Journal of the Neurological Sciences 435 (2022) 120196

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review article

The pathophysiology of Parkinson's disease tremor

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ARTICLE INFO

Keywords:
Parkinson's disease
Pathophysiology
Tremor

ABSTRACT

Tremor is one of the primary motor symptoms of Parkinson's disease (PD), and it is characterized by a highly phenomenological heterogeneity. Clinical and experimental observations suggest that tremor in PD cannot be interpreted merely as an expression of dopaminergic denervation of the basal ganglia. Accordingly, other neurotransmitter systems and brain areas are involved. We here review neurochemical, neurophysiological, and neuroimaging data as the basis of the presence of a dysfunctional network underlying tremor in PD. We will discuss the role of altered oscillations and synchronization in two partially overlapping central motor circuitries, e.g., the cerebello-thalamo-cortical and the basal ganglia-cortical loops. We will also emphasize the pathophysiological consequences of the abnormal interplay between the two systems. While there are many currently unknown and controversial aspects in the field, we will highlight the possible translational and practical implications of research advances in understanding tremor pathophysiology in PD. A better understanding of this issue is likely facilitating future therapeutic approaches to PD patients based on medications and invasive and non-invasive stimulation techniques.

This article is part of the Special Issue "Tremor" edited by Daniel D. Truong, Mark Hallett, and Aasef Shaikh.

1. Introduction

Tremor is one of the main motor symptoms of Parkinson's disease (PD) which occurs in roughly 75% of patients and is often present at disease onset [1,2]. Tremor in PD is classically seen in rest at a frequency of 4–6 Hz and typically affects the upper limb but may also occur in other body areas including lower limb, chin, jaw or tongue [5,6]. Tremor is a highly heterogeneous symptom: it may range from mild to severe manifestations, is highly sensitive to stress [7] and although classically at rest, postural and kinetic tremor are also frequently observed. In fact, multiple subtypes of postural tremor in PD have been described, including the frequently observed "re-emergent tremor" (which is assumed to be an extension of rest tremor that re-emerges in a stable posturing position) and the less prevalent "pure postural tremor" (which displays a higher frequency and smaller amplitude) [8–10].

The phenomenological heterogeneity of tremor in PD reflects the complexity of the underlying pathophysiological mechanisms, which to date are not fully understood. Tremor has a unique pathophysiology when compared to the other cardinal motor symptoms in PD (e.g., bradykinesia and rigidity). For example, tremor progresses at its own pace and tremor severity does not correlate with the severity of bradykinesia or rigidity, nor with striatal dopamine depletion [11,12]. Accordingly, tremor in PD can have a variable response to dopaminergic replacement [13,14]. This suggests that tremor in PD cannot be interpreted merely as an expression of dopaminergic denervation of the basal ganglia, but that other neurotransmitter systems and brain areas are involved. Furthermore, tremor-dominant PD patients often follow a more benign disease course, which may be due to a significantly lower

Abbreviations: DAT, dopamine transporter; DBS, deep brain stimulation; EEG, electroencephalography; EMG, electromyography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MPTP, 1-metyhyl 1–4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; PPMI, Parkinson's Progression Markers Initiative; M1, primary motor cortex; NIBS, Non-invasive brain stimulation; PET, positron emission tomography; TES, transcranial electrical stimulation; TMS, transcranial magnetic stimulation; VIM, ventral intermediate nucleus; VLpv, posterior ventral part of ventral lateral; VoP, ventralis oralis posterior.

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https://doi.org/10.1016/j.jns.2022.120196
Received 30 August 2021; Received in revised form 8 November 2021; Accepted 17 February 2022
Available online 19 February 2022

load of cortical Lewy bodies, particularly in neocortical areas, as well as lower amyloid-b plaque deposition and cerebral amyloid angiopathy compared to other disease phenotypes [3].

Over the last years, a series of experimental observations have made it possible to delineate in greater detail the pathophysiological basis of tremor in PD. This is primarily due to recent advances in basic sciences, particularly with respect to new insights into the interconnections between the various movement control systems, e.g., the basal ganglia and cerebellum, which are no longer considered functionally segregated systems but are now thought to influence each other [15]. In addition, there have been advances in the field of neurophysiology, particularly the introduction of new experimental techniques and the advent of functional magnetic resonance imaging (fMRI). Further pathophysiological insight has been gained through studies that combine neurophysiological and neuroimaging techniques [16]. Beyond general considerations, the key aim of current research is to better understand the specific mechanisms of tremor in PD in light of the considerable clinical heterogeneity of this symptom.

The purpose of this paper is to summarize the main knowledge in the research field of tremor pathophysiology in PD. More specifically, we will discuss the contribution of different neurotransmitter systems, cerebral and peripheral networks onto the generation of PD tremor and how they may differ on an inter-individual basis. We will mainly focus on the classical rest tremor (here generally referred to as PD tremor), as there are only a few studies investigating the pathophysiological basis of other tremor types in PD. Finally, we will end this review with the possible translational and practical implications of pathophysiological findings and future perspectives.

2. The neurochemical basis of Parkinson's disease tremor

The hallmark of PD is nigrostriatal dopamine depletion, but the relationship between dopamine and PD tremor is more complicated. Specifically, unlike bradykinesia and rigidity, tremor does not correlate with striatal dopamine depletion [12] and the effects of dopamine replacement on tremor are rather unpredictable [13,14]. However, dopaminergic medication remains the best available treatment option [17], indicating at least a partial role of dopamine in the pathophysiology of tremor. Previous studies tried to explain these apparent contradictive findings by suggesting that extra-striatal dopamine depletion gives rise to PD tremor. Indeed, a nuclear imaging study has shown that dopamine transporter (DAT) density in the pallidum rather than striatum correlates with PD tremor [16]. Interestingly, dopaminergic cells of the retrorubral area in the midbrain (which project to the pallidum) seem to be specifically degenerated in PD patients with a tremor-dominant subtype, whereas cell loss of the substantia nigra pars compacta is relatively spared in this group of patients [18]. However, a larger and more recent study could not replicate the relationship with pallidal dopamine depletion and PD tremor [19]. Another study using metabolic imaging (combined electromyography-functional magnetic resonance imaging [EMG-fMRI]) provided a different explanation by showing that dopamine's primary target regarding PD tremor is not the basal ganglia but the cerebellar thalamus (VIM or VLpv depending on nomenclature) [20]. Although initially surprising, several post-mortem studies in both primates and humans show that the thalamus, including the VLpv is a key target for dopamine [21,22]. Moreover, one study not only showed that the primate thalamus is innervated by collateral nigrostriatal pathways to the thalamus, but also that these pathways degenerate after injecting a vervet monkey with 1-metyhyl 1–4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [23]. Furthermore, the retrorubral area also projects to the thalamus and specifically the VLpv [21]. Importantly, dopamine was only able to inhibit tremor-related activity in the cerebellar thalamus in a subset of patients with a clinically relative dopamine-responsive tremor [20]. A subsequent study confirmed this, and showed that patients with a relative dopamine-resistant tremor have increased activity in non-dopaminergic regions (i.e., cerebellum), which may in turn yield the VLpv less susceptible to a dopaminergic intervention [24]. However, it should be noted that also in the dopamine-resistant group dopamine targeted the VLpv, albeit to a lesser extent. This raises the possibility that dopamine-resistance of tremor is a dose dependent phenomenon [25], suggesting that tremor sometimes requires higher doses of dopamine than the other motor symptoms. This has never been properly tested and it would be interesting to investigate this by calculating a dose-response function for different PD symptoms. However, a counter argument for this theory comes from a recent study using a data-driven clustering approach suggesting that there are two PD tremor phenotypes: one with a strong dopaminergic basis (dopamine-responsive tremor) and one with a weak dopaminergic basis (dopamine-resistant tremor) [13]. This emphasizes that other neurotransmitter systems are involved in the pathophysiology of tremor as well and that the relative contribution of each system may differ between patients, which we will discuss next.

First, there is increasing evidence that serotonin plays an important role in the pathophysiology of PD tremor. Specifically, recent evidence from the Parkinson's Progression Markers Initiative (PPMI) cohort shows that the raphe serotonin transporter availability is decreased in PD patients and that tremor severity is correlated with serotonin transporter depletion [26]. Moreover, the raphe/putamen binding ratio of ^{123}I-FP-CIT measured transporter binding (i.e., raphe serotonin transporter availability normalized to putamen dopamine transporter availability) correlated with PD tremor and its response to dopaminergic medication. This means that patients with a relatively dopamine-resistant tremor show relatively low raphe serotonergic transporter availability. This emphasizes that there are interindividual differences in the contribution of different neurotransmitter systems to the generation of PD tremor. It also suggests that serotonergic treatments may proof to be a promising therapy in patients with a relatively dopamine-resistant tremor. However, there is currently no data supporting this theory besides some anecdotal evidence that clozapine (an atypical anti-psychotic which targets the serotonin receptor among others) is sometimes used as an effective treatment option for PD tremor [27].

Besides serotonin, there are several pieces of evidence which link the noradrenergic system to PD tremor. For example, tremor-dominant PD patients have less degeneration of the locus coeruleus (the main source of cerebral noradrenalin) [28] and noradrenalin receptor binding in the locus coeruleus is increased in PD patients versus controls, and particularly in tremor-dominant patients [29]. Furthermore, cognitive stress [7] and intravenous injection of adrenaline [30] (which both activate the noradrenergic system) can increase PD tremor. A recent EMG-fMRI study provided a mechanistic account for the observation that PD tremor increases during periods of cognitive load by showing that activation of the ascending arousal system (likely including noradrenergic afferences) leads to increased PD tremor-related activity [31]. As levodopa seems to be less effective during these periods of cognitive load [7], it raises the question whether alternative treatment options targeting the noradrenergic system can be used to treat PD tremor during periods of cognitive load and probably stress in general. Although beta-blockers have been suggested as an effective therapy of tremor in PD [17], there are no high-quality randomized controlled trials performed on the efficacy of beta-blockers on PD tremor [32]. Moreover, the few trials that have been conducted did not distinguish between different subtypes of PD tremor (e.g. rest versus (subtypes) of postural tremor) or different contexts (e.g. stress-induced tremor amplification versus spontaneous fluctuations in tremor amplitude). Future studies may address these questions.

Finally, anti-cholinergic medication was among one of the first effective therapies in treating motor symptoms in PD, including tremor [33]. Although not much is known about the exact pathophysiological mechanism, it was suggested that striatal cholinergic interneurons may be overactive in PD which in turn inhibits release of dopamine by muscarinic activation [34], but this remains speculative.

In summary, dopaminergic deficiency plays a role in the

pathophysiology of PD tremor although it is not sufficient to fully interpret the heterogeneity of this motor disorder. Inconsistencies with clinical and experimental observations are possibly explained by extrastriatal dopamine depletion or the contribution of other neurotransmitters, e.g., serotoninergic, noradrenergic and cholinergic systems. It remains to be clarified how individual differences in the various neurotransmitter systems contribute to the pathophysiology of PD tremor, which will be the topic of the following section of the paper.

3. Neural mechanisms underlying the generation and propagation of PD tremor

In the past, both invasive and non-invasive electrophysiological techniques were used to study PD tremor. More specifically, invasive micro- and macroelectrode recordings during stereotactic surgery or deep brain stimulation (DBS) revealed electrophysiological activity of single neurons or population of neurons (referred to as a local field potential - LFPs) of selected brain regions [35]. In addition, surface electromyography (EMG) combined with electroencephalograpy (EEG) and/or magnetoencephalography (MEG) was used to determine coherence between cerebral and muscular activity [36,37].

Electrophysiological recordings in parkinsonian animals, e.g. MPTP-treated monkeys, showed that during tremor, the mean firing rate of neurons in the pallidal and cerebellar territories of the thalamus increases [38,39]. Likewise, early studies using invasive recordings and single unit analyses in PD show tremor related activity in both the thalamus and basal ganglia. More specifically, neurons with oscillatory activity at tremor frequency were detected in the VIM suggesting an intrinsic thalamic pacemaker [40,41]. It was hypothesized that oscillations at tremor frequency occur due to hyperpolarization of thalamic cells, possibly via low-threshold calcium channels. However, the presence of oscillatory activity at tremor frequency, which is associated with low-threshold calcium spike bursts, has been questioned in PD patients [42]. Therefore, the role of these low-threshold calcium channels (and their potential use as a therapeutic target) remains unclear. Furthermore, microelectrode recordings also demonstrated the presence of oscillatory activity at tremor frequency in neurons of the ventral portion of the internal pallidum (GPi) and subthalamic nucleus (STN) of PD patients [41,43–45], particularly in its dorsal layers [46]. In addition to single-unit recordings, PD tremor is associated with a variety of LFP signal changes in basal ganglia (most notably STN) at variable frequencies. More specifically, STN power increments near tremor frequency (range 4–8 Hz) have been observed in PD [47,48], but also much higher frequencies, for example in the low gamma frequency range (35–55 Hz) were associated with PD tremor [49,50]. Accordingly, PD tremor reduction by DBS was associated with gamma (but not beta) power suppression [50]. These results thus indicate that an altered balance between beta and gamma oscillations in the STN contribute to the pathophysiology of PD tremor. In addition, changes in high frequency oscillations (HFOs >150 Hz; which occur in many tremor syndromes [51]) show that the ratio between slow (200–300 Hz) and fast (300–400 Hz) HFOs in STN increased with PD tremor severity [52].

The experimental data discussed so far clearly indicate that intrinsic oscillatory properties of the thalamus, GPi and STN may be involved in the generation of tremor in PD. However, the temporal relationship with PD tremor, that is, whether these signals reflect tremor onset, maintenance or simply afferent tremor-related activity is still debated. For example, it is unclear which brain region determines PD tremor frequency, i.e., acts as the pacemaker. Previous accounts have suggested that the PD tremor pacemaker may be either part of basal ganglia (e.g. loss-of-segregation between dopamine-depleted pallidal neurons) [53] or recurrent loops between external pallidum and subthalamic nucleus [54]) or the thalamus, e.g. via hyperpolarization of thalamic neurons possibly mediated via increased inhibitory influences by the GPi (which projects to the motor thalamus or VLa) [55]. A more recent study suggested that both the thalamus (VIM) and the basal ganglia (STN) have pacemaker properties, as evidenced by the ability of DBS to entrain activity in these regions [56]. This would not, however, explain why basal ganglia oscillations are only transiently and inconsistently present with PD tremor [57], whereas fluctuations in the VIM are highly synchronous [58]. Moreover, other experimental approaches demonstrated a greater level of complexity concerning the pathophysiology of PD tremor and indicate that oscillatory activity propagates in a wide network of cortical and subcortical brain areas. For example, a combined EMG-MEG study showed a strong coherence between the EMG tremor signal and activity in the contralateral primary motor cortex (M1) [36]. Importantly, further analysis revealed cerebro-cerebral coherence between M1 and a wide network including pre-motor areas (lateral premotor cortex and cingulate/supplementary motor areas), parietal areas (e.g., secondary somatosensory cortex and posterior parietal cortex) and subcortical areas (e.g., the diencephalon assumed to be the thalamus, and the contralateral cerebellum) [36]. Additionally, EMG-MEG recordings have also revealed coherent sources in the cerebellum for PD tremor and a flow of oscillatory activity from cerebellum to cerebral cortex [59]. These data overall demonstrate the involvement of two circuits in the pathophysiology of PD tremor: basal ganglia and a cerebello-thalamo-cortical motor loop. Crucially, this is confirmed by clinical intervention studies showing that targeting either basal ganglia or (parts of) the cerebello-thalamo-cortical circuit are effective in the treatment of PD tremor. For instance, stereotactic lesioning of both basal ganglia (GPi, STN) and the thalamus (VIM) either via DBS or neurosurgical disruption is an effective treatment of PD tremor [60–62]. Furthermore, non-invasive brain stimulation (NIBS) techniques, including transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES), show that rest and postural tremor in PD can be temporarily suppressed (tremor resetting) by delivering single-pulse TMS to M1 [63–66]. Tremor resetting was present bilaterally even after focal, unilateral stimulation and depended on the stimulus intensity [63]. Postural (but not rest) tremor in PD was also reset by cerebellar stimulation [65]. These findings suggest that M1 controls both the amplitude and the rhythm of rest tremor, while the cerebellum may play a specific role in controlling the rhythm of postural but not rest tremor. It is likely that rest and re-emergent tremor share common pathophysiological mechanisms, in which M1 plays a key role [66]. Pure postural tremor may be mediated by different neuronal pathways [65], but this remains to be tested.

Although PD tremor is most likely caused by central rather than peripheral mechanisms [67] there is neurophysiological evidence suggesting a close interaction between proprioceptive input and tremor generation in PD as well [68]. Previous studies show a modification of PD tremor amplitude by supramaximal peripheral nerve shocks, passive joint movements or muscle vibration [69–71]. However, PD tremor frequency and phase does not seem to be affected by these or other peripheral interventions such as surgically removing the dorsal roots [72], weighing of the joints [73] or mechanical displacement of wrist and joint [74]. These observations suggest a possible modulatory contribution of afferent proprioceptive input onto PD tremor amplitude but not on the occurrence of PD tremor per se. Indeed, it has been proposed that PD tremor may be generated via an intrinsic cerebral network (likely involving basal ganglia and cerebello-thalamo-cortical circuit) but is stabilized and maintained via an extrinsic spino-cerebellar-thalamo-cortical feedback loop [75,76]. Moreover, it was suggested that inter-individual differences in processing afferent signals may result in phenotypical differences such as dopamine-responsiveness of tremor [24]. However, the exact role of afferent and efferent neural signals in the genesis of PD tremor remains open to debate.

In summary, based on electrophysiological evidence it seems that PD tremor is of central origin that arises due to oscillatory properties of a tremor network (encompassing the basal ganglia-thalamo-cortical and the cerebello-thalamo-cortical circuitries) which may interact with peripheral circuits. However, several outstanding issues remain, including the exact generator “node” in the tremor network and other aspects, e.g.,

how multispectral oscillations in one single area, e.g., the STN, or synchronization within and between brain areas translates into PD tremor. In the next section of the paper, we will discuss further studies, mainly based on neuroimaging methods that provide further understanding of the pathophysiology of PD tremor.

4. The dimmer-switch model - an integrated network model explaining PD tremor

In addition to electrophysiological studies, several neuroimaging studies including Positron Emission Tomography (PET), functional and structural MRI all point towards the involvement of both basal ganglia and a cerebello-thalamo-cortical circuit in the generation of PD tremor. First, early PET studies show that VIM-DBS which resulted in PD tremor suppression was associated with decreased blood flow in the contralateral cerebellum [77] and ipsilateral sensorimotor cortex [77,78]. Furthermore, it was shown that PD tremor is covariant with regional hypermetabolism in a network consisting of cerebellum, thalamus (VLp) and motor cortex [79], Finally, FDG-PET of tremor-dominant PD patients showed tremor-related activity of the putamen and a cerebello-thalamo-cortical network, which was reduced after VIM-DBS [80]. In addition, structural MRI studies using voxel-based morphometry show that tremor-dominant PD patients have reduced grey matter volume in the cerebellum [81] and increased grey matter in the posterior VL of the thalamus [82].

Although the involvement of both basal ganglia and cerebello-thalamo-cortical circuit is clear, the exact role and interaction of both circuits has long remained elusive. In recent years several studies combining EMG with functional MRI have tried to integrate the differential role of both circuits [83]. Specifically, the dimmer-switch hypothesis was posed stating that in PD the basal ganglia initiate a tremor episode (analogous to a light-switch) and the cerebello-thalamo-cortical circuit modulate tremor amplitude (analogous to a light-dimmer) [84]. This was based on the finding that fluctuations in tremor amplitude correlate with activity in a cerebello-thalamo-cortical circuit, whereas fluctuations related to tremor change (i.e., maximal at tremor onset) seem co-dependent on activity within the basal ganglia [16]. This finding appeared robust across multiple subsequent studies [20,24,85]. The elegance of this theory is that it explains the crucial role of both the basal ganglia and the cerebello-thalamo-cortical circuit, and why interventions aimed at either circuit (for example with DBS) are able to treat PD tremor. Interestingly, using computational methods such as Dynamic Causal Modelling (DCM) a basic cerebral circuit fitting the dimmer-switch hypothesis could be constructed [85]. Moreover, (extensions of) this model were used to explain several outstanding questions regarding the phenotypical heterogeneity of PD tremor. For example, it was shown that dopamine can treat PD tremor by targeting the cerebellar thalamus, but only in a proportion of patients with a relative dopamine-responsive tremor [20] due to increased activity of non-dopaminergic areas in patients with a dopamine-resistant tremor [24]. Furthermore, during periods of cognitive load, a cognitive control network amplifies tremor via stimulation of tremor-related activity in the cerebello-thalamo-cortical circuit through the thalamus [31].

Although (extensions of) the dimmer-switch model is able to explain several features of PD tremor, a number of questions remain unanswered. First, given the limited temporal resolution of fMRI, it remains an open question which brain region(s) determine PD tremor frequency. Interestingly, DBS systems with online recording capabilities are now being used [87], which in combination with fMRI may further specify how oscillations relate to network dynamics. Second, it is unclear how the basal ganglia are able to trigger a tremor episode. One explanation comes from a recent case report showing that there is a transient increase in subthalamic power at alpha/low beta frequencies at tremor onset [88], perhaps representing the tremor trigger. However, the temporal causality is not exactly clear as the increased STN power occurs shortly after onset of a tremor episode. Also the mechanism by which this trigger is communicated to the cerebello-thalamo-cortical circuit is unsure, although a recent study suggests that the GPi (i.e. the output hub of the basal ganglia) is able to modulate cortical excitability and plasticity of M1 via a direct connection [89]. Third, it is unclear how spontaneous fluctuations in tremor arise. One of the striking hallmarks of PD tremor is that it waxes and wanes spontaneously. The dimmer-switch model incorporates an explanation for the execution of these fluctuations, but it does not say anything about the underlying trigger. A recent study showed that cognitive load is able to amplify tremor via increased activity of the ascending arousal system which likely includes the locus coeruleus noradrenergic system [31]. A similar mechanism may be responsible for spontaneous fluctuations in tremor as evidenced by a correlation between pupil diameter and spontaneous fluctuations in tremor amplitude [31]. How increased arousal may trigger a tremor episode remains speculative. One possible explanation is through direct projections of the locus coeruleus onto the cerebello-thalamo-cortical circuit and/or basal ganglia [90,91], similar as was shown during periods of cognitive load [92]. Alternatively, it was shown that the ascending arousal system may stimulate a brain state of increased between network-level integration [93], and that some of the motor symptoms in PD may also be related to the increased integration of cerebral networks [94,95]. Thus, the ascending arousal system may facilitate spontaneous fluctuations in tremor by switching between different brain states. Future studies may test these hypotheses.

In summary several neuroimaging studies have provided novel information on PD tremor pathophysiology. The major advance is insight into the maladaptive interaction between cerebello-thalamo-cortical and the basal ganglia-cortical motor circuitries which has led to the development of the dimmer-switch hypothesis as a new interpretive key for a better understanding of PD complexity (Fig. 1).

5. Concluding remarks and translational implications

We show that PD tremor is associated with the synchronization of cerebral oscillations in two partially overlapping central networks, e.g., the the cerebello-thalamo-cortical circuit and basal ganglia-cortical loop. The dimmer-switch hypothesis (Fig. 1) provides an explanatory framework integrating both circuits, but several outstanding questions remain. Importantly, the complex heterogeneity of PD tremor is likely reflected by (sometimes subtle) inter-individual differences in pathophysiology including the contribution of different neurotransmitter systems, the exact architecture of the cerebral tremor circuitry, and processing of afferent tremor-related signals, although more research is necessary to further elucidate this.

An important question that arises is how we can translate the pathophysiological knowledge into information for clinical decision making. Several pieces of evidence illustrate that electrophysiological characteristics and correlates of PD tremor may be used for the improvement of PD tremor treatment. For example, algorithms for the detection of tremor with wearable sensors are becoming increasingly accurate and are already being used in practice [96,97]. These wearables may be superior to qualitative assessment in the evaluation of treatment effect and reduce both under- and overtreatment [98], especially in case of less experienced clinicians. In addition to the optimization of drug treatment, neural correlates of PD tremor could also have important implications for the development of more individualised invasive and non-invasive stimulation therapies in PD patients. For example, tremor detection in PD by STN-LFPs (which may be recorded from the in-situ DBS electrode) was shown to be robust even over short time periods and can be used for closed-loop adaptive DBS systems [99]. Indeed, initial studies show that this is feasible and may be more efficient [100]. NIBS of M1 or cerebellum [101–103] or electrical stimulation of the peripheral nerve [104] may also be effective in treating tremor, but the effects appear variable and not always reproducible [70]. Therefore, larger studies should be conducted to clarify their potential therapeutic use.

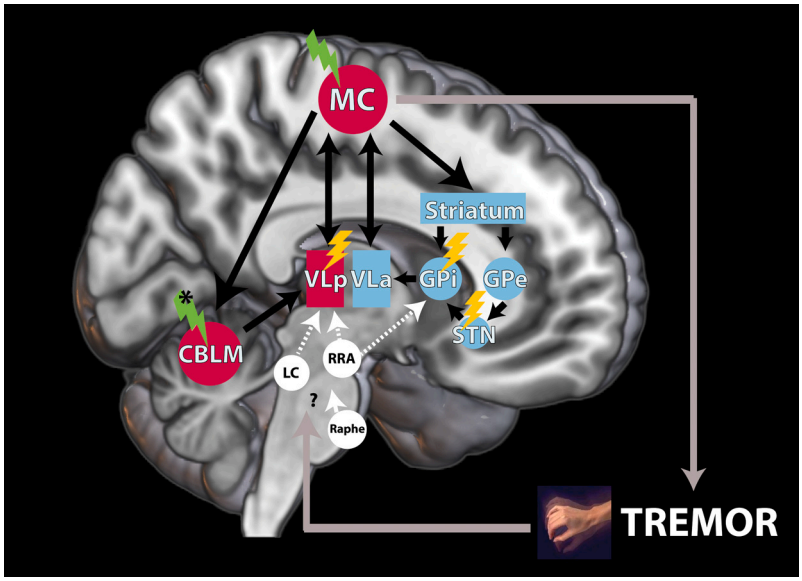

Fig. 1. The pathophysiology of PD tremor. This figure shows the hypothetical cerebral circuit responsible for the initiation and propagation of PD rest tremor. According to the dimmer-switch hypothesis, the basal ganglia (blue) initiate a tremor episode whereas the cerebello-thalamo-cortical circuit (red) produces tremor amplitude. Both circuits converge at the level of the motor cortex. Importantly, multiple neurotransmitter systems are involved, including the dopaminergic retrorubral area (which influences the cerebral tremor circuit through basal ganglia and VLp), noradrenergic locus coeruleus (which influences the cerebral tremor circuit through the VLp) and serotonergic raphe nuclei (unsure where this region targets the cerebral tremor circuit). Afferent activity derived from trembling muscles may converge with cerebral networks, possibly at the level of the cerebellum and/or thalamus, although this remains to be investigated. Yellow bolts indicate targets for DBS and neurosurgical lesioning whereas green bolts represent targets for non-invasive brain stimulation techniques.
*The cerebellum is only a target in case of postural tremor in PD.
MC = motor cortex, GPe = globus pallidus externa, GPi = globus pallidus interna, STN = subthalamic nucleus, VLa = anterior ventrolateral nucleus of the thalamus, VLp = posterior ventrolateral nucleus of the thalamus, CBLM = cerebellum, LC = locus coeruleus, RRA = retrorubral area. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In contrast to electrophysiological techniques, the role of (functional) neuroimaging in the development of improved treatment strategies is so far limited. However, as advanced neuroimaging techniques are increasingly being used to explain the large phenomenological heterogeneity of PD tremor, it would be interesting to see whether these techniques can be adapted to predict the clinical phenotype at an individual level. For example, extensions of the dimmer-switch model may be used to elucidate the relative contribution of each neurotransmitter system and thus predict an optimal patient-specific treatment strategy with dopaminergic-, serotonergic-, noradrenergic and anti-cholinergic drugs. One condition for this technique to be implemented in clinical practice is that these models are able to provide an individual cerebral fingerprint that can be used for classification and prediction. Recent studies suggest that this is possible with new computational methods such as (extensions of) Dynamic Causal Modelling [105]. Whether these techniques can also be applied to PD tremor remains a topic for future research.

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