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# Tremor: Pathophysiology

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SUMMARY

The precise way that tremors emerge is not well known, but there is some good information and hypotheses. This review will focus on the classic ("rest") tremor of Parkinson disease and essential tremor. Both have their genesis in central oscillators, which appear to be malfunctioning networks. With classic Parkinson tremor, there appears to be dysfunction of the basal ganglia network and the cerebello–thalamo–cortical network. There is evidence that the basal ganglia network triggers the onset of tremor and the cerebellar network is responsible for the amplitude. Since it is a tremor of stability, the beta activity of the basal ganglia may be the trigger. With essential tremor, the cerebello–thalamo–cortical network itself is dysfunctional and perhaps the inferior olive–cerebellar network as well. This is a tremor of action, and the associated ataxia suggests that delays in motor control processing may set up the oscillation.



## 1. Introduction

Given how common tremor is, it is surprising how little we really understand about its pathophysiology. There are many different types of tremor and the pathophysiologies will certainly differ. This review will begin with a broad theoretical background and then emphasize the most common types of tremor.

The motor system attempts to control the position of body parts either at rest, in posture or during certain tasks. The control problem is difficult with many degrees of freedom of each body part and a complex central nervous system controller. The general description of a controller is that there is a motor command for a certain position, a system to implement the command, and feedback to indicate how well the command is being carried out. Feedback is used to modulate the command if the body part does not have the exact desired position. However, feedback takes time and the interaction of the original command and the feedback information might be complicated. This process may well become unstable; such instabilities are often oscillatory and this would generate tremor.

Any body part is a physical object with mechanical properties. Two of those properties are its weight and its stiffness. If the object gets some mechanical energy, it will tend to oscillate with a frequency proportional to the square root of the ratio of the stiffness divided by the weight. This defines the resonant frequency of an object. With more weight, for example, the frequency will be slower. Thus, any body part will have some tremor depending on its characteristics and the amount of energy. One source of energy in humans comes from cardiac motion. If a body part is unsupported it will oscillate at its resonant frequency. This is the origin of an important component of physiological tremor, the natural low amplitude tremor of all body parts. Physiological tremor can be recognized by its characteristic that it will change frequency depending on weight and stiffness. In the laboratory, weighting a limb will lead to a lower frequency.

Each body part is connected to the central nervous system. Muscles get the motor command and feedback returns from a variety of sensory receptors. Some of these sensory afferents feedback immediately on the alpha-motoneurons in the spinal cord, producing short loops. The shortest loop comes from the monosynaptic connection of the Ia spindle afferent on the alpha motoneuron, which is responsible for the tendon reflex and much of the H reflex. There are other short loops as well all within the spinal segment, but there are also longer loops, some to brainstem and others to the cerebellum or all the way back to the motor cortex. Hence there are multiple feedback loops all with different timing, critical for optimal control, but providing considerable opportunity for instability. When the excitability of the short latency spinal feedback loops is enhanced, it can couple with the natural resonance of a body part and produce exaggerated physiological tremor. In this circumstance, the tremor frequency will still change with weighting, but the reflexes will participate as demonstrated by EMG bursting in phase with the tremor. In this situation, the peripheral oscillation is the tremor generator and is augmented by the increased spinal excitability.

Another mechanism is responsible for most pathological tremors and that is a central nervous system generator. Central nervous

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system generators can be of two types. One would be an unstable loop circuit within the central nervous system, similar to the peripheral loop described earlier. Another would be a nucleus with spontaneous rhythmicity, the spontaneity arising from ion channels in the membrane of the neurons that lead to repetitive depolarizations, generally following hyperpolarizations. A relevant channel in this regard is a low threshold calcium channel. Such nuclei can participate in recurrent circuits in the brain, so there might be abnormal local rhythmicity that drives an otherwise normal circuit.

## 2. Classic Parkinson tremor

Patients with Parkinson disease can have many tremor types. The most common is often called tremor at rest, but this tremor can reappear in posture after a pause ("re-emergent tremor"). Then it is a type of action tremor. There are also separate types of action tremors that can be seen in Parkinson patients. Hence, this tremor is best referred to as "classic tremor" without the erroneous implication that it is only seen at rest. The tremor can be most annoying, for example, when a patient is holding a newspaper to read. It appears that it might be a tremor that is most prominent in stable states – either rest or an unchanging posture. It tends to go away with kinetic movements, such as going from rest to posture or doing a specific task.

There is good evidence that classic tremor is pathophysiologically separate from bradykinesia and rigidity [1]. Clinically, the manifestations are separate, and the response of tremor to dopaminergic agents is less certain than bradykinesia. Putaminal dopamine content, measured with SPECT or PET or even post-mortem, does not correlate with tremor. There is a possible dopamine connection, however. One post-mortem study linked dopamine content of the retrorubral area to tremor severity. A more recent study linked dopamine SPECT of the globus pallidus to tremor [2,3]. Hence, if there is a dopamine connection, it is not the traditional nigrostriatal pathway that is relevant.

There is evidence from neuroimaging studies that serotonin might be more relevant than dopamine to classic tremor. A PET study with a ligand that binds to the 5-$HT_{1A}$ receptor indicated that there is more tremor with less binding in the raphe [4]. A more recent study, however, re-evaluating this observation in more detail, indicated that the correlation is more with postural tremor than rest tremor [5]. It has been uncertain what to make of these observations, since, at least so far, manipulating serotonin does not seem to be an influential modulator of tremor.

The oscillatory network in the brain that correlates with tremor has been identified with several techniques. A pattern has emerged from FDG PET scans. In a large group of patient scans, the correlate to the amount of tremor included activity in the dentate nucleus and rostral parts of the cerebellum, the putamen and the motor cortex [6]. Using magnetoencephalography during tremor, it is possible to look at the link between brain activity and EMG bursting with corticomuscular coherence and corticocortical coherence [7]. Corticomuscular coherence shows the contralateral primary motor cortex (M1) most strongly indicating that M1 is the main driver of the tremor. Corticocortical coherence reveals those structures oscillating with M1 to be the secondary somatosensory cortex, the posterior parietal cortex, the cingulate and supplementary motor areas, the diencephalon and the cerebellum. In another study, fMRI was used and separately correlated brain activity with the onset of tremor periods and the amplitude of tremor during the tremor periods (Fig. 1) [3]. Correlating with onset is activity in the putamen and both divisions of the globus pallidus. Correlating with amplitude is activity in the cerebellum, VIM nucleus of the thalamus and motor and premotor cortex. While these studies are

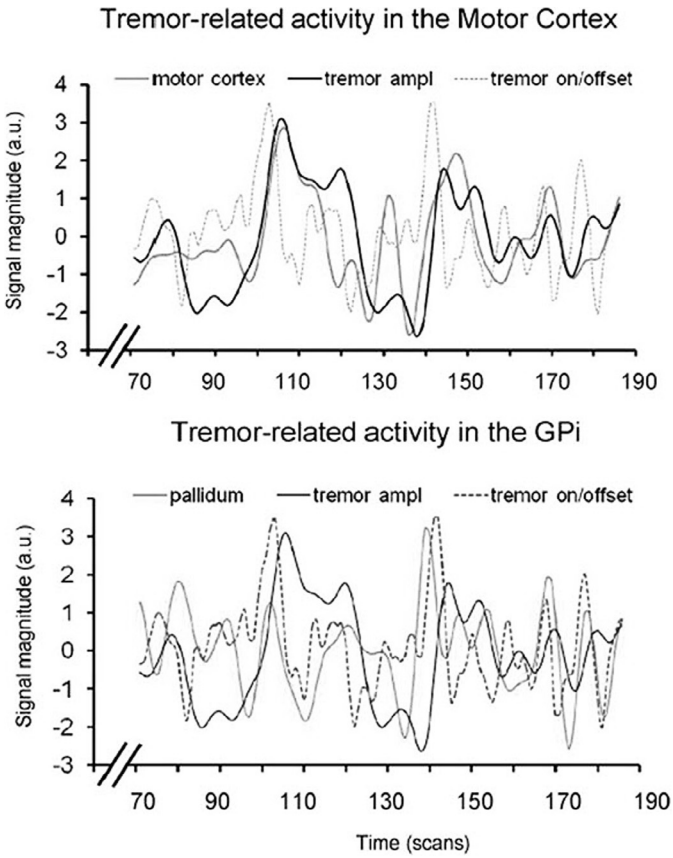


**Fig. 1.** Functional MRI of Parkinson classic tremor. The graphs show activation in the motor cortex on top and in the internal division of the globus pallidus on the bottom. In each part, there are lines for the MRI activity, the tremor amplitude and the tremor on or offset. Note the correlation of tremor amplitude and motor cortex activity and the correlation of tremor on/offset with pallidal activity. Figure modified from [3] with permission.

not completely concordant, some features emerge. M1 is likely the major driver and its network with the cerebellum via the thalamus seems to be the principal circuit for tremor amplitude. The fact that the VIM nucleus is such a good surgical target for tremor is consistent. The clever idea of looking particularly at tremor onset activity reveals a role for an abnormal basal ganglia, and suggests that the basal ganglia triggers the cortical–cerebellar circuit to produce the tremor. The model emerges of coupled oscillators of basal ganglia and cerebellar circuits [2,3]. This idea now has strong support from the relatively new anatomical observations showing bidirectional links between basal ganglia and cerebellum.

Where in these circuits is the abnormality that produces the tremor? In Parkinson disease there is the basal ganglia abnormality and, of course, that is an important suspect. The possible neurotransmitter abnormalities noted earlier might be a clue in this regard. Recordings from patients undergoing surgery for Parkinson's disease demonstrate that there are cells in STN and GPi that burst at tremor frequency and can be demonstrated to be in phase with tremor. It is known that different body parts generally oscillate out of phase with each other and this can be appreciated in the cellular recordings as well, as the cells will be in phase with only certain body parts. The tremor frequency cells are intermixed with cells firing at beta frequency, an abnormal activity related to bradykinesia (Fig. 2) [8]. This finding indicates involvement of the basal ganglia, but does not constitute proof of being the initiating factor.

The VIM of the thalamus also has cells bursting in tight phase with tremor and since thalamic cells have a low threshold calcium