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Mini review article

Pathophysiology of parkinsonian tremor: a focused narrative review

Onanong Jitkritsadakul[a], Priya Jagota[a], Roongroj Bhidayasiri[a,b]
[a]*Chulalongkorn Center of Excellence on Parkinson Disease and Related Disorders, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, 10330, Thailand*
[b]*Biomedical Signal Processing Laboratory, Department of Neurology, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles 90095, USA*

Tremor is one of the most common and most debilitating symptoms of Parkinson's disease (PD). Classic pill-rolling resting tremor is characteristic of PD and distinguishes it from other neurodegenerative disorders. Although it represents the most typical and most common form of tremor in PD, other tremor manifestations have also been reported to occur in PD. In this article, we review the current clinical classification of tremor with a focus on different types of parkinsonian tremor based on the consensus statement of the Movement Disorders Society. We also provide an overview of different hypotheses on the central mechanisms of the pathophysiology of parkinsonian tremor, and provide evidence for why peripheral mechanisms may play a role in the modulation of PD tremor.

Keywords: Parkinson's disease, pathophysiology, tremor

Tremor is defined as a rhythmical, involuntary, oscillatory movement of a body part produced by alternating or synchronous contractions of antagonist muscles [1]. Although it is the most common abnormal movement, only a small number of those affected seek treatment [2]. Tremor is of concern because it can cause considerable disability for the individual, limit their daily activities, contribute to stigma or a feeling of shame, and could be related to psychological disorders such as anxiety and depression [3-5].

Tremor classification

Tremor can be classified by the position that accentuates the tremor most into rest tremor and action tremor [1, 6]:

1. Rest tremor is defined as tremor that occurs in a body part that is completely supported against gravity while there is no voluntarily activated muscle contraction.

Correspondence to: Roongroj Bhidayasiri, Chulalongkorn Center of Excellence on Parkinson Disease and Related Disorders, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand. E-mail: roongroj.b@chula.ac.th, rbh@g.ucla.edu

2. Action tremor involves voluntary muscle contractions and occurs during movements. It can be subdivided into postural, kinetic, task-specific, and isometric tremors as follows:

- *Postural tremor*—occurring while maintaining a posture against gravity.
- *Kinetic tremor*—occurring while performing any voluntary movement.
- *Intention tremor*—occurring when approaching a targeted object.
- *Task-specific tremor*—occurring while performing certain specific tasks such as writing or playing a musical instrument.
- *Isometric tremor*—occurring while holding a stationary object.

Tremor can be classified by etiology into physiological tremor and pathological tremor [7, 8].

1. Physiological tremor is tremor occurring in normal persons. It is usually asymptomatic or symptomatic, but rarely visible, has no clinical significance and does not require medical attention [1, 7]. The term "enhanced physiological tremor" is used when the normal physiological tremor is exacerbated during anxiety, exercise, fatigue, or other

conditions that are known to enhance peripheral β-adrenergic activity, and it may result in a visible postural tremor [1]. Physiological and enhanced physiological tremors are the most common forms of postural tremor [1, 8].

2. *Pathological tremors* are tremors that impair a patient's functioning, caused by some abnormalities within the nervous system and usually require some medical management [7, 8]. Pathological tremors can result from disorders in both the central and the peripheral nervous system. These include: Parkinson's disease (PD) tremor, essential tremor (ET), dystonic tremor (DT), cerebellar tremor (CT), neuropathic tremor (NT), and orthostatic tremor (OT). These tremors usually present with high amplitude, specific frequency, and consist of features that can be distinguished from each other as follows:

- Unilateral resting tremor is often seen in PD.
- Bilateral action (mainly postural) tremor is usually seen in essential tremor.
- Tremor occurring in body parts affected by dystonia is called dystonic tremor.
- Intention tremor is often seen in cerebellar disorders.
- Leg tremor, called orthostatic tremor, tends to occur while standing and subside when walking.

Tremor characterization in parkinsonian disorders

PD is characterized by its cardinal motor symptoms: resting tremor, rigidity and bradykinesia [9]. PD was first described by James Parkinson in his publication "An essay on the shaking palsy" [10]. He described the clinical characteristics of 6 individuals, 2 of whom he met on the street. He described their peculiar characteristics in the following key statement:

"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellect being uninjured."

In this statement, he gave a detailed description of the symptoms specific to PD, especially "*the tremulous motion in parts not in action",* which probably refers to resting tremor.

Tremor at rest is one of the most characteristic symptoms of PD and is usually the first symptom to be noticed, occurring in up to 70 percent of the patients [6, 8]. The amplitude of resting tremor usually increases during mental stress (or mental load) and during movements of another body part such as walking [1]. Tremor in PD, or parkinsonian tremor, may have various manifestations in which both resting and postural/kinetic tremors can be seen [1]. Tremor in PD can be classified into 3 types [1] (**Figure 1**).

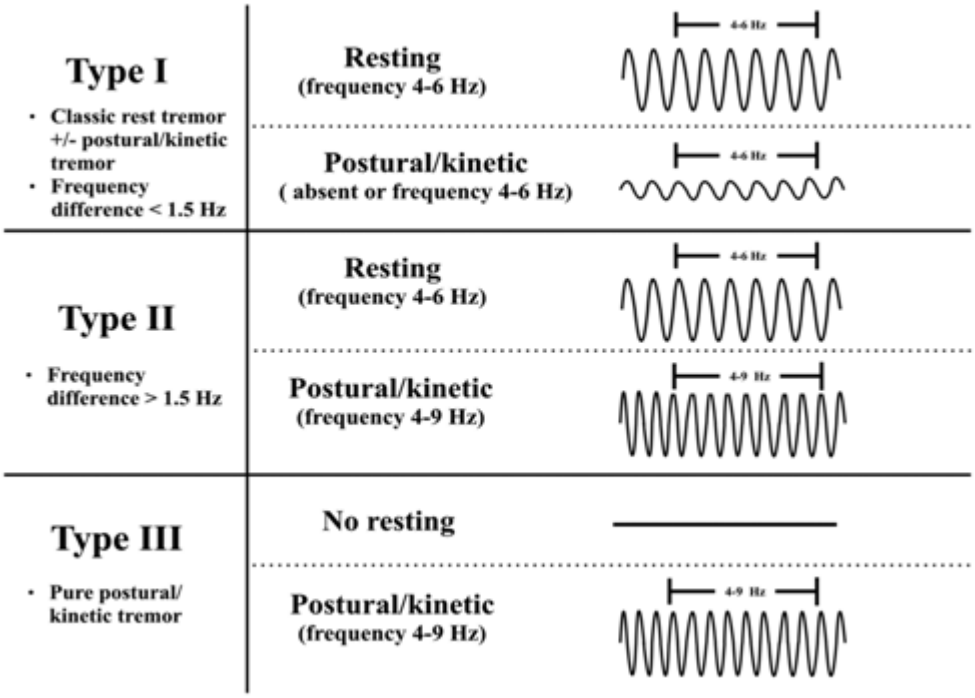

Figure 1. The diagram illustrates different types of tremor that can occur in Parkinson's disease based on the consensus criteria of the Movement Disorders Society [1]

1. Type 1: Classic parkinsonian tremor

PD patients with type 1 tremor usually have resting tremor of around 4–6 Hz frequencies that may occur with or without postural/kinetic tremor. The postural tremor usually occurs after a short pause when holding the arm in position against gravity. This is called reemergent tremor and is characteristic of PD tremor. Higher tremor frequencies up to 9 Hz can be found in PD patients at the early stage. Tremor frequencies for both resting and postural/kinetic tremor are similar with no more than 1.5 Hz difference. This type of tremor is the most common form of tremor in PD.

2. Type 2: Resting and postural/kinetic tremors of different frequencies

PD patients with type 2 tremor have both resting tremor and postural/kinetic tremor. However, the frequency of postural/kinetic tremor is more than 1.5 Hz higher than the frequency of resting tremor. This type of tremor is uncommon and may be considered as a combination of parkinsonian tremor and essential tremor.

3. Type 3: Pure postural/kinetic tremor

PD patients with type 3 tremor have isolated postural and kinetic tremor in 4–9 Hz frequencies. This type of tremor is usually seen in the akinetic-rigid variant of PD.

Pathology of parkinsonian tremor

The pathological hallmark of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta associated with presence of intraneuronal inclusions called Lewy bodies [11]. The pathology of tremor-dominant PD subtype has shown milder cell loss in the lateral substantia nigra (A9) and locus ceruleus, and higher cell loss in the retrorubral area (A8), when compared with the akinetic–rigid PD subtype [12, 13]. This finding indicates that degeneration of the retrorubral area may play a greater role in the occurrence of resting tremor in PD [14]. Patients with tremor-dominant PD have a relatively slow disease progression, preserved cognitive function, and better prognosis than those with the akinetic–rigid subtype [15].

Pathophysiology of tremor

Tremor results from complex connections within the central and the peripheral nervous systems. Different types of tremor have different pathophysiology. There are two main mechanisms for tremor generation: the central and the peripheral mechanisms (**Figure 2**) [14, 16, 17].

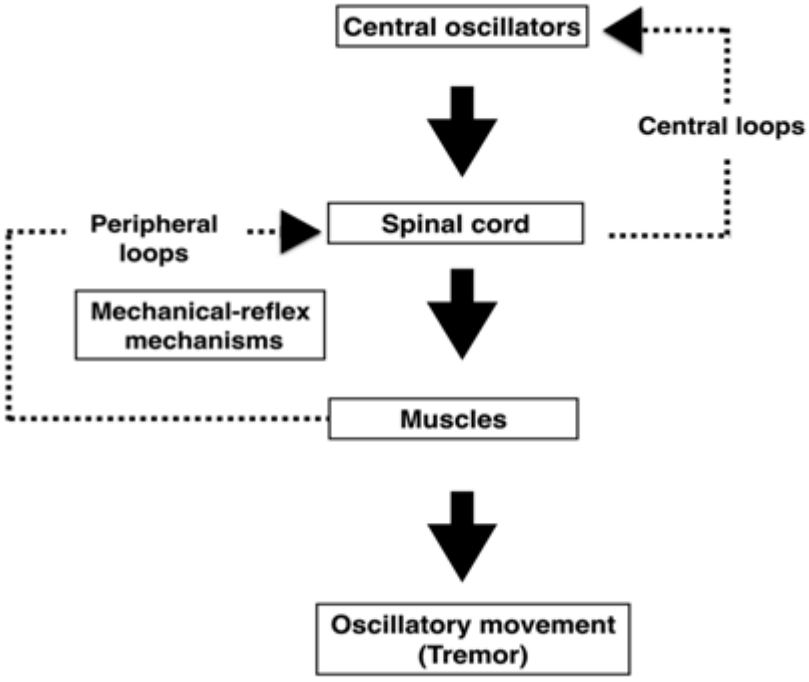

Figure 2. Schematic diagram showing the complex interaction between central oscillators and the peripheral reflex mechanism in producing tremor. Dashed lines indicate feedback loops in which peripheral loops send signals from muscles to the spinal cord, and back again while central loops start from the motor neuron pool within the spinal cord and connect with various central oscillators.

Central mechanism

Some neurons within the central nervous system can demonstrate oscillatory behavior. Oscillations refer to the rhythmic firing of neurons, occurring from the intrinsic properties of the ion channels within individual neurons [18]. Central oscillators refer to neurons in the basal ganglia or its connectivity and the cerebellothalamocortical circuit that give rise to spontaneous oscillations [14, 19, 20]. Physiologically, the central oscillators are thought to drive the tremor, but these oscillators may be different in different pathological forms of tremor [16, 17]. Although the exact locations of central oscillators responsible for tremors are not well identified, lesions in some specific basal ganglia nuclei and thalamus are capable of suppressing tremor [21, 22].

Peripheral mechanism

Peripheral mechanisms (or mechanical-reflex mechanisms) are composed of mechanical resonance and feedback resonances [17]. Mechanical resonances refer to mechanical factors of bone, muscle, and soft tissue that may have an influence on tremor manifestation.[17] Perturbing the mechanical factors by changing mass, external load, and stiffness of the limbs usually influence resonance frequency as shown by the following
formula [16, 23].

In the equation above, K represents stiffness of a structure and J represents the moment of inertia. Tremor frequency is decreased by loading or adding mass and is increased by adding stiffness.

Feedback resonance or peripheral stretch reflex plays a role on tremor by connecting muscles to the CNS. They are composed of central and peripheral loops [16]. Peripheral loops transfer signals from muscles to the spinal cord and back again, and the central loops transfer to higher segments of the spinal cord, brainstem, and higher brain [16]. The simplest loop is the peripheral monosynaptic stretch reflex loop where the Ia afferent fibers from the muscle spindle synapse directly with the α motor neurons in the spinal cord, which send axons to the extrafusal muscle fibers [16]. Theoretically, flexion movements will stretch and cause afferent volley eliciting reflexes in the antagonistic extensors. When an extensor muscle is activated, a similar pattern occurs, causing an afferent volley to the flexors [23]. These reflex loops are then connected and oscillate over time. Under certain circumstances, when the frequencies of the mechanical and reflex oscillations are similar, two frequencies will be integrated into a single frequency and behave like a mechanical system, which is called the local mechanical-reflex mechanism [16].

Pathophysiology of parkinsonian tremor

Although there is strong evidence supporting the hypothesis that parkinsonian tremor is centrally generated, the location of and signal transmission from these central oscillators are still not well understood. Central oscillators are thought to be the main generator and driver of parkinsonian tremor. Peripheral mechanisms are unlikely to generate tremors, and may have little role in modulating the tremor [16, 23].

Central mechanisms in parkinsonian tremor generation

In PD, the central oscillators play a major role in resting tremor generation, but their specific locations remain uncertain [14]. Because lesions in several locations within the basal ganglia nuclei and the thalamus can suppress parkinsonian tremor, it is therefore possible that these subcortical nuclei or their circuitry might be involved in resting tremor. Five possible hypotheses have been proposed for the generation of parkinsonian resting tremor [20]:

1. The thalamic pacemaker hypothesis
2. The thalamic filter hypothesis
3. The subthalamic nucleus–globus pallidus pacemaker hypothesis
4. The loss of segregation hypothesis
5. The connectivity between the basal ganglia and the cerebellothalamocortical circuits or the *"dimmer-switch model"*

1. The thalamic pacemaker hypothesis

In 1984, Jahnsen and Llinas, using in vitro studies of guinea pig thalamic cells, found that these neurons had intrinsic biophysical properties to oscillate themselves (as a pacemaker) at two distinct frequencies: 5–6 Hz and 9–10 Hz [24], which are the frequencies of classic resting tremor in PD and of physiological tremor. However, thalamic cell

recordings in vivo did not confirm the presence of these thalamic pacemaker cells nor did it support the 6 Hz oscillation during thalamic recording in PD patients [25]. It is now generally accepted that thalamus is not a generator of PD resting tremor.

2. The thalamic filter hypothesis

This theory suggested that "filter" properties of the thalamus produce parkinsonian resting tremor [26]. Based on in vitro studies, it was suggested that the tremor pacemakers may be located within the basal ganglia and its frequency is filtered by the thalamus as it was shown that the pallidal cells oscillating at 12–15 Hz could be transformed to 4–6 Hz by thalamic cells [26]. However, a number of in vivo studies have demonstrated that there are cells in the internal segment of the globus pallidus (Gpi) of PD patients oscillating at a low frequency and they were coherent to the frequency of tremor in the corresponding limb [27, 28].

3. The subthalamic nucleus–globus pallidus pacemaker hypothesis

The subthalamic nucleus (STN) and the external segment of the globus pallidus (GPe) might be responsible for synchronized oscillatory activities in basal ganglia based on an in vitro study [29]. However, the cultured cells oscillated at 0.4, 0.8, and 1.8 Hz, which is much lower than the frequency of PD tremor. Moreover, the presence of these cells has not been confirmed in vivo and it is not known whether they are coherent with the resting tremor.

4. The loss of segregation hypothesis

This theory is based on study of neuronal activities in globus pallidus of nonhuman primates [14, 30]. In normal monkeys, neighboring pallidal neurons fired independently and their firing were uncorrelated, suggesting that there are multiple segregated subcircuits within the basal ganglia. In monkeys with dopamine-depleted brains as a result of treatment with 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP), there were intermittent episodes of synchronous periodic bursting of neural firing. Thus, the dopamine-depletion resulted in both increased synchronization–loss of segregation, and the appearance of oscillatory activities in the pallidum.

5. The connectivity between the basal ganglia and the cerebellothalamocortical circuits or the "dimmer-switch model"

Helmich et al. used functional magnetic resonance imaging and electromyography, studied 21 tremor-dominant PD patients, 23 PD patients without tremor, and 36 controls [19]. They found that the GPi, GPe, and putamen were transiently activated at the onset of tremor episodes, whereas activity in the cerebellothalamic circuit (ipsilateral cerebellum, contralateral ventral intermediate nucleus of the thalamus (VIM) and contralateral motor cortex (MC)) cofluctuated with tremor amplitude. The activity was stronger in the more affected hemisphere than it was in the less affected hemisphere. Functional connectivity analyses showed that in tremor-dominant patients the GPi and putamen had increased functional connectivity with the cerebellothalamic circuit via the motor cortex in the more affected side when compared with the PD patients without tremor and control patients [19, 20].

It was proposed that the basal ganglia triggers the onset of tremor (like a light switch), while the cerebellothalamic circuit produces the tremor and modulates the amplitude (like a light dimmer). This hypothesis is called the "dimmer-switch model" [20].

Dopamine transporter (DAT) imaging obtained in this study showed that pallidal (but not striatal) dopamine depletion correlated with clinical tremor severity [19]. Striatal dopamine depletion correlated with bradykinesia. This fits with pathological studies stated above that tremor-dominant PD patients have less degeneration in the lateral substantia nigra, which sends dopaminergic projections mainly to the striatum, and more degeneration in the retrorubral area (A8), which sends dopaminergic projections mainly to the pallidum, when compared to akinetic-rigid PD patients [12, 13].

In addition to the above, this "dimmer switch" model explains many previously unanswered questions, such as why the cerebellothalamic circuit is activated in patients with rest tremor and why deep brain stimulation of VIM nucleus improves tremor [20]. Because of a limitation of the imaging techniques the role of STN, which is a small nucleus, could not be studied. Nevertheless, this is currently the most accepted theory regarding the genesis and modulation of parkinsonian classical resting tremor [20].

Peripheral mechanism in parkinsonian tremor

Most of the literature states that peripheral mechanisms are unlikely to be primarily involved in parkinsonian tremor [16, 23]. Although peripheral mechanisms do not contribute to the generation of PD

tremor, we suggest that peripheral mechanisms may have some role in the modulation or manifestation of PD tremor. An early study, which involved cutting the posterior root of the spinal nerve in a patient with parkinsonian, found that the tremor was not abolished even when the entire limb was deafferented, but there were changes in amplitude, rhythm, and rate [31]. Some later and more recent studies have shown that using electrical muscle or nerve stimulation, PD tremor could be attenuated or reset [32-35]. These data support a role for the peripheral mechanism in modulation, or at least manifestation, of PD tremor.

Explaining the cessation of resting tremor during voluntary movements

According to the "dimmer-switch" model, the basal ganglia are activated transiently to trigger the onset of resting tremor. The striatopallidal circuit may not project their pathological activities to trigger the cerebellothalamocortical circuit during voluntary movements [20]. The basal ganglia control the precision of motor movements by facilitating movements of the required muscles, which is done by focusing facilitative activities in the precise motor cortical area and inhibiting the surrounding cortical areas of the nonrequired motor program (focused selection and surround inhibition, or the center–surround model) [36, 37]. During this process, the motor cortical area involved with tremor-related cerebellothalamocortical circuit might be inhibited, or the tremor-related activities in the pallidum may have been replaced by the activities of voluntary movements, thus causing the cessation of tremor during voluntary movement. This model can also explain how reemergent tremor occurs in PD as the basal ganglia are mainly involved in changes in movements, but not in maintaining posture.

Resting tremor and voluntary movements activities may arise from similar oscillations in the motor cortex. Therefore, the cessation of tremor during movements may be from replacement of tremor-related activities by movement-related activities in the motor cortex itself.

Conclusion

Tremors in PD have heterogeneous characteristics. Dominant resting tremor or classic resting tremor is the most common pattern, and although there has been considerable advancement in understanding its pathophysiology, unanswered questions remain. The focus has been shifted to the study of the interaction of networks and their malfunction rather than single tremor oscillators. The connection between the basal ganglia and the cerebellothalamocortical circuits in resting tremor generation seems to be the most accepted theory. Peripheral mechanisms are unlikely to play a role in PD tremor generation, but may contribute to its manifestation or its modulation.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

Authors' contributions

1. Research project: A. Conception, B. Organization, C. Execution
2. Statistical analysis: A. Design, B. Execution, C. Review and critique
3. Manuscript preparation: A. Writing of the first draft, B. Review and critique

Onanong Jitkritsadakul: 1A, 1B, 1C, 2A, 2B, 3A
Priya Jagota: 3B
Roongroj Bhidayasiri: 1A, 1B, 1C, 2C, 3B

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