Pathophysiology and Management of Parkinsonian Tremor

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Abstract

Parkinson's tremor is one of the cardinal motor symptoms of Parkinson's disease. The pathophysiology of Parkinson's tremor is different from that of other motor symptoms such as bradykinesia and rigidity. In this review, the authors discuss evidence suggesting that tremor is a network disorder that arises from distinct pathophysiological changes in the basal ganglia and in the cerebellothalamocortical circuit. They also discuss how interventions in this circuitry, for example, deep brain surgery and noninvasive brain stimulation, can modulate or even treat tremor. Future research may focus on understanding sources for the large variability between patients in terms of treatment response, on understanding the contextual factors that modulate tremor (stress, voluntary movements), and on focused interventions in the tremor circuitry.

Keywords
- Parkinson's disease
- tremor
- basal ganglia
- treatment

Tremor is one of the cardinal motor symptoms of Parkinson's disease (PD). Tremor is defined as a rhythmic, involuntary, oscillating movement of one or more body parts. The pathophysiology of tremor is poorly understood, and the treatment of tremor is often more challenging than that of bradykinesia and rigidity—the other cardinal motor symptoms of PD. In this review, we will discuss how pathophysiological changes in the basal ganglia and cerebellothalamocortical circuit give rise to tremor. We will also discuss how interventions in these regions influence tremor.

It is clear that tremor has a different pathophysiology than other PD motor symptoms. For instance, tremor does not increase at the same pace as other motor symptoms; accordingly, tremor severity does not correlate with the severity of bradykinesia and rigidity.[1,2] More specifically, tremor is an early symptom of PD that often completely disappears as the disease progresses. Some patients have pre-dominant tremor on the side contralateral to bradykinesia and rigidity, a phenomenon called "wrong-sided tremor."[3] Also, unlike other motor symptoms, tremor severity does not correlate with the degree of striatal dopamine depletion, which is the pathophysiological hallmark of PD.[4] Indeed, tremor does not respond as well or as reliably to dopaminergic medication as bradykinesia and rigidity.[5] Finally, patients with a tremor-dominant subtype often follow a more benign disease course than patients without tremor.[6]

In addition to its distinctive character, tremor itself is also highly heterogeneous. That is, tremor can be seen in rest or action, and in separate body parts including arms, legs, and lips.[7] The classical Parkinson's tremor occurs at rest and has a frequency of 4 to 6 Hz. This type of tremor usually diminishes after voluntary movement, although it may re-emerge in a stable position (i.e., re-emergent tremor).[8] In addition, PD patients may also exhibit other types of action tremors that usually display a higher ($>$ 1.5 Hz) nonharmonically related frequency to the resting tremor. Some have suggested this tremor to be an incidental finding of co-occurring essential tremor,[9] but it seems more plausible that it is a manifestation of PD itself.

Below we will focus on the underlying pathophysiology and current management of Parkinson's tremor. We will mainly focus on the classical rest tremor. Specifically, we will first elaborate on the pathophysiology by discussing the

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neurochemical basis and cerebral mechanisms underlying rest tremor. Next, we will give an overview of current and future treatment strategies for tremor.

The Dopaminergic Basis of Parkinson's Tremor

The pathological hallmark of PD is dopaminergic cell loss in the midbrain, which leads to dopamine depletion in the striatum.[10] Postmortem studies have shown differences in the pattern of dopaminergic cell loss between tremor-dominant PD patients and nontremor PD patients. Specifically, tremor-dominant PD patients have a milder degeneration of the substantia nigra pars compacta (SNc), but instead more extensive loss of dopaminergic cells in the retrorubral area (RRA) of the midbrain.[11] A similar pattern has been observed in animal models of PD. After the administration of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxin, vervet monkeys develop a tremor-dominant phenotype, which is associated with damage to the RRA.[12] In contrast, rhesus monkeys develop a nontremor dominant phenotype, which is associated with damage to the SNc.[13] This suggests that the RRA, or brain regions receiving dopaminergic input from this area, is involved in the generation of resting tremor.[11] In primates, the RRA projects to several brain regions, such as the frontal cortex (including the primary motor cortex[14]), the globus pallidus,[15] the subthalamic region,[16] the dorsolateral putamen,[17] and the ventrolateral thalamus.[18] Interestingly, this includes the posterior ventrolateral thalamus (VLp), which receives cerebellar inputs. This suggests dopaminergic influences not only on the basal ganglia, but on the cerebellothalamocortical circuit as well. As outlined below, all these regions are involved in the pathophysiology of Parkinson's tremor.

Nuclear imaging has shown that dopamine transporter (DAT) density in the striatum correlates with the severity of all motor symptoms, except resting tremor.[4] In contrast, DAT density in the pallidum correlated with tremor severity, but not with bradykinesia or rigidity.[19] Accordingly, it has been hypothesized that specific loss of dopaminergic cells in the RRA may produce pallidal dopamine depletion, leading to resting tremor.[6]

Using metabolic imaging (combined electromyography–functional magnetic resonance imaging [EMG-fMRI]) in tremor-dominant PD, we recently showed that dopaminergic medication specifically reduced tremor-related activity in the pallidum and the ventral intermediate nucleus (Vim).[20] A multivariate network analysis (dynamic causal modeling) demonstrated that dopaminergic medication specifically increased thalamic inhibition in the Vim. This effect was correlated with the clinical dopamine response of tremor. Taken together, this study raises the possibility that dopaminergic projections to the cerebellothalamic circuit have a role in PD resting tremor.

The Role of Serotonin, Noradrenaline, and Acetylcholine in Tremor

Several studies have pointed toward a role of serotonergic dysfunction in the generation of parkinsonian tremor, but the findings do not all point in the same direction. Specifically, an (11)C-WAY 100635 positron emission tomography (PET) study showed a reduction of 5-HT(1A) receptor binding in the raphe nuclei of PD patients, which correlated with resting tremor severity.[21] Using a different ligand (11C-DASB PET, which binds to the 5-HT transporter), the same group later reported a reduction of 5-HT binding in the caudate, putamen, and raphe nuclei of tremor-dominant PD. However, in this group, 5-HT binding correlated with postural tremor severity, but not resting tremor severity. A large [123]I-FP-CIT SPECT study in 345 drug-naïve early PD patients reported reduced transporter availability in the brainstem raphe nuclei (where it binds to the serotonin transporter) compared with controls, which correlated with rest tremor amplitude and constancy.[22] This study did not report a relationship with action or postural tremor. Thus, it remains unclear whether serotonin depletion in the raphe correlates with resting tremor, with postural tremor, or both. It is also unclear how exactly serotonin contributes to the generation of tremor. Finally, another (123)I-β-CIT SPECT study found lower thalamic transporter binding in tremor-dominant versus nontremor PD patients.[23] This was interpreted as altered 5-HT binding (given the density of serotonergic vs. dopaminergic transporters in the thalamus), but this ligand also binds to the dopamine transporter. Given the presence of dopaminergic projections to the thalamus,[18] the reduced thalamic binding may thus involve both dopaminergic and/or serotonergic cell loss.

Clinically, it is clear that tremor increases during stress.[24–27] This may suggest that noradrenaline has a role in modulating tremor amplitude, but clear empirical evidence is lacking. Previous work has shown that intravenous injection of adrenaline increases tremor, possibly by activating the cerebral locus coeruleus noradrenaline system.[28] Furthermore, although the locus coeruleus, which produces noradrenaline, is affected in early-stage PD,[29] this nucleus is only mildly affected in tremor-dominant patients.[24] These findings may suggest that an intact noradrenergic system is associated with tremor. Interestingly, the locus coeruleus sends noradrenergic projections to all nodes of the cerebellothalamocortical circuit,[30] which is strongly linked to tremor.[19] Thus, noradrenergic projections to this circuit may facilitate tremulous activity, resulting in tremor amplification. Future studies are necessary to test this hypothesis.

Finally, the role of acetylcholine in the generation of tremor was established by the effectiveness of anticholinergic medication over placebo in treating motor symptoms, including tremor.[31] Although the exact mechanism remains unclear, striatal cholinergic interneurons appear to be overactive as a result of dopamine deficiency, which in turn inhibits further dopamine release, causing a vicious circle.[32] This may explain why anticholinergic medication is not as effective in treating motor symptoms as dopaminergic medication: It merely facilitates dopaminergic release, which requires the presence of dopamine to begin with. As outlined above, tremor is associated more with pallidal than with striatal dopamine depletion.[19] It remains to be tested whether the interactions between cholinergic and dopaminergic neurons, as described for the striatum, are similar in the pallidum.

The Cerebral Circuit of Parkinsonian Rest Tremor

It is generally agreed that central rather than peripheral mechanisms underlie parkinsonian tremor.[33] Consequently, over the last decades both electrophysiological and neuroimaging studies have investigated cerebral mechanisms underlying rest tremor. Importantly, both types of studies have generally found the involvement of (parts of) the basal ganglia and/or a cerebellothalamocortical circuit in the generation of tremor. This is supported by strong clinical evidence showing that high-frequency deep brain stimulation (DBS) of the basal ganglia (globus pallidus internus [GPi][34] and STN[35]) and the cerebellar nucleus of the thalamus (Vim[36]) is effective in treating tremor. In the following section, we will first give an overview of the evidence for the involvement of the basal ganglia and cerebellothalamocortical circuit in the generation of tremor, and subsequently discuss current cerebral tremor models.

Electrophysiological studies using intraoperative recordings have found neural oscillations with the same frequency of tremor in the basal ganglia (subthalamic nucleus [STN][37] and GPi[38]) and the Vim.[39] Furthermore, magnetoencephalography studies show tremor-related STN-cortical coherence[40] and tremor-related oscillatory activity within a cerebral network consisting of a cerebellodiencephaliccortical loop.[41] Thus, these studies show the involvement of the basal ganglia and cerebellothalamocortical circuit in the generation of tremor. An important difference is that pallidal neurons are only transiently and inconsistently coherent with tremor,[42] whereas Vim neurons are highly synchronous.[39] This may suggest that the thalamus rather than the basal ganglia is the driving force behind tremor (see below).

Several neuroimaging studies such as PET and fMRI have also identified nodes from the basal ganglia and the cerebellothalamocortical circuit to be involved with tremor. Specifically, a recent PET study described activity in a network consisting of the sensorimotor cortex, the cerebellum, the cingulate cortex, and the putamen which (1) correlated with rest tremor amplitude, (2) was higher in tremor-dominant versus nontremor patients, and (3) was suppressed by Vim-DBS and STN-DBS.[43] Furthermore, using fMRI, we previously demonstrated that tremor amplitude correlated with activity in the cerebellothalamocortical circuit, whereas cerebral activity time-locked to the onset of tremor episodes was related to activity in the basal ganglia.[19] This was confirmed by a recent fMRI DCM study, where we found that tremulous activity first emerges in the basal ganglia and then perturbs the cerebellothalamocortical circuit through the motor cortex.[44] These findings suggest that tremulous activity starts in the basal ganglia and is amplified in the cerebellothalamocortical circuit.[6]

Is Tremor Caused by a Single Oscillator?

Several studies have argued that either the basal ganglia or the thalamus may act as the tremor pacemaker, mostly based on local recordings of a limited set of neurons. One of the first hypotheses was the thalamic pacemaker theory, suggesting that hyperpolarized cells in the thalamus might act as the tremor pacemaker.[45,46] This hypothesis is based on in vitro studies showing that slightly depolarized thalamic cells tend to oscillate at 10 Hz, whereas hyperpolarized cells oscillate at 6 Hz. However, the presence of this 6-Hz oscillatory mode, which is associated with low-threshold calcium spike bursts, has been questioned in PD patients.[47]

Several other theories argue that the tremor pacemaker resides within the basal ganglia. For example, the loss-of-segregation hypothesis,[48] which is based on intraoperative recordings of the pallidum in parkinsonian primates, posits that excessive synchronization related to β-rhythm in the dopamine-depleted pallidum results in tremor. This would also explain why voluntary movements (that have been known to suppress β−oscillations in the basal ganglia[49]) diminish tremor. In close relation to the previous theory is the STN-globus pallidus externus (GPe) pacemaker hypothesis (also based on in vitro data[50]), which proposes that the STN forms a central pacemaker together with the GPe. However, the fact that basal ganglia oscillations are only transiently coherent with tremor[42] and that Vim-DBS is an effective treatment, argues that these theories are at least incomplete.

More recent studies provide evidence in favor of multiple oscillators. For example, pulsed stimulation at tremor frequency over different cerebral regions can all entrain the ongoing tremor, when applied using DBS electrodes (Vim-DBS and STN-DBS) or transcranially over the motor cortex or cerebellum (transcranial alternating current stimulation [TACS]).[51–53] This suggests that all these nodes have pacemaker properties, although it is also possible that these effects were mediated by influences on brain areas that are connected to the stimulated brain region. Furthermore, a recent study showed that PD tremor (as opposed to essential tremor) has a broad frequency tolerance,[54] meaning that tremor amplitude remains relatively stable over a range of frequencies. This indicates the presence of multiple, uncoupled oscillators.

Dimmer-Switch Model

This hypothesis attempts to provide an explanatory framework for tremor that integrates the basal ganglia and cerebellothalamocortical circuits and specifies the unique role of each circuit in tremor. Using concurrent EMG and fMRI recordings, we showed that activity in the cerebellothalamocortical circuit correlated with spontaneous fluctuations in tremor amplitude.[19] In turn, activity in the basal ganglia correlated with changes in tremor amplitude (i.e., maximal at the onset of tremor episodes). This suggests that the basal ganglia operate analogous to a light switch (turning tremor on) and that the cerebellothalamocortical circuit operates analogous to a light dimmer (modulating tremor amplitude).[6] These findings were confirmed in a recent EMG-fMRI study using dynamic causal modeling. In that study, we statistically compared models that differed in terms of (1) the brain region that perturbed the rest of the network

during changes in tremor amplitude (i.e., GPi, GPe, STN, cerebellum, Vim, or motor cortex), and (2) the architecture of the model (i.e., effective connectivity between basal ganglia and cerebellothalamocortical circuit via the GPi-motor cortex connection or via the STN-cerebellum connection).[44] Across two independent cohorts, we found that tremor (as recorded by EMG) could be best explained by a model where cerebral activity related to tremor first arises in the GPi and is then propagated to the cerebellothalamocortical circuit via the motor cortex, where both circuits anatomically converge. It should be borne in mind, however, that this hypothesis adopts a network point of view, where slow changes in cerebral activity (over seconds) are associated with ongoing tremor dynamics. Electrophysiological recordings (that have a much higher temporal resolution) do not always show a clear tremor onset (or "trigger").

More recently, a theoretical extension of the dimmer-switch model (the "finger-switch-dimmer model" has been proposed.[55] This model suggests that tremor is induced by pathological activity in the basal ganglia (the finger), generated by changes in thalamic activity (switch) and modulated by cerebellar activity (dimmer). To support this hypothesis, the authors argue that the increased inhibitory output of the GPi (as described in the classical pathophysiological model of PD) induces rhythmic bursting activity at tremor frequency in the basal ganglia nucleus of the thalamus (anterior ventrolateral nucleus [VLa]), which is subsequently enhanced and transmitted to the posterior ventrolateral nucleus (VLp), which overlaps with the Vim, and other thalamic nuclei via convergence and divergence of inhibitory and excitatory relay neurons within the thalamus, including the reticulate nucleus. Next, the bursting activity is projected onto the motor cortex via thalamocortical projections, where in turn it may be sent to the periphery or amplified via a corticothalamic feedback loop. Last, they propose that the cerebellum is involved by comparing an efferent copy of cortical oscillations to sensory information coming from the periphery to ensure stable oscillatory properties of tremor, such as frequency and amplitude. This model remains to be empirically tested.

Tremor Interventions: General Principles

Treatments should ideally be tailored to the specific tremor of a patient. As outlined above, PD has different tremors that may respond differently to treatment. Specifically, resting tremor and re-emergent tremor likely have a similar response to dopaminergic treatment, whereas action tremors do not.[56] Instead, these tremors may respond better to drugs that are used for treating essential tremor (e.g., β-blockers, primidone, and topiramate), but empirical evidence is lacking. Furthermore, cognitive stress is an important "modulator" of Parkinson's tremor, which may be present to a variable extent in individual patients. More specifically, many patients experience that cognitive stress, which is associated with noradrenergic activity, can dramatically amplify tremor amplitude.[25] Because many patients suffer most from their tremor when under stress (e.g., when giving a talk or dining in public), this could be an important therapeutic clue. We recently compared patient–clinician agreement on the antitremor effect of levodopa between two conditions: tremor at rest and tremor under cognitive stress.[27] The findings indicate that patient–clinical agreement is much larger for tremor under stress than for tremor at rest. This suggests that patients judge the effect of levodopa by its ability to reduce tremor under stress.[27] On the other hand, the antitremor effect of levodopa was smaller for tremor under stress than for tremor at rest.[26] This suggests that nondopaminergic mechanisms (possibly the noradrenergic system) have a context-dependent role in amplifying resting tremor. This may partly explain why tremor appears to be dopamine-resistant in some patients. These patients may benefit from medication that reduces noradrenergic overactivity, e.g., β−blockers, or they may benefit from learning relaxation strategies.[57] To clinically identify tremor modulators, tremor rating scales (that enable quantification of treatment effects) should focus more on tremor severity in different contexts (e.g., under cognitive stress or relaxed).

Medication

Previous studies have reported beneficial effects of several drugs on Parkinson's tremor. In many cases, effects were averaged across resting tremor and (different types of) postural tremor. For instance, the difference between re-emergent tremor and other forms of postural tremor has only been systematically described by the end of the 1990s.[8,58] Averaging across tremors of different etiologies may introduce variance that precludes clear conclusions. For instance, a Cochrane analysis concluded that there was insufficient evidence for an effect of β−blockers on Parkinson's tremor,[59] but was based on studies that included very different types of Parkinson tremors.

Dopaminergic drugs are the first choice for treating Parkinson's resting tremor,[60–62] and probably also re-emergent tremor. It has been suggested that dopamine agonists are able to reduce levodopa-resistant tremor.[63] However, there are no head-to-head comparisons between levodopa and dopamine agonists with tremor improvement as the primary outcome measure, so this remains unclear. In young (below 60 years) PD patients with a tremor-dominant phenotype, anticholinergic medication can be considered. In addition to dopaminergic drugs, anticholinergic medications have been shown to be an effective treatment for tremor as well.[31] However, anticholinergics have the disadvantage of cognitive side effects, especially in elderly patients.[64]

In patients with a "pure postural tremor" resembling essential tremor (i.e., not re-emergent tremor), or in patients with a clear stress component worsening their tremor, β−blockers may be considered, but empirical evidence is lacking. Finally, in patients with a multiresistant tremor, clozapine may be used, although the evidence is not particularly strong and there is a risk of potentially serious side effects (agranulocytosis).[60]

Stereotactic Interventions

There is clear evidence that neurosurgical inventions (DBS or focal lesions) both in the basal ganglia (GPi and STN[65]) and in

the cerebellothalamocortical circuit (the cerebellum-recipient nucleus of the thalamus, i.e., the Vim[36]) are effective in treating Parkinson's tremor. These effects are similar for different tremor types (postural, resting, and action tremor),[66] although no difference was made between re-emergent and pure postural tremor. A small study suggested that STN-DBS was more effective in treating tremor than GPi-DBS,[67] but this was not found in larger samples.[68,69] Interestingly, DBS in the basal ganglia is effective for treating tremor even when it does not respond to levodopa. In those patients, tremor may be pseudo-resistant to levodopa (e.g., insufficient dose), or tremor may be linked to abnormalities in other neurotransmitter systems that also influence the basal ganglia.[5]

MRI-guided focused ultrasound is a relatively new technique that involves making a stereotactic brain lesion. When targeting the thalamic Vim nucleus, this approach can successfully treat essential tremor.[70] Studies are underway testing whether this technique can be used to treat Parkinson's tremor as well.[71]

Several promising new methods may further increase the clinical efficacy of DBS. For instance, recent studies have shown that specific electrophysiological markers in the basal ganglia (measured using DBS electrodes) can predict the occurrence of tremor.[72] This opens the door to closed-loop DBS that is switched on when tremor emerges. Furthermore, in some centers diffusion tensor imaging (DTI) is now used to localize the Vim—which, unlike the STN, cannot be accurately identified using standard anatomical imaging. For example, Coenen and colleagues have shown, both for essential tremor and PD patients, that thalamic stereotactic lesions are most effective when they are localized in the cerebellothalamocortical tract.[73] In a similar vein, Klein and colleagues found that effective Vim-DBS sites were strongly connected to the cerebellum and motor cortex.[74] Finally, it was recently shown that DTI tractography can accurately localize the Vim in individual patients, an approach that was validated using electrophysiological and clinical testing during DBS.[75] These studies provide evidence for the causal involvement of the cerebellothalamocortical circuit in tremor, and they suggest that advanced neuroimaging techniques are useful for accurately localizing the Vim.

Stroke

There have been several cases describing how a stroke in specific brain regions alters Parkinson's tremor. This is informative for understanding the causal role of these regions in tremor production. Two studies reported a Parkinson patient whose tremor was markedly reduced after a "stereotactic stroke" in the ventrolateral motor thalamus.[76] One study reported how a cerebellar stroke transformed a Parkinson patient's resting tremor into a Holmes tremor—at a lower frequency and occurring both at rest and during actions.[77] A similar phenomenon was observed in a patient who had undergone a hemicerebellectomy in the past, and later developed PD: He developed a Holmes tremor on the side ipsilateral to the cerebellectomy, and a resting tremor on the contralateral side.[78] These studies suggest that the ventrolateral thalamus is necessary for the occurrence of tremor, whereas the cerebellum may have a role in determining tremor frequency. Furthermore, these cases suggest that the cerebellum suppresses tremor during voluntary actions, although the exact underlying mechanisms remain unclear.

Noninvasive Brain Stimulation Approaches

Transcranial magnetic stimulation (TMS) has been used to inhibit tremor-related activity in the cerebellothalamocortical circuit. Single-pulse TMS over the primary motor cortex, but not the cerebellum, can reset resting tremor, but this effect lasts only a few tremor cycles.[79,80] Repetitive TMS protocols, either at high or low frequencies, have generally been unsuccessful in treating PD symptoms, including tremor.[81,82]

A relatively novel and promising approach has been the application of TACS through electrodes applied to the skull. Two effects on tremor have been observed: tremor entrainment (i.e., the peripheral tremor adopted the phase of stimulation) and tremor amplitude modulation (i.e., tremor amplitude increased or decreased). Tremor entrainment has been observed when TACS was applied over the motor cortex[53] and over the cerebellum.[54] Furthermore, both Vim-DBS and STN-DBS at tremor frequency were able to entrain the tremor rhythm.[52] These results suggest that the entire basal ganglia and cerebellothalamocortical circuit has pacemaker properties. On the other hand, all these stimulation protocols may have achieved tremor entrainment through distant effects in interconnected brain regions. Tremor amplitude modulation was only obtained when TACS was applied over the motor cortex, and it was maximal (42% tremor power reduction) when TACS was time-locked to a particular phase in the ongoing tremor cycle (assessed using accelerometry[53]). This suggests that the motor cortex has a specific role in controlling tremor amplitude, whereas the rest of the network is necessary for generating the tremor rhythm. If this finding is replicated in larger studies, then it may have therapeutic potential for tremor-dominant patients who are not suitable for DBS.

Conclusion

Empirical evidence from different modalities clearly shows that tremor arises from abnormal activity in the integrated basal ganglia and the cerebellothalamocortical circuit. This abnormal activity may emerge due to reduced dopaminergic (and serotonergic) projections to these areas, as well as increased noradrenergic influences (►**Fig. 1**). We propose that the basal ganglia are involved in initiating tremor, whereas the cerebellothalamocortical circuit has a role in maintaining tremor amplitude. Future research may further test whether components of the cerebellothalamocortical circuit have a specific role in tremor frequency, tremor amplitude, and the context in which it occurs (at rest or during voluntary actions).

It is exciting that advanced neuroimaging techniques are now being used to optimize the clinical treatment of tremor, for example, by localizing the Vim in individual patients prior

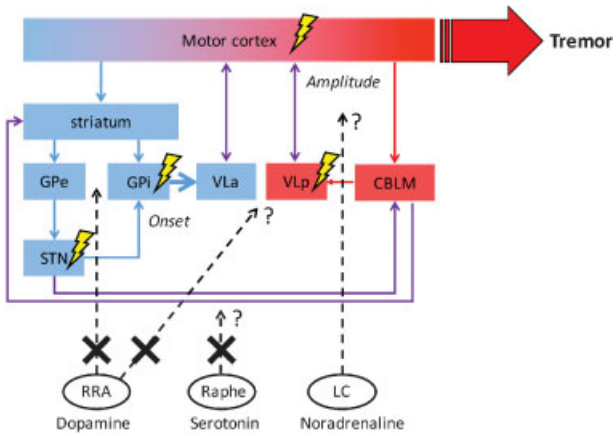

Fig. 1 The cerebral network of Parkinson's tremor. This figure shows the hypothetical cerebral network involved in Parkinson's tremor. The basal ganglia (in blue) and the cerebellothalamocortical circuit (in red) are regions where tremor-related activity has been found. Both circuits converge in the motor cortex (purple). Blue and red arrows indicate connections within each circuit; purple arrows indicate connections between the basal ganglia and cerebellothalamocortical circuits. The open circles indicate neurotransmitter systems that project to these circuits, and where changes have been reported in tremor-dominant Parkinson's disease: reduced dopaminergic projections from the retrorubral area (RRA), reduced serotonergic projections from the raphe nuclei, and (possibly) increased noradrenergic projections from the locus coeruleus (LC). In italic, the hypothesized roles of nodes of this network in generating tremor: triggering the onset of tremor (globus pallidus internus [GPi]) and maintaining tremor amplitude (the cerebellothalamocortical circuit). CBLM, cerebellum; GPe, globus pallidus externus; STN, subthalamic nucleus; VLa, anterior ventrolateral nucleus; VLp, posterior ventrolateral nucleus.

to DBS. Future studies may use neuroimaging to better understand clinical differences between tremor-dominant patients, for example, response to treatment. In this way, individual differences in the tremor circuitry may form the basis for individualized treatments.

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