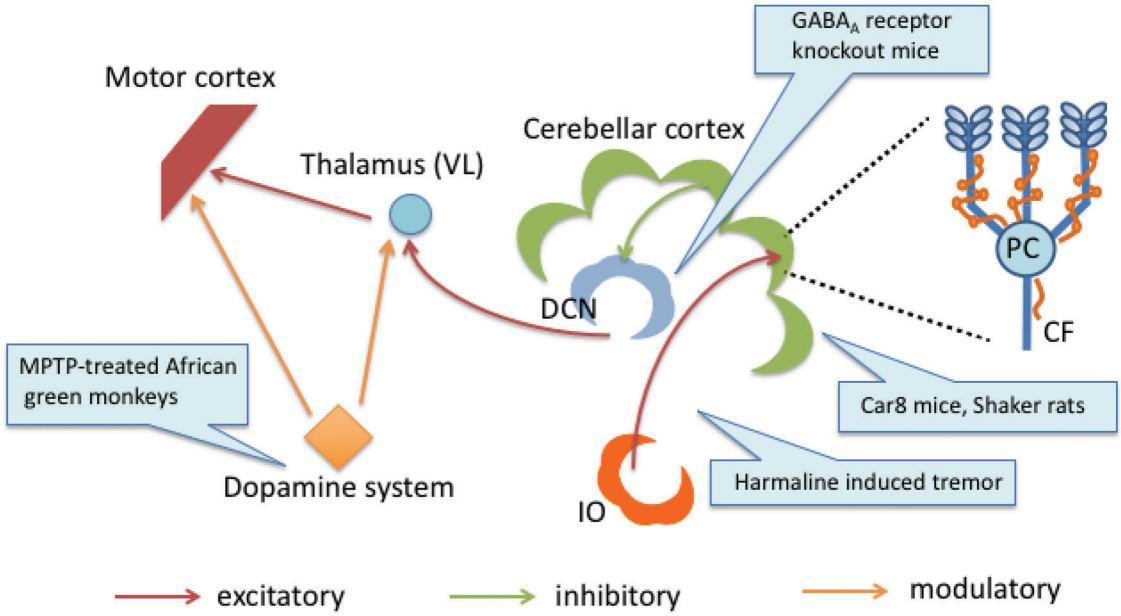

Figure 3. **Brain Circuitry for Tremor.** Schematics for the brain circuitry involved in the tremor of animal models. The brain circuitry alterations in each animal model of tremor are highlighted. CF, Climbing Fiber; DCN, Deep Cerebellar Nucleus; IO, Inferior Olive; PC, Purkinje Cell; VL, Ventrolateral Nucleus of the Thalamus.

assessment. Third, the rapid tolerance of harmaline in animals such as rats and pigs present difficulty for large-scale drug screening. However, the aforementioned animal models still have significant value for the validation of specific agents.

Nonetheless, harmaline-induced action tremor models indicate that the olivocerebellum is capable of generating action tremor and neuronal rhythmicity and synchrony might underlie the pathophysiology of tremor. Along these lines, the structural alterations that can lead to neuronal synchrony and/or rhythmicity within the olivocerebellar circuitry may contribute to tremor. For example, abnormal CF–PC synaptic connections have been identified in post-mortem studies of ET cerebellum. Specifically, CFs form synaptic connections with the distal, spiny branchlets of PC dendrites, which should have been the parallel fiber territory.[9,34–37] This CF–PC synaptic pathology distinguishes ET from other cerebellar degenerative disorders.[35] Furthermore, this CF–PC synaptic pathology may occur across different subtypes of ET, regardless of age of tremor onset and family history of tremor.[9] The extension of CF synapses onto the parallel fiber synaptic territory on PCs is likely to increase the influence of IO activities on PCs, which might enhance the synchrony and rhythmicity in the cerebellar circuitry.[38,39] The other source of neuronal synchrony within the cerebellar circuitry may occur at the level of downstream of PC dendritic synapses. For example, PC axonal collaterals and sprouting have been found in post-mortem studies of ET cerebellum,[40] possibly in response to partial PC loss. It is possible that this PC axonal sprouting process could set up rhythmicity and synchrony within the cerebellar circuitry. Note that post-mortem studies of human pathology need to be interpreted with caution. In particular, observations in human studies cannot establish whether the structural changes are the consequences of longstanding neuronal activities associated with tremor or the primary causes for tremor. Detailed tremor measurements and physiology studies in animal models with the above-mentioned pathological alterations will likely provide further mechanistic insight.[41] In addition, changes in ion channels and/or receptors have not been extensively studied post-mortem in human brains affected by tremor, which might shed light on the pathomechanism of tremor.

In summary, different levels of neuronal synchrony within the cerebellar system are believed to set up the pathophysiological substrate for tremor generation, which may partly explain the clinical heterogeneity of ET.[4]

Animal models of rest tremor

Rest tremor is one of the cardinal features of PD. While dopamine neuronal loss in the nigrostriatal system is the pathological hallmark of PD,[42] dopamine depletion in animals leads to bradykinesia, with rest tremor not consistently reported in such models.[43,44] The most commonly used toxin to deplete dopamine terminals in mice is 6-hydroxydopamine (6-OHDA) injection into the striatum; this procedure can infrequently induce rest tremor.[44] Even in mice models with 6-OHDA-induced rest tremor, tremor is usually not a prominent feature. It is currently unknown why some mice develop rest tremor while others don't. Detailed mechanistic studies are required.

The early work for rest tremor comes from studies in monkeys: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated vervet (African green) monkeys develop robust rest tremor while MPTP-treated rhesus (*Macaca mulatta*) monkeys have only very infrequent rest tremor.[43] The rest tremor in vervet monkeys is approximately 5–7 Hz, measured using an accelerometer, with corresponding synchronous firing of pallidal neurons. This tremor is very similar to that in PD patients.[43] Detailed neuropathological studies comparing these two types of MPTP-treated monkeys found that vervet monkeys have more affected dopamine neurons in the retrorubral area, whereas rhesus monkeys have more profound dopamine neuronal loss in the substantia nigra pars compacta.[45–47] The retrorubral dopamine system has preferential projection to the pallidum, suggesting that pallidal dopamine might play a role in rest tremor generation,[48] which is consistent with recent findings in human functional magnetic resonance imaging (fMRI) studies.[7,49] However, there are few studies focusing on the anatomy and functions of the pallidal dopamine pathway, and its role in tremor generation remains largely unknown. Further comparisons of the neuropathology and physiology between animal models will lead to a better understanding of the mechanism of rest tremor.

Recent advancement of knowledge of rest tremor comes from human neuroimaging studies[7,49] which demonstrate that the interaction between the basal ganglia and the cerebellum is important for rest tremor generation. Specifically, the "dimmer-switch" model proposes that the basal ganglia initiate tremor whereas the cerebellum modulates tremor amplitude and rhythmicity[50] (Figure 3). The involvement of the cerebellum system is further supported by the effectiveness of deep-brain stimulations in the region of the thalamus that receives cerebellar output both in 6-OHDA-treated mice with rest tremor[44] and in PD patients.[51] Another evidence of the cerebellar involvement in rest tremor is that PD patients have hyper-metabolism in the cerebellum based on the positron emission tomography (PET).[52] Whether this hypermetabolism in the cerebellum has a structural basis or merely reflects functional neuronal activities remains to be studied. Intriguingly, a study recently found abnormal CF–PC synaptic organization and other PC pathology in post-mortem brain studies of PD cases with rest tremor,[35] which may suggest that structural changes in the cerebellum contribute to rest tremor. The detailed mechanism of how the interaction between the basal ganglia and the cerebellum generates rest tremor requires further studies in animal models to test the causal relationship between structural alterations in the brain circuitry and tremor.

Other tremor animal models with quantitative tremor measurement

Recently, several quantitative studies of novel animal models have been performed. However, it is unclear whether these animals have predominantly action tremor or rest tremor. Therefore, we have included these animal models and the related pathophysiology in this section.

A recent discovery of tremor of *Waddles* (*wdl*) mice, which have spontaneous mutations in the *Car8* gene,[53] has greatly advanced our understanding of tremor in animal models. CAR8 protein is predominantly expressed in PCs and the loss-of-function mutation of *Car8* in *wdl* mice results in tremor of 5–15 Hz. *wdl* mice have altered frequency and regularity of simple spike and complex spikes of PCs, which likely underlie the physiology of tremor. Another interesting feature of *wdl* mice is the disturbance of the microzonal organization of the cerebellum. The cerebellar circuitry has been organized in the microzones, for which there are specific sets of CF–PC–DCN connections that govern motor control.[54] The afferent inputs to the cerebellum, mossy fibers, also follow such microzonal rules. The microzones of the cerebellum could be traced by a set of PC markers, such as zebrin II or excitatory amino acid transporter type 4 (EAAT4).[55,56] The disturbance of microzonal organization within the cerebellum may cause improper neuronal signaling, leading to tremor. It remains to be studied in detail how this altered PC firing in the context of microzonal organization can lead to tremor in *wdl* mice. Further postmortem studies in microzonal organization of tremor disorders using the human brain will test the relevance of such findings in patients. Nonetheless, mutations of *Car8* have been found in patients with tremor and ataxia,[57,58] which further contribute to the translational aspect of this mouse model and human disorders.

One of the main hypotheses of tremor generation is PC loss,[8,32] which may potentially be modeled by the recent identification of the *Shaker* rat. This natural mutant rat develops low-frequency tremor of around 5 Hz; the predominant pathology of this rat is PC loss, particularly in the anterior lobe of the cerebellum.[59] Interestingly, the tremor is present at the stage of mild to moderate PC loss whereas the *Shaker* rats eventually develop frank ataxia with severe PC loss, indicating that tremor might arise in the intermediate stage of PC degeneration.[60] However, if partial PC loss is sufficient to cause tremor, one would expect to observe tremor in the early stage of hereditary ataxias with PC degeneration such as spinocerebellar ataxias (SCAs). However, tremor only occurs in a minor subset of SCA patients.[61] Within the common types of SCAs, SCA2 often has tremor when compared with SCA1 and SCA6.[61] Therefore, further comparisons of varied subtypes of SCAs with PC degeneration might provide further insight into the pathophysiology of tremor.

Another hypothesis for tremor states that GABA deficiency within the cerebellar circuitry leads to enhanced pacemaking neuronal activities.[62] This hypothesis originated from the observation of a subset of ET patients who responded to GABAergic medications, such as primidone and alcohol.[63,64] Relevant to this clinical observation, a moderate decrease in GABA receptors has been identified postmortem in the ET dentate nucleus.[65] Along these lines, knockout mice with $GABA_A$ receptor α1 subunit deficiency have been found to develop tremor that is responsive to propranolol and primidone.[66] However, the detailed physiological alterations in dentate neurons and PCs in the freely moving $GABA_A$ receptor α1 subunit knockout mice still need to be determined, and whether this mouse model has predominant rest or action tremor requires further investigation. The aforementioned mouse model has some unique characteristics that are distinct from those of ET patients. First, diazepam, a medication than may lessen tremor in ET patients,[63] can dramatically enhance tremor in this mouse model. The $GABA_A$ receptor α1 subunit knockout mice have a 15–19 Hz tremor,[66] which is at a significantly higher frequency than that in ET patients.[11] Third, a recent neuroimaging finding showed that ET patients do not have obvious GABA deficiency in the dentate nucleus,[67] which questions the relevance of this mouse model to ET in humans. Another possibility is that GABA deficiency in ET patients occurs outside the dentate nucleus, such as in the thalamic nucleus[68] or IO neurons,[24] which might cause oscillatory neuronal activities and tremor. Alcohol responsiveness remains a phenomenon of interest in studies of ET. While this mouse model does not possess the $GABA_A$ receptor α1 subunit, mouse tremor can be suppressed by alcohol, indicating that an alternative factor, such as different subtypes of GABA receptors, might be responsible for this tremor-suppression effect. Future studies on the neuronal population-specific $GABA_A$ receptor α1 subunit knockout will advance our understanding of the role of GABAergic synaptic transmission in tremor.

Animal models of tremor with less defined tremor measurement

In our extensive literature search, we found that animal models of tremor could be divided into two broad categories: chemical- or lesion-induced (Table 2), or based on genetic mutations (Table 3). However, tremor is usually not the primary interest of these published animal models, and tremor frequency and amplitudes are less defined than in the above-mentioned animal models. In addition, for those with objective tremor measurement, confirmatory studies are needed to better delineate these tremor phenotypes. Moreover, ataxia and tremor are two symptoms related to cerebellar dysfunction. Ataxia is associated with motion irregularity, whereas tremor is movement with defined frequency and rhythm. Therefore, detailed measurement of frequency and variability of motions in animal models should enhance understanding of the brain circuitry for ataxia and tremor.

In chemically induced animal models of tremor[69–81] (Table 2), we found that agents working on the cholinergic axis are able to induce tremor. For example, agents that promote the cholinergic nervous system, such as oxotremorine,[70] arecoline,[70] nicotine,[75] pilocarpine,[72] and physostigmine,[74] can produce tremor in rodents. Interestingly, promoting muscarinic (oxotremorine), nicotinic (arecoline, pilocarpine, and nicotine), or both (physostigmine) types of cholinergic receptor systems can produce tremor, but whether the tremor characteristics differ in these animal models requires further investigation. One of the clinical implications is that rest tremor in PD can be treated with anticholinergics;[82] therefore, rest tremor may be associated with a hypercholinergic state. Further investigation is needed.

In lesion-induced animal models of tremor, we found that cerebellar lesions could produce tremor[81] and/or change the frequency of physiological tremor[80] in monkeys, highlighting the contribution of the cerebellum to tremor (Table 2).

Finally, there is a list of animal models of tremor with different genetic mutations[83–103] (Table 3). Most of the tremor measurements in

Table 2. **Chemical- or Lesion-induced Animal Models of Tremor**

	Chemical/Lesion	Tremor Type and Frequency (Hz)	Tremor Measurement	Reference
Mouse	Harmaline-induced	10–16 Hz body tremor	Force plate-based measurement	19
	6-OHDA-induced	4–5 Hz body tremor	Electromyography or force plate-based measurement	44
	Galantamine-induced	Oral tremor (3–7.5 Hz frequency range, with a peak frequency of approximately 6 Hz)	Observation	69
	Oxotremorine-induced and arecoline-induced	Tremor	Multiple electrical physiological signals real-time analyzer	70
	Phenol-induced	Tremor	Observation	71
	Pilocarpine-induced	Oral tremor	Observation	72
Rat	Harmaline-induced	8–12 Hz body tremor	Force plate-based measurement	19
	Chlordecone-induced	Tremor	Force plate setting	73
	Ethanol withdrawal physostigmine-induced, arecoline-induced	Tremor(6–7 Hz)tremor (11–13 Hz) tremor (peak of 13 Hz)	Objective measure, not detailed in method	74
	Nicotine-induced	Tremor	Observation	75
	p-Chloroamphetamine-induced	Tremor	Observation	76
	p,p'-DDT-induced	Tremor	Observation	77
	Tacrine-induced	Oral tremor	Observation	78
Monkey	MPTP-induced	5–7 Hz limb tremor	Accelerometer	43
	Electrical coagulation of the brainstem area including the substantia nigra and the red nucleus	Resting tremor (stable frequency of 4.46 $\pm$ 0.59 Hz)	An accelerometer connected to a computer system	79
	Repeated electrode penetration of the dentate and interpositus nuclei	Change the physiological tremor frequency from 11–13 Hz to 5–7 Hz	EMG	80
	Partial cerebellectomy (including unilateral DCN)	Tremor	EMG	81

Abbreviations: EMG, Electromyography; DCN, Deep Cerebellar Nucleus.

these animal models are based on observation only and require objective assessment to delineate rest and action tremor, which are the defining features for human tremor disorders. Many of these genetic tremor animal models have a dysfunctional cerebellar circuit (Table 3). The genetic models provide an invaluable resource for stable tremor phenotypes. Additionally, tremor in some of the models is regulated developmentally and throughout adulthood, which can be further studied to understand the role of aging in the underlying neuropathology and physiology.

The relevant knowledge learned from animal models in the context of controversies in the tremor field

Animal models of tremor allow researchers to perform detailed physiological studies and brain circuitry dissections using optogenetic tools or electric stimulations. Therefore, animal models can be considered as tools to understand tremor disorders. In the present paper we posit a question: "How do animal models of tremor help us to move towards a better understanding of the current controversies in

Table 3. **Genetic Animal Models of Tremor**

	Gene/Lesion	Tremor Type (Hz)	Tremor Measure	Ataxia/Others	Cerebellar Pathology/Physiology	Reference
Mouse	*Car8* mutation	Tremor (4–14 Hz)	Tremor monitor (San Diego instruments)	Ataxia	Microzonal organization defects, abnormal Purkinje cell firing	53
	crv4 mutation	Intention tremor	Observation	Ataxia		83
	Cp/Heph mutation	Tremor	Observation	Ataxia		84
	D801N mutation	Tremor	Observation	Abnormal motor coordination		85
	$GABA_A$ α1 subunit knockout	Tremor (15–19 Hz)	Tremor measured by suspending the tail and attached to the stereo speaker		Absent spontaneous GABAergic inhibitory postsynaptic potentials	66
	NPC1 mutation	Tremor	Observation	Motor impairment, hyperactivity, impaired learning and memory		86
	SCN8A mutation	Tremor	Observation	Ataxia and dystonia	Impaired repetitive firing of Purkinje cells in cerebellar slices	87
	SOD1 mutation	Tremor	Observation	Loss of extension reflex in hind-limbs, decreased grip strength and paralysis		88
	SULT4A1 mutation	Tremor	Observation	Ataxia and absence seizures		89
	Vglut2 deletion in the climbing fiber synapses	Tremor (4–14 Hz)	Tremor monitor (San Diego instruments)	Dystonia	Abnormal Purkinje cell simple spike firing (Silencing climbing fiber synaptic transmission)	90
	Wdr81 mutation	Tremor	Observation	Abnormal gait	Purkinje cell degeneration	91
	β-*III spectrin* knockout	Tremor	Observation	Motor incoordination and a wide hindlimb gait	Purkinje cell loss and cerebellar atrophy	92

Table 3. Continued

	Gene/Lesion	Tremor Type (Hz)	Tremor Measure	Ataxia/Others	Cerebellar Pathology/ Physiology	Reference
	Fig4 knockout	Intention tremor	Observation		hypomyelination of the cerebellum and spongiform degeneration in the deep cerebellar nuclei	93
	Pura knockout	Action tremor	Observation	Waddling gait	Reduced number of Purkinje cells and granule cells	94
	Sticky mouse (*Aars* mutation)	Tremor	Observation	Ataxia	Purkinje cell degeneration	95
	Scrambler mouse	Body tremor	Observation	Abnormal gait		96
	Toppler mouse	Action tremor	Observation	Ataxia	Purkinje cell loss	97
	Wobbler mouse	Head tremor	Observation	Unsteady gait and muscle atrophy		98
	Weaver mouse	Tremor	Observation	Ataxia and hypertonia		99
Rat	*VF* mutation	Generalized tremor (especially the caudal body) that peaks between 4–8 weeks and gradually subsides	Observation		Abnormal myelin-associated vacuoles in the white matter of cerebellum	100
	Shaker mutation	Tremor (4–5 Hz)	Force plate-based measurement	Ataxia	Purkinje cell degeneration	60
	TRM/Kyo mutation	Whole body tremor, responsive to propranolol	Observation			102
Hamster	*bt* mutation	Tremor	Observation		Defective myelination in the central nervous system	101

the tremor field?" To answer this question, we will discuss two major controversies in the tremor field: 1) the relationship between tremor and dystonia, 2) the relationship between ET and PD.

Many ET patients have co-existing dystonic features.[4] It remains unclear whether dystonia and tremor are generated from the same or different sources in ET patients with dystonic features. Therefore, we reviewed the literature in animal models, and aimed to find a similarity between tremor and dystonia. Interestingly, both tremor and dystonia could originate from the dysfunctional cerebellum. From a harmaline-induced tremor model, PC rhythmic firing could drive real-time rhythmic motor activities (i.e., tremor).[15] In mouse models with viral-mediated DYT1 or DYT12 knockdown in the cerebellum, dystonia may be induced, with a corresponding increased burst firing of PCs.[104–106] These studies suggest that real-time abnormalities of PC firing might lead to involuntary movements, which has also been demonstrated by artificially driving PC activities using optogenetics.[107] Therefore, abnormal PC firing may be a common neurophysiological underpinning for tremor and a subset of dystonia. Abnormal PC firing could be at times rhythmic and at times high-frequency, burst firing depending on the different stages of the disease process, and these abnormal PC firing patterns may be temporally and spatially segregated within the cerebellar cortex. This can lead to overlapping tremor and dystonia symptoms in different body regions and/or hand positions. Within this framework, the dystonic feature in a subset of ET patients might originate in the cerebellar region. Future studies of different animal models of tremor and dystonia should help to settle this controversy.

The overlapping of symptoms between ET and PD remains controversial. According to epidemiological studies, ET patients have a fivefold increased risk for PD, and these PD patients are often the tremor-predominant type.[108,109] Severe ET patients will have rest tremor,[108] whereas PD patients often have postural and/or action tremor.[110] It is possible that overlap between ET and PD occurs at the brain circuitry level. As mentioned above, the structural changes in the ET cerebellum may generate oscillatory neuronal activities to drive tremor. In PD, dopamine deficiency may cause infrequent tremor, but the structural changes in the cerebellum can amplify this tremor. This dopamine deficiency associated with rest tremor might be at the level of the globes pallid us internal or the ventrolateral thalamus based on human fMRI studies.[7,111] A recent study found abnormal CF–PC synaptic connections in the cerebellum of both ET and PD patients,[35] possibly demonstrating common brain circuitry abnormalities in these two disorders (Figure 3). This concept is further supported by evidence of the ability of harmaline to intensify rest tremor in monkeys.[28] Future studies in animal models should aim to simulate structural changes in the cerebellar circuits and the dopamine system in ET and PD, respectively, such studies should help decode this pathomechanism.

Conclusions

The use of animal models in tremor research is an emerging field. As we begin to comprehensively understand tremor disorders based on genetic, neuroimaging, and neuropathological studies in humans, modeling these genetic and pathological alterations in animal models will greatly advance our understanding of how tremor is generated. Established animal models are likely to provide an important platform to screen therapies for tremor disorders.

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