NEURAL REGENERATION RESEARCH
www.nrronline.org

Cerebral cortex contributions to Parkinson's disease tremor: what exactly generates the tremor?

Manuel Bange*, Hao Ding, Muthuraman Muthuraman

Pathological tremor is one of the cardinal symptoms in Parkinson's disease (PD). Tremor is comprised of involuntary, rhythmic, and oscillating movements that can vary according to the circumstances under which they occur, the body parts that are involved, and the frequency at which they present. For example, tremors can be mild to severe, are stress sensitive, and can affect arms, legs, or the head (Dirkx and Bologna, 2022). Furthermore, it can appear at rest (rest tremor), while holding a posture (postural tremor), or even during active movement (kinetic tremor). Among these variants, rest tremor is the most common manifestation, usually expressing itself as an asymmetric, pill-rolling movement of the hands at frequencies from 4 to 6 Hz which is inhibited during voluntary movement. Paradoxically, people with rest tremors may additionally experience a tremor that re-appears after a brief delay (on average 10 seconds) when maintaining a stable postural position, a phenomenon known as re-emergent tremor (Jankovic et al., 1999). Given that the phenomenological and electrophysiological characteristics of rest and re-emergent tremor are similar and patients with re-emergent tremor do not differ clinically from patients with isolated rest tremor, re-emergent tremor was initially suggested to be a clinical variant of rest tremor and assumed to share the same central tremor circuit (Jankovic et al., 1999).

Tremor has a distinct pathophysiology when compared with other primary motor symptoms in PD, such as bradykinesia, rigidity, or postural and gait impairments. For example, tremor progresses independently, and its severity does not align with the severity of other symptoms, nor with the extent of striatal dopamine depletion. Consequently, the response of tremors to dopaminergic replacement therapy can be inconsistent (Dirkx et al., 2019). This indicates that tremor in PD is not solely a manifestation of dopaminergic denervation of the basal ganglia, but rather involves other neurotransmitter systems and brain regions as well. The complexity of the underlying pathophysiological mechanisms and the neural origin of PD tremor remains poorly understood to date. In the following paragraphs, we will briefly discuss the dimmer-switch model and review novel evidence that suggests that the cortex has a crucial role within the tremor oscillating network.

The dimmer-switch model: The dimmer-switch model, developed more than 10 years ago by Helmich et al. (2012), integrates pathological mechanisms within the basal ganglia and the cerebello–thalamo–cortical loop to describe how rest tremor is triggered and modulated. According to this model, pathological signaling in the basal ganglia (importantly, in this context not within the nigrostriatal pathway, but in a parallel loop providing dopaminergic inputs to the pallidum) alters thalamic activity in the ventrolateral part, which could be responsible for tremor initiation (analogous to a light-switch), whereas fluctuations in the cerebello–thalamo–cortical loop are thought to modulate the tremor's amplitude, thus acting like a light-dimmer. The dimmer-switch model is based on findings showing that fluctuations in tremor amplitude correlate with activity in the cerebello-thalamo-cortical circuit, while changes in tremor (most pronounced at onset) appear to be co-dependent on activity within the basal ganglia. A later study confirmed and expanded on these initial results, demonstrating that dopamine replacement therapy reduces tremors by inhibiting the cerebellar thalamus in patients with a relative dopamine-responsive tremor (Dirkx et al., 2017). In contrast, patients with dopamine-resistant tremors exhibit increased tremor-related activity in non-dopaminergic regions, particularly the cerebellum (Dirkx et al., 2019).

The elegance of the dimmer-switch model lies in its explanation of the crucial roles of both the basal ganglia and the cerebello-thalamo-cortical circuit, and why interventions targeting either circuit (such as deep brain stimulation) can effectively treat PD tremor. Importantly, it links both loops via the motor cortex, which is thought to relay the tremor signals to the end effector, i.e. the muscles that produce tremor. Readers seeking a more comprehensive exploration of the topic are encouraged to read more detailed reviews summarizing recent findings about the dimmer-switch model, discussing the role of the cerebellum, or proposing an extension, called the finger-dimmer-switch model (Duval et al., 2016; Dirkx and Bologna, 2022; Zhong et al., 2022).

The role of the cortex in Parkinson's disease tremor: One highly relevant question is not resolved so far: What exactly generates the tremor? Apart from the suggestion that the thalamus could be a critical node (Duval et al., 2016), we here aim to emphasize the potential role of the motor cortex. While the dimmer-switch model considers this region as the point of convergence between the basal ganglia and cerebello–thalamo–cortical pathways, novel evidence suggests that it has a more direct role in the tremor oscillating network and its suppression during voluntary movements. For example, single-pulse transcranial magnetic stimulation applied to the motor cortex both during rest tremor and re-emergent tremor can reset the tremor, shifting the subsequent tremor bursts by a small, yet constant amount of time away from the expected onsets (Leodori et al., 2020; Helmich et al., 2021). Furthermore, motor cortical transcranial magnetic stimulation additionally reduces the tremor power. Applying transcranial magnetic stimulation over the cerebellum, moreover, introduces only a transient, unstable shift, exclusively during a re-emergent tremor, and does not affect the tremor power (Helmich et al., 2021). This indicates that the key oscillator is unlikely located within the cerebellum, because its stimulation only affects the tremor transiently, meaning that the original oscillation takes over again. Instead, the motor cortex may play a significant role in regulating the tremor's frequency, potentially through resonance or entrainment mechanisms. This is supported by observations in a MPTP-induced Parkinson's disease model in nonhuman primates, where motor cortical neurons were sharply tuned to match tremor frequencies during repetitive movements at similar frequencies (Rahamim et al., 2023).

Novel evidence regarding the role of the motor cortex was recently presented by Wilken et al. (2024) who recorded local field potentials from the basal ganglia (either the subthalamic nucleus or the internal segment of the globus pallidus) during rest tremor, re-emergent tremor, and the period in between. Their results show that oscillatory activities within the basal ganglia that are functionally linked to tremors sustain their firing frequency even during active tremor suppression induced by movement. However, not all neurons remain active during the pause and re-emergence, and the peaks are slightly higher in frequency with reduced power. These findings suggest that the basal ganglia are not directly involved in tremor attenuation during movement. If the basal ganglia sustain their tremor-related activity in the absence of a tremor, another question is how this activity can suddenly trigger a tremor. One possibility is that PD causes tremor-promoting activities in the basal ganglia, which alone are not yet sufficient to generate tremor. However, this activity could be increasingly amplified either by dynamically entraining neighboring neurons or in response to network activities coming from connected regions to abruptly "spill over" to other regions within the tremor network.

Further emphasizing the cortical contributions to tremors, our group recently demonstrated that tremor frequencies within the cerebellum are driven by the motor cortex, while the same frequencies within the basal ganglia are driven by the supplementary motor area (Ding et al., 2024). Interestingly, both the motor cortex and the cerebellum are increasingly coupled to the periphery during rest tremor in comparison to re-emergent tremor in the presence of levodopa. Although withdrawing levodopa substitution abolishes the difference in central-peripheral coupling between the two tremor conditions, the cortical drive to the cerebellum remains present and is even enhanced in the dopamine-depleted state. In contrast, the basal ganglia and the supplementary motor area present an elevated coupling to the periphery during rest versus re-emergent tremor in the absence of levodopa, indicating that the peripheral coupling of these regions is increased during re-emergence by dopaminergic substitution, which thus differentially modifies the coupling of relevant regions to muscle activity during different tremor conditions. Similarly to the communication patters for the motor cortex and the cerebellum, the cortical drive of the basal ganglia presents both with and without levodopa substitution and is elevated in the dopamine depleted state. Together, these results suggest two cortical regions that could potentially amplify tremor-related oscillations from the basal ganglia and thus render crucial for initiating those abnormal movements.

We additionally found enhanced cross-frequency coupling between the tremor frequency and beta oscillations and reduced cross-frequency coupling between the tremor frequency and gamma oscillations within the tremor network, which was normalized by levodopa substitution. It has previously been shown that elevated beta activity is related to the tremor onset, and that periods of sustained tremor are associated with increased beta power in the premotor cortex (Hirschmann

et al., 2019; Lauro et al., 2021). Beta oscillations are thought to be indicative of a stable motor system, related to maintaining the "status quo," and it has thus been hypothesized that tremor occurs specifically during stable states (Swinnen et al., 2023). In this regard, an enhanced coupling between beta power and the tremor frequency could reflect defective interactions between these oscillations, potentially occurring during the tremor onset and being maintained thereafter. One question to consider is whether the disruption of beta oscillations by deep brain stimulation causally relates to alleviation of tremor activity.

Taken together, novel evidence related to tremors highlights the importance of the motor cortex within the tremor network (**Figure 1**). It is a critical region that drives tremor frequencies within the cerebellum. Furthermore, applying transcranial magnetic stimulation can reset the tremor, showing that the underlying neural oscillation can be modulated from outside the basal ganglia. Thus, modulating motor cortical oscillations via transcranial magnetic stimulation could provide an entrance to the tremor network, independent of whether the tremor is originating from pathological oscillations within the basal ganglia or the motor cortex. Further investigating cortical contributions during tremor onset and sustained tremor could improve our understanding of tremor generation, extending the dimmer-switch model. A better comprehension of the role of the motor cortex and the supplementary motor area for the generation and suppression of tremor is crucial for both pathophysiological insights and therapeutic advancements. Currently, the most effective treatments for PD tremors include deep brain stimulation of the basal ganglia and thalamus, as well as focused ultrasound-mediated lesioning. However, these methods are highly invasive, costly, and lack reversibility. Therefore, elucidating the relationship between cortical regions and tremors could pave the way for developing non-invasive neuromodulation techniques aimed at mitigating parkinsonian tremors.

This work was supported by the German Research Foundation (SFB-TR 295) (to MM).

Manuel Bange*, Hao Ding, Muthuraman Muthuraman
Informatics for Medical Technology, Institute of Computer Science, University Augsburg, Augsburg, Germany (Bange M, Muthuraman M)
Department of Neurology, Neural Engineering with Signal Analytics and Artificial Intelligence (NESA-AI), University Clinic Würzburg, Würzburg, Germany (Ding H, Muthuraman M)
***Correspondence to:** Dr. Manuel Bange, manuel.bange@uni-a.de.
https://orcid.org/0000-0002-5247-8810 (Manuel Bange)
Date of submission: July 30, 2024
Date of decision: September 26, 2024
Date of acceptance: October 17, 2024
Date of web publication: December 7, 2024

https://doi.org/10.4103/NRR.NRR-D-24-00853
How to cite this article: *Bange M, Ding H, Muthuraman M (2025) Cerebral cortex contributions to Parkinson's disease tremor: what exactly generates the tremor? Neural Regen Res 20(12):3535-3536.*

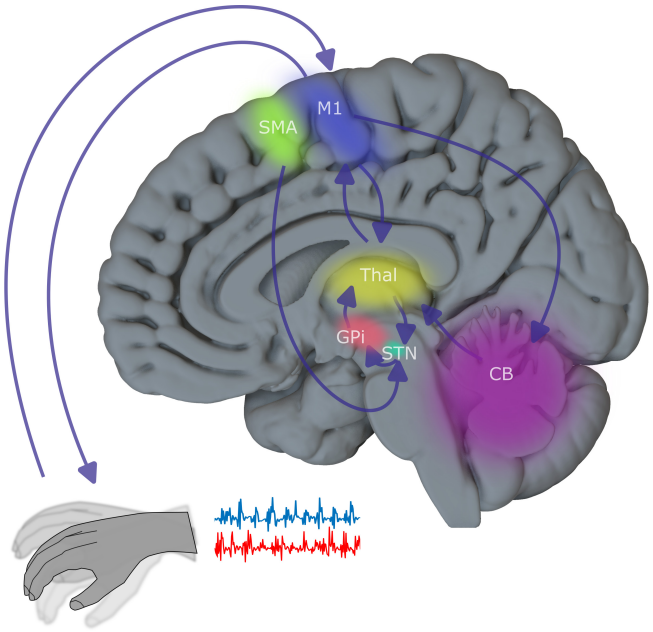

Figure 1 | **The tremor network.**
According to the dimmer-switch model, pathological nigro-pallidal activity is relayed via the internal segment of the globus pallidus (GPi) towards the thalamus (Thal). This activity is conveyed to the motor cortex (M1) to trigger the tremor (indicated by the blue and red time series representing alternating bursts of extensor and flexor muscle activity). M1 drives cerebellar (CB) tremor frequencies, which could be fed back via the thalamus. Recent evidence suggests that M1 has a more direct role in the tremor oscillating network because (a) stimulating M1 with transcranial magnetic stimulation shifts the subsequent tremor bursts by a consistent time interval (Leodori et al., 2020; Helmich et al., 2021), (b) tremor oscillations remain active in the basal ganglia while tremor is suppressed (Wilken et al., 2024), and (c) M1 drives cerebellar tremor activity (Ding et al., 2024). Interestingly, the supplementary motor area has been shown to drive tremor activities in the basal ganglia (Ding et al., 2024). Brain surface was generated in Surf Ice (version 6-October-2021, https://www.nitrc.org/projects/surfice) and LeadDBS (version 3.1, https://www.lead-dbs.org/, Horn and Kühn (2015)) using the MNI152NLin2009bAsym standard brain. The elements were combined with inkscape (1.3.2 (091e20e, 2023-11-25, custom)). CB: Cerebellum; GPi: internal segment of the globus pallidus; M1: motor cortex; SMA: supplementary motor area; STN: subthalamic nucleus; Thal: thalamus.

References

Ding H, Nasseroleslami B, Mirzac D, Isaias IU, Volkmann J, Deuschl G, Groppa S, Muthuraman M (2024) Re-emergent tremor in Parkinson's disease: evidence of pathologic β and prokinetic γ activity. Mov Disord 39:778-787.
Dirkx MF, den Ouden HE, Aarts E, Timmer MH, Bloem BR, Toni I, Helmich RC (2017) Dopamine controls Parkinson's tremor by inhibiting the cerebellar thalamus. Brain 140:721-734.
Dirkx MF, Zach H, van Nuland A, Bloem BR, Toni I, Helmich RC (2019) Cerebral differences between dopamine-resistant and dopamine-responsive Parkinson's tremor. Brain 142:3144-3157.
Dirkx MF, Bologna M (2022) The pathophysiology of Parkinson's disease tremor. J Neurol Sci 435:120196.
Duval C, Daneault JF, Hutchison WD, Sadikot AF (2016) A brain network model explaining tremor in Parkinson's disease. Neurobiol Dis 85:49-59.
Helmich RC, Hallett M, Deuschl G, Toni I, Bloem BR (2012) Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? Brain 135:3206-3226.
Helmich RC, Van den Berg KRE, Panyakaew P, Cho HJ, Osterholt T, McGurrin P, Shamim EA, Popa T, Haubenberger D, Hallett M (2021) Cerebello-cortical control of tremor rhythm and amplitude in Parkinson's disease. Mov Disord 36:1727-1729.
Hirschmann J, Abbasi O, Storzer L, Butz M, Hartmann CJ, Wojtecki L, Schnitzler A (2019) Longitudinal recordings reveal transient increase of alpha/low-beta power in the subthalamic nucleus associated with the onset of parkinsonian rest tremor. Front Neurol 10:145.
Horn A, Kühn AA (2015) Lead-DBS: a toolbox for deep brain stimulation electrode localizations and visualizations. NeuroImage 107:127-135.
Jankovic J, Schwartz KS, Ondo W (1999) Re-emergent tremor of Parkinson's disease. J Neurol Neurosurg Psychiatry 67:646-650.
Lauro PM, Lee S, Akbar U, Asaad WF (2021) Subthalamic-cortical network reorganization during Parkinson's tremor. J Neurosci 41:9844-9858.
Leodori G, Belvisi D, De Bartolo MI, Fabbrini A, Costanzo M, Vial F, Conte A, Hallett M, Berardelli A (2020) Re-emergent tremor in Parkinson's disease: the role of the motor cortex. Mov Disord 35:1002-1011.
Rahamim N, Slovik M, Mevorach T, Linkovski O, Bergman H, Rosin B, Eitan R (2023) Tuned to tremor: increased sensitivity of cortico-basal ganglia neurons to tremor frequency in the MPTP nonhuman primate model of Parkinson's disease. J Neurosci 43:7712.
Swinnen B, de Bie RMA, Hallett M, Helmich RC, Buijink AWG (2023) Reconstructing re-emergent tremor. Mov Disord Clin Pract 10:1293-1296.
Wilken M, Andres DS, Bianchi G, Hallett M, Merello M (2024) Persistence of basal ganglia oscillatory activity during tremor attenuation by movement in Parkinson's disease patients. Mov Disord 39:768-777.
Zhong Y, Liu H, Liu G, Zhao L, Dai C, Liang Y, Du J, Zhou X, Mo L, Tan C, Tan X, Deng F, Liu X, Chen L (2022) A review on pathology, mechanism, and therapy for cerebellum and tremor in Parkinson's disease. NPJ Parkinsons Dis 8:82.

C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y