

The Cerebral Basis of Parkinsonian Tremor: A Network Perspective

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ABSTRACT: Tremor in Parkinson's disease is a poorly understood sign. Although it is one of the clinical hallmarks of the disease, its pathophysiology remains unclear. It is clear that tremor involves different neural mechanisms than bradykinesia and rigidity, the other core motor signs of Parkinson's disease. In particular, the role of dopamine in tremor has been heavily debated given clinical observations that tremor has a variable response to dopaminergic medication. From a neuroscience perspective, tremor is also a special sign; unlike other motor signs, it has a clear electrophysiological signature (frequency, phase, and power). These unique features of tremor, and newly available neuroimaging methods, have sparked investigations into the pathophysiology of tremor. In this review, evidence will be discussed for the idea that parkinsonian tremor results from increased interactions between the basal ganglia and the cerebello-thalamo-cortical circuit, driven by altered dopaminergic projections to nodes within

both circuits, and modulated by context-dependent factors, such as psychological stress. Models that incorporate all of these features may help our understanding of the pathophysiology of tremor and interindividual differences between patients. One example that will be discussed in this article is the "dimmer-switch" model. According to this model, cerebral activity related to parkinsonian tremor first arises in the basal ganglia and is then propagated to the cerebello-thalamo-cortical circuit, where the tremor rhythm is maintained and amplified. In the future, detailed knowledge about the architecture of the tremor circuitry in individual patients ("tremor fingerprints") may provide new, mechanism-based treatments for this debilitating motor sign. © 2017 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; tremor; basal ganglia; cerebellum; functional connectivity

Tremor is one of the cardinal motor signs of Parkinson's disease (PD). The classical parkinsonian tremor occurs at rest at a frequency of 4 to 6 Hz and mainly involves the distal limbs. It is often visible as a pill-rolling movement. However, the majority of patients also have a postural tremor.¹ In many cases, this is the resting tremor that reemerges after stable posturing.

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Funding agencies: This work was supported by Dutch Brain Foundation Grant F2013(1)-15 and by Netherlands Organization for Scientific Research VENI Grant 91617077.

Relevant conflicts of interests/financial disclosures: Nothing to report.

Received: 1 May 2017; Revised: 6 September 2017; Accepted: 17 September 2017

Published online 9 November 2017 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27224

This has led to the idea that the classical parkinsonian tremor is actually a "tremor of stability," which emerges when the motor system has reached a status quo.^{2,3} A minority of PD patients have a postural tremor that has a significantly higher frequency (>1.5 Hz difference) than resting tremor and starts immediately after posturing. This type of "pure postural tremor" is thought to have a different pathophysiology than resting tremor (and reemergent tremor), but empirical evidence for this idea is lacking.⁴ Most studies have focused on the classical parkinsonian resting tremor, which is also the topic of this paper.

Although tremor was observed by James Parkinson 200 years ago and is one of the most prominent and visible signs of PD, its pathophysiology remains poorly understood. Several reasons indicate that tremor has a different pathophysiology than bradykinesia and rigidity. For instance, tremor does not increase at the same pace as other motor signs, and tremor severity does not correlate with the severity of bradykinesia and

rigidity.^{5,6} In fact, tremor is an early sign of PD that sometimes diminishes as the disease progresses,⁷ although medication effects may play an additional role. Some patients have predominant tremor on the side contralateral to bradykinesia and rigidity, a phenomenon called “wrong-sided tremor.”⁸ Also, unlike other motor signs, tremor severity does not correlate with the degree of striatal dopamine depletion, which is the pathophysiological hallmark of PD.⁹ Indeed, tremor does not respond as well or as reliably to dopaminergic medication as bradykinesia and rigidity.¹⁰ Finally, patients with a tremor-dominant subtype often follow a more benign disease course than patients without tremor.³

In the next paragraphs, the role of the basal ganglia and the cerebello-thalamo-cortical circuit in tremor will be discussed. Furthermore, I will discuss the role of dopamine in the pathophysiology of tremor and context-dependent factors such as psychological stress. Finally, new network approaches for modelling tremor, which may have future potential for providing pathophysiological tremor fingerprints in individual patients, will be outlined.

The Dimmer-Switch Model of Parkinsonian Tremor

Previous findings suggest that parkinsonian tremor involves both the basal ganglia and the cerebello-thalamo-cortical circuit. The evidence comes from several sources. Magneto-encephalography (MEG) studies have shown tremor-related oscillatory activity in the cerebellum (and a diencephalic area that is possibly the thalamus)¹¹; deep brain recordings have found tremor oscillations in the cerebellum-recipient ventral intermediate nucleus (VIM) of the thalamus¹² and in the basal ganglia (GPi and STN^{13,14}); PET studies have found tremor-related hypermetabolism of the cerebello-thalamo-cortical circuit and the putamen,¹⁵ and clinical studies have shown that stereotactic interventions in both the basal ganglia (GPi and STN) and the cerebello-thalamo-cortical circuit (VIM) are highly effective in reducing tremor.¹⁶⁻¹⁸

The localization of tremor cells within the thalamus and the optimal site for stereotactic interventions within the thalamus provide some of the first evidence that the cerebellar circuit is involved in parkinsonian tremor. Regarding the thalamic nomenclature, it is important to keep in mind that the neurosurgical and neuro-anatomical ways of labeling thalamic nuclei are slightly different. The VIM (according to Hassler’s nomenclature) is localized during surgery based on the presence of tremor-synchronous bursts and kinesthetic cells anterior to cutaneous receptive cells.¹⁹ In contrast, the ventrolateral thalamus (VL), according to Jones’ nomenclature, is divided into anterior (VLa)

and posterior parts (VLp) based on its anatomical connectivity with the GPi (VLa) or the cerebellum (VLp).²⁰ It is thought that Hassler’s VIM corresponds to (part of) Jones’ VLp, more specifically, the ventral portion of the VLp, where most tremor cells are located.²¹ Thus, it has been known for quite some time that stereotactic interventions in the VIM reduce tremor by deafferenting the thalamus from cerebellar input (ie, by lesioning the dentato-rubro-thalamic tract).¹² This has been confirmed more recently using a combination of deep brain stimulation (DBS) and structural imaging.^{22,23} Here, I will use the terms VIM and VLp interchangeably, depending on the type of study (neurosurgical or neuro-anatomical) that is discussed.

A few years ago we performed a functional magnetic resonance imaging (fMRI) study to parse the role of the basal ganglia and the cerebello-thalamo-cortical circuit in parkinsonian tremor.²⁴ Unlike previous studies, we tested for cerebral activity that was associated with slow fluctuations in tremor power (Fig. 1). Specifically, during MRI scanning we measured tremulous activity in wrist extensor and flexor muscles with electromyography. Rather than testing for neuromuscular correlations at (double) tremor frequency, as is typically done in electrophysiological studies (Fig. 1C-D),¹¹ we focused on brain activity that was correlated with slower changes in tremor power (ie, the envelope of the oscillatory activity at tremor frequency; Fig. 1B). This was done because fMRI does not have the millisecond temporal resolution to test for cycle-by-cycle oscillatory activity at tremor frequency. On the other hand, fMRI has a temporal resolution in the range of seconds, which matches spontaneous changes in amplitude that are characteristic of parkinsonian tremor. Using this approach, we found that cerebral activity in the cerebello-thalamo-cortical circuit was correlated with tremor power (Fig. 1A). This finding is robust; we have recently replicated this result in an independent cohort of tremor-dominant PD patients.²⁵ Furthermore, unlike electrophysiological approaches such as electroencephalography (EEG) or MEG, fMRI has a high spatial resolution. This allowed us to be very specific about the location of tremor-related activity. In the thalamus, tremor-related activity was specifically localized to the VLp, which receives cerebellar afferents, and not present in the neighboring VLa, which receives pallidal afferents.²⁶ In the cerebellum, tremor-related cerebral activity was seen in the hand area of lobules V and VI, that is, the sensorimotor portion of the cerebellum. In the motor cortex, tremor-related activity spanned a larger area, involving both the primary motor cortex (Brodmann area [BA] 4, 60% of the activity cluster) and the premotor cortex (BA 6, 26% of the activity cluster).²⁴ Within the cortex, there was also tremor-related activity in the

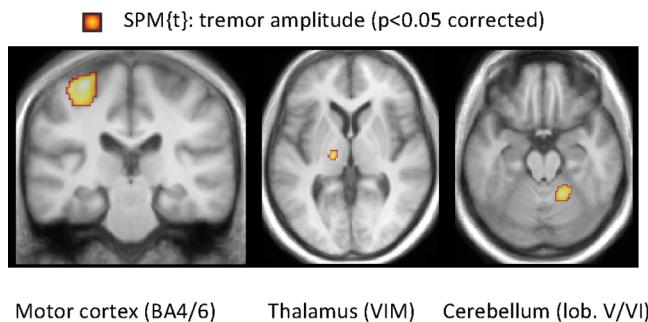
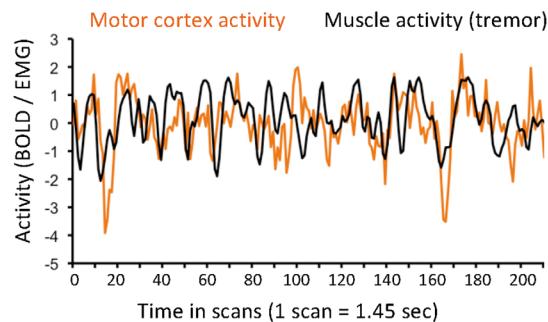
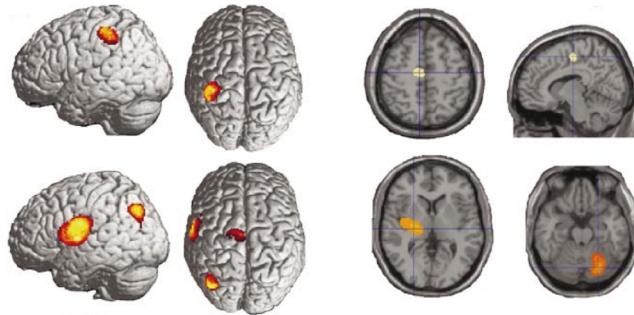
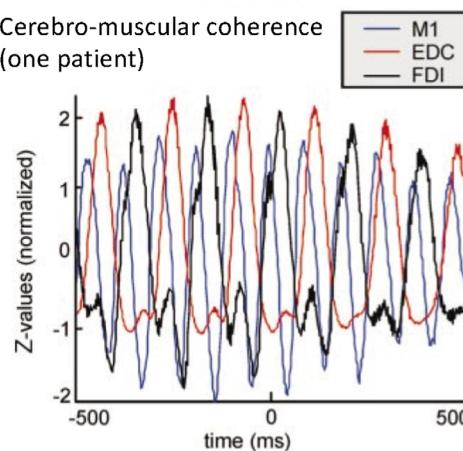
A Tremor amplitude-related activity (group effect)**B** Cerebro-muscular correlation (one patient)**C** Cerebro-muscular coherence (group effect)**D** Cerebro-muscular coherence (one patient)

FIG. 1. The role of the cerebello-thalamo-cortical circuit in parkinsonian tremor. This figure shows 2 different ways of looking at tremor. (A and B) fMRI was used to test for cerebral activity correlated with slow fluctuations in muscle activity at tremor frequency (ie, tremor power). (Taken from ref. ²⁴ with permission.) Temporal resolution is in the order of seconds. In panels C and D, MEG was used to test for cerebral oscillatory activity coherent with muscular activity at double tremor frequency. Here the temporal resolution is in the order of milliseconds. Both methods show involvement of the cerebello-thalamo-cortical circuit in parkinsonian tremor. Taken from ref. ¹¹ with permission. SPM: Statistical Parametric Mapping; M1: primary motor cortex; EDC: Extensor Digitorum Communis muscle; FDI: First Dorsal Interosseous muscle; BOLD: Blood Oxygen Level Dependent signal. [Color figure can be viewed at wileyonlinelibrary.com]

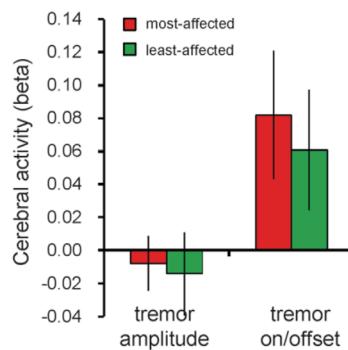
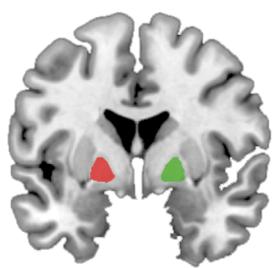
somatosensory cortex (particularly BA 3a and 3b, not BA 2), but these effects were much smaller.^{24,27}

There was no tremor amplitude-related activity in the basal ganglia (Fig. 2A). This finding left us with a paradox: the basal ganglia appear to be involved in parkinsonian tremor, but activity in the basal ganglia was not associated with tremor amplitude. We then focused on the variability in tremor power and asked which neural mechanisms are responsible for the spontaneous increases (and decreases) in tremor power that occur within the time span of seconds. Brain regions that drive this variability should have transiently increased activity at the onset of tremor episodes. To empirically test this, we devised a separate regressor modeling this pattern of activity: the first temporal derivative of tremor amplitude, which peaks whenever tremor amplitude increases. We found that cerebral activity in the basal ganglia motor loop (ie, putamen and globus pallidus) was correlated with this regressor (Fig. 2A).²⁴ Taken together, this study showed that the basal ganglia are activated transiently at the onset of tremor episodes, whereas activity in the cerebello-

thalamo-cortical circuit is linked tightly to tremor power. This formed the basis for the “dimmer-switch” hypothesis of parkinsonian tremor.³

According to this hypothesis, the basal ganglia operate analogous to a light switch (activating tremor), and the cerebello-thalamo-cortical circuit operates analogous to a light dimmer (modulating tremor amplitude). An appealing feature of this model is that it provides a possible solution to the basal ganglia paradox of parkinsonian tremor. That is, although the basal ganglia themselves do not drive the tremor on a cycle-by-cycle basis, they are critical for tremor because they push the cerebello-thalamo-cortical circuit into driving it. As such, interventions in the basal ganglia will remove the tremor trigger, whereas interventions in the cerebello-thalamo-cortical circuit will remove the tremor maintainer. The dimmer-switch hypothesis fits with electrophysiological recordings, which show that pallidal neurons are only transiently and inconsistently coherent with tremor,^{14,28} whereas the neurons in the VIM are highly synchronous with tremor.²⁹ It also fits with the low-pass filter properties

A Tremor onset-related activity in the GPi



B Effective connectivity

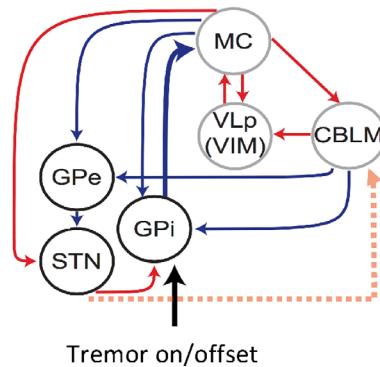


FIG. 2. The role of the basal ganglia in parkinsonian tremor. (A) Cerebral activity in the GPi, separately for the most-affected (red columns) and least-affected hemispheres (green columns), and separately for tremor amplitude-related activity and for changes in tremor amplitude-related activity (on/off-set; x-axis). The data show evidence for on/off-set related activity in the GPi. (Taken from ref. ²⁴ with permission.) (B) The winning model from a dynamic causal modeling analysis that compared (i) different patterns of connectivity between the basal ganglia and the cerebello-thalamo-cortical circuit and (ii) different nodes in which tremulous activity first emerged. In the winning model, tremulous activity first emerged in the GPI, and this node was effectively connected to the cerebello-thalamo-cortical circuit via the pallido-thalamo-cortical pathway (bold blue line) rather than the STN-cerebellum pathway (dotted red line). Blue lines indicate inhibitory connections; red lines indicate excitatory connections. Taken from ref. ²⁵ with permission. VLa, ventrolateral anterior thalamus; VLp, ventrolateral posterior thalamus; CBLM, cerebellum. MC, motor cortex; VIM, ventral intermediate nucleus. [Color figure can be viewed at [wileyonlinelibrary.com](#)]

of the pallido-motor system identified in nonhuman primates.³⁰ That is, in the parkinsonian state, motor neurons responded to pallidal stimulation at low frequencies (<5 Hz), but not at higher frequencies in the tremor range. These findings suggest that the globus pallidus does not drive tremor on a cycle-by-cycle basis (tremor maintenance), but it may modulate the motor cortex on a slower time scale (ie, consistent with the temporal properties of tremor triggers).

Further studies have shed more light on the individual roles of the cerebellum, thalamus, and motor cortex in modulating tremor. Specifically, stimulation of the thalamus (with DBS electrodes) and cerebellum (with transcranial alternating current stimulation) at near-tremor frequency entrained the ongoing tremor (meaning that the tremor adopted the phase of the stimulation), but it did not change its amplitude.^{31,32} In contrast, transcranial alternating current stimulation over the primary motor cortex influenced both the tremor phase and its amplitude. This may suggest that, within the cerebello-thalamo-cortical circuit, the motor cortex has a specific role in determining tremor amplitude (ie, the dimmer), whereas the thalamus and cerebellum may be important for maintaining the tremor rhythm.³¹

The Role of the STN in Parkinsonian Tremor

The role of the STN in the integrated basal ganglia and cerebello-thalamo-cortical circuit is not entirely clear from the dimmer-switch model. This is a result of the fact that the fMRI data on which this model

was based did not allow an accurate detection of tremor-related activity in small nuclei such as the STN. Electrophysiological evidence from deep brain recordings indicates the role of the STN in tremor. There is a clear synchronization of STN neurons at (double) tremor frequency,¹³ and there are specific patterns of very high-frequency oscillatory activity in the STN during tremor episodes.³³ Furthermore, there is increased coherence between oscillatory activity (at tremor frequency) in the STN and primary motor cortex activity during tremor episodes.³⁴ Finally, STN-DBS at near-tremor frequency is able to entrain the ongoing tremor in a similar way as VIM-DBS, which suggests that the STN has a role in maintaining the tremor rhythm.³¹

Neuroanatomical evidence shows that the STN has a unique, “spider in the web” position within the tremor circuitry. It receives direct projections from the primary motor cortex (hyperdirect pathway³⁵) and sends output to the cerebellar cortex through the pons.³⁶ In primates, the STN also projects directly to the ventrolateral thalamus, although it is unclear whether this concerns cerebellum-recipient thalamic nuclei.³⁷ Clinical evidence shows that interfering with abnormal STN activity, either with DBS^{16,38} or with stereotactic lesioning,³⁹ reduces tremor. Given the anatomical position of the STN, these effects may be mediated through multiple pathways within the tremor circuitry. That is, STN-DBS may interfere with local pacemaker activity,⁴⁰ it may have orthodromic effects on the GPi (or thalamus),^{37,41} antidromic effects on the primary motor cortex (hyperdirect pathway),⁴¹ remote effects on neighboring fiber bundles (ie, the dentato-rubro-thalamic tract²²), or all of these

effects. Taken together, the STN may be involved in triggering tremor (through its connectivity with the GPi) in maintaining the tremor rhythm (through its connectivity with the primary motor cortex and the cerebellum) or both.

Limitations of the Dimmer-Switch Model

It is important to keep in mind that this model, similar to any model, has its limitations. For example, the concurrent EMG-fMRI approach can identify musculo-cerebral correlations, but it cannot make inferences about the causal nature of these correlations. Furthermore, the temporal perspective of this model is in the order of seconds. Accordingly, “tremor onset” concerns a change in activity that builds up over seconds rather than being a discrete moment in time that can easily be distinguished using electrophysiological recordings.³⁴ It is also possible that the brain regions that modulate tremor amplitude (as detected using fMRI) are not the same brain regions that drive tremor on a cycle-by-cycle basis (as detected using EEG or MEG). For example, EEG and MEG studies have shown the involvement of parietal and medial frontal areas in tremor, whereas these areas are not found in fMRI studies (Fig. 1).^{11,24,25} Combined EEG-fMRI studies may resolve this issue.

A second limitation of the dimmer-switch model is that not all brain regions are included. This is a result of the fact that the fMRI data on which the model was based did not allow accurate detection of brain activity in small nuclei (such as the STN, see earlier). Other regions, such as the somatosensory cortex, were omitted from the model because tremor-related activity was insignificant using conservative group statistics. Clinical observations suggest that parkinsonian tremor can sometimes be influenced by somatosensory afferents, such as minor adaptations of limb posture. This has been substantiated by a study in which the authors found that parkinsonian tremor could be reset by median nerve stimulation.⁴² On the other hand, other studies have shown that mechanical perturbations of the tremulous limb were not able to reset the tremor in most patients (in contrast to essential tremor [ET]),⁴³ or only under particular conditions.⁴⁴ Furthermore, deafferentation of the tremulous limb (with novocaine injections) left parkinsonian tremor unaltered in amplitude and frequency.⁴⁵ Taken together, most of the evidence suggests that somatosensory afferents have only a minor role in parkinsonian tremor, although it may stabilize or maintain the tremor rhythm within the cerebello-thalamo-cortical circuit.⁴⁶

Finally, although it is attractive to interpret these findings in terms of a “pushing” role of the basal ganglia

versus a “following” role of the cerebello-thalamo-cortical circuit, the underlying causal interaction implied is not evidenced from the data. As outlined next, we partly countered these limitations by performing dedicated network analyses on the fMRI data.

Increased Between-Circuit Coupling in Parkinsonian Tremor

The dimmer-switch model implies that patients with tremor-dominant PD have increased functional interactions between the basal ganglia and the cerebello-thalamo-cortical circuit and that this interaction involves a driving role of the basal ganglia. We tested this hypothesis in 2 different ways. First, we compared resting state functional connectivity between the pallidum (ie, the output nucleus of the basal ganglia motor loop) and the regions of the cerebello-thalamo-cortical circuit between tremor-dominant and nontremor PD patients. The findings showed increased pallido-cortical coupling in tremor-dominant PD patients when compared with nontremor PD patients and healthy controls, specifically in the hemisphere contralateral to the tremor.²⁴ Others have found increased functional connectivity between the STN and the cerebellum,⁴⁷ between the STN and motor cortex,⁴⁸ and between the cerebellum-recipient nucleus of the thalamus (VIM) and the basal ganglia in tremor-dominant patients.⁴⁹ These findings indicate that tremor is associated with increased functional connectivity between basal ganglia and the cerebello-thalamo-cortical circuit.

Second, we used a network approach to test for different possible models underlying the increased interactions between basal ganglia and the cerebello-thalamo-cortical circuit in parkinsonian tremor.²⁵ To this end, we used dynamic causal modeling (DCM). DCM is a Bayesian method of inference where one defines models based on predefined hypotheses to assess the causal influence that one neuronal system exerts over another.⁵⁰ These models of interacting brain regions are built by specifying connectivity parameters between a set of regions of interest, including (1) fixed connections between nodes, (2) modulation of these fixed connections by exogenous inputs, and (3) exogenous inputs that directly cause perturbations of included nodes. The output of this analysis is typically a model comparison where one statistically compares the probability of each model given empirical data (in this case, fMRI Bold Oxygen Level Dependent (BOLD) signal time series).

We used this feature of DCM to test for interactions between the basal ganglia and the cerebello-thalamo-cortical circuit in 2 independent cohorts of tremor-dominant PD patients.²⁵ The literature provides support for the following 2 separate pathways that may mediate these interactions⁵¹: a transcortical pathway

(from GPi via the VL to the motor cortex, which projects to the cerebellum through the pons)⁵² and a subcortical pathway (from the STN via pontine nuclei to the cerebellar cortex).³⁶ When we directly compared models that contained either of the 2 pathways, we found clear evidence in favor of the transcortical pathway (Fig. 2B). We also tested where in the distributed network tremor first emerges to determine which region drives the other regions. To this end, we modeled “tremor on/offset,” as derived from EMG recordings (ie, the regressor describing changes in tremor power), as an input into several different nodes of the network. In DCM, this input is regarded as a perturbation of ongoing cerebral activity in the network, which can be conceptualized in our study as a state-change from stochastic activity to tremulous activity. In this way, we compared models where tremulous activity first emerges in the basal ganglia with models where activity first emerges in a node of the cerebello-thalamo-cortical circuit. The findings clearly favored a model where tremulous activity first starts in the basal ganglia (GPi) and then spreads to the cerebello-thalamo-cortical circuit (through pallido-thalamo-cortical connectivity; Fig. 2B).²⁵

Taken together, these findings support the dimmer-switch hypothesis of parkinsonian tremor. It is unclear how the cerebello-thalamo-cortical circuit, which is not primarily affected by the disease, is driven into tremor by the basal ganglia. Postmortem studies in PD have shown that there is less severe Lewy body pathology in the cerebellum recipient nuclei of the thalamus (including the VLp) than in the basal ganglia recipient nuclei of the thalamus, and there is no evidence for Lewy body pathology in the cerebellum itself.⁵³ Clinically, PD patients do not have ataxia, even if they have severe tremor. This is different from ET, which is also linked to the cerebello-thalamo-cortical circuit⁵⁴; some ET patients experience a mild form of ataxia, which fits with postmortem studies that show cerebellar abnormalities.⁵⁵ Accordingly, neuroimaging studies have pointed to the cerebellum as the driving force within the cerebello-thalamo-cortical circuit of ET patients.^{56,57} Thus, in ET the primary pathology likely resides inside the cerebello-thalamo-cortical circuit, but in PD external factors (ie, the basal ganglia) play an additional role. I next discuss how projections of several neurotransmitter systems (particularly dopamine), both to the basal ganglia and to the cerebello-thalamo-cortical circuit, may contribute to parkinsonian tremor.

Is Parkinsonian Tremor Related to Dopamine Depletion?

The dopaminergic basis of parkinsonian tremor is very unclear. Clinicians commonly find that resting tremor, unlike bradykinesia, has a rather unpredictable response to dopaminergic medication. *Unpredictable* is the key

word here because on average tremor is not less responsive to dopaminergic medication than, for example, bradykinesia. For instance, we recently showed in 43 PD patients that tremor improved on average by $\pm 49\%$ after 200/50 mg levodopa-benserazide, whereas bradykinesia and rigidity (combined) improved by 40%.⁵⁸ Thus, it appears that there are patients where tremor has an excellent dopamine response and patients where tremor has a very poor dopamine response. This suggests that there may be 2 distinct tremor phenotypes (dopamine-responsive and dopamine-resistant tremor), but empirical evidence for this idea is lacking. Another possibility is that resting tremor is less sensitive to lower doses of levodopa than other motor signs.¹⁰ This has never been properly tested. To do so, one would have to calculate a dose-response function for different PD signs, which is an interesting topic for future research. It should be kept in mind that, despite its unpredictable nature, dopamine replacement therapy remains the best available pharmacological treatment for resting tremor. This suggests that dopamine depletion at least plays a partial role in the pathophysiology of parkinsonian tremor.

Postmortem studies have shown that tremor-dominant PD patients have less severe degeneration of dopaminergic cells in the substantia nigra pars compacta than nontremor PD patients.⁵⁹ This fits with nuclear imaging studies that show higher dopamine transporter density in the striatum of tremor-dominant patients.^{24,60} It also fits with clinical studies that indicate that tremor-dominant PD patients have a milder disease course.^{3,61} One postmortem study has reported increased dopaminergic cell death in the retrorubral area of the midbrain of tremor-dominant patients when compared with nontremor patients.⁶² This has led to the idea that tremor may not be related to dopamine depletion per se but, rather, to degeneration of specific dopaminergic projections to specific nuclei. The physiological role of the retrorubral area is not well known. Animal studies have shown that this area projects to several subcortical nuclei, including the striatum, globus pallidus, STN, and thalamus.⁶³⁻⁶⁵ If dopaminergic denervation of nonstriatal nuclei is related to tremor, then this would solve the dopamine paradox of parkinsonian tremor, that is, the finding that tremor (a core sign of PD) is not related to nigrostriatal dopamine depletion (the pathological hallmark of PD).⁹ As outlined later, there is some evidence that dopamine depletion in nuclei other than the striatum (ie, the pallidum and VLp) may play a role in parkinsonian tremor.^{24,26} Nevertheless, the empirical evidence that degeneration of the retrorubral area is related to parkinsonian tremor is rather thin and mainly based on a single postmortem study. This finding has yet to be replicated *in vivo*, for example, using dedicated structural MRI.

Findings from nuclear imaging studies have raised the possibility that parkinsonian tremor may have a

serotonergic basis. Specifically, a series of PET studies has shown that serotonergic depletion in the raphe is associated with parkinsonian resting tremor,⁶⁶ action tremor,⁶⁷ or both combined.⁶⁸ To my knowledge, there is no convincing empirical evidence that shows the efficacy of serotonergic medication for treating resting tremor. On the contrary, in parkinsonian rodents, serotonin reuptake inhibitors worsen tremor by further depleting dopamine.⁶⁹ Furthermore, postmortem studies have not found different patterns or degrees of serotonergic cell death between tremor-dominant and nontremor PD patients.⁵⁹ This casts some doubt on the idea that resting tremor is related to the serotonergic system.

How Dopamine Controls Tremor in PD

We have recently tested how dopamine influences the cerebral tremor circuit in PD.²⁶ To this end, we used the same methods as outlined previously (combined EMG and fMRI recordings) and tested patients both ON and OFF dopaminergic medication. When we contrasted these 2 sessions, we found that dopamine reduced tremor amplitude-related activity in the thalamus (VLp) and tremor onset-related activity in the pallidum (Fig. 3A-B). The finding in the pallidum fits with a previous study, where we showed that nigro-pallidal dopamine depletion (quantified using dopamine transporter imaging, dopamine transporter single-photon emission computed tomography (DAT SPECT)) was correlated with clinical tremor severity.²⁴ These findings raised the question as to whether the effect in the VLp was a downstream effect of dopamine acting on the pallidum (thereby reducing, indirectly, tremor-related activity in the VLp), or whether there was a direct effect of dopamine on the VLp. A model comparison with DCM allowed us to distinguish between these 2 options. Specifically, we compared a model where dopamine acted on the pallidum with a model where dopamine acted directly on the VLp. The latter model won convincingly, suggesting that the VLp itself is sensitive to dopamine (Fig. 3C). Importantly, the effects of dopamine onto the VLp explained a relevant clinical parameter where patients with stronger dopamine-induced thalamic inhibition showed a stronger clinical response to dopamine (Fig. 3D). This effect was specific to tremor and absent for the other 2 cardinal motor signs, bradykinesia and rigidity.²⁶

This finding is at first sight rather surprising because the VLp is a cerebellum-recipient nucleus of the thalamus, and the cerebello-thalamo-cortical circuit is not traditionally associated with dopamine. On the other hand, there is evidence from postmortem studies, both in primates and in humans, that the thalamus is a key target for dopaminergic projections, including the

VLP.^{70,71} Interestingly, a primate study showed that the ventrolateral thalamus receives considerable dopaminergic innervation from the retrorubral area, in fact more than from the substantia nigra pars compacta.⁶⁵ This suggests that the degeneration of dopaminergic neurons in the retrorubral area in tremor-dominant PD patients may lead to dopamine depletion in the pallidum and VLp, thereby contributing to abnormal activity and connectivity of these regions and ultimately resulting in resting tremor. The idea that dopaminergic denervation of thalamic nuclei has a role in the pathophysiology of PD, particularly tremor, requires further validation, for example, in postmortem studies. The finding that dopamine influenced both the pallidum and the VLp may explain why levodopa reduces both the occurrence of tremor (possibly by acting on the pallidum) and the amplitude of the tremor (possibly by acting on the VLp).^{58,72} It may also explain why dopaminergic dysfunction of the pallidum per se is not sufficient for tremor development. For instance, a postmortem study showed increased pallidal dopamine content in tremor-dominant versus akinetic-rigid PD patients,⁷³ and a task-based fMRI study showed reported increased motor-related pallidal activity in tremor-dominant versus nontremor PD patients.⁷⁴

One question is what the physiological role is of dopaminergic projections to the cerebellar thalamus in the healthy motor system. Although there is a large body of research detailing the role of the nigrostriatal dopamine system in motor control,⁷⁵ the role of dopaminergic projections to the cerebello-thalamo-cortical system is less clear. The role of the cerebellum in motor control has been related to forward modeling, that is, predicting how a selected action will unfold in real time.⁷⁶ In contrast, the basal ganglia are thought to be important for selecting the most optimal action given the current environmental and internal context.⁷⁶ For optimal motor control, the activity in both circuits must be coordinated. This may be implemented by the anatomical pathways linking both circuits, that is, through the motor cortex and through the pons.^{36,77} Another way to functionally link both circuits could be through the dopamine system. In this way, dopaminergic projections to the cerebello-thalamo-cortical circuit may enable gating: the selective learning of beneficial forward models.⁷⁸ This speculation would explain why dopaminergic projections may bind the basal ganglia and cerebello-thalamo-cortical circuit together, but it does not explain why tremor oscillations emerge within this circuit in PD. Research in healthy participants has shown that the cerebello-thalamo-cortical circuit has a natural tendency to generate oscillatory rhythms,⁷⁹ which possibly serves to represent temporal aspects of movement in the healthy state.⁸⁰ In the parkinsonian

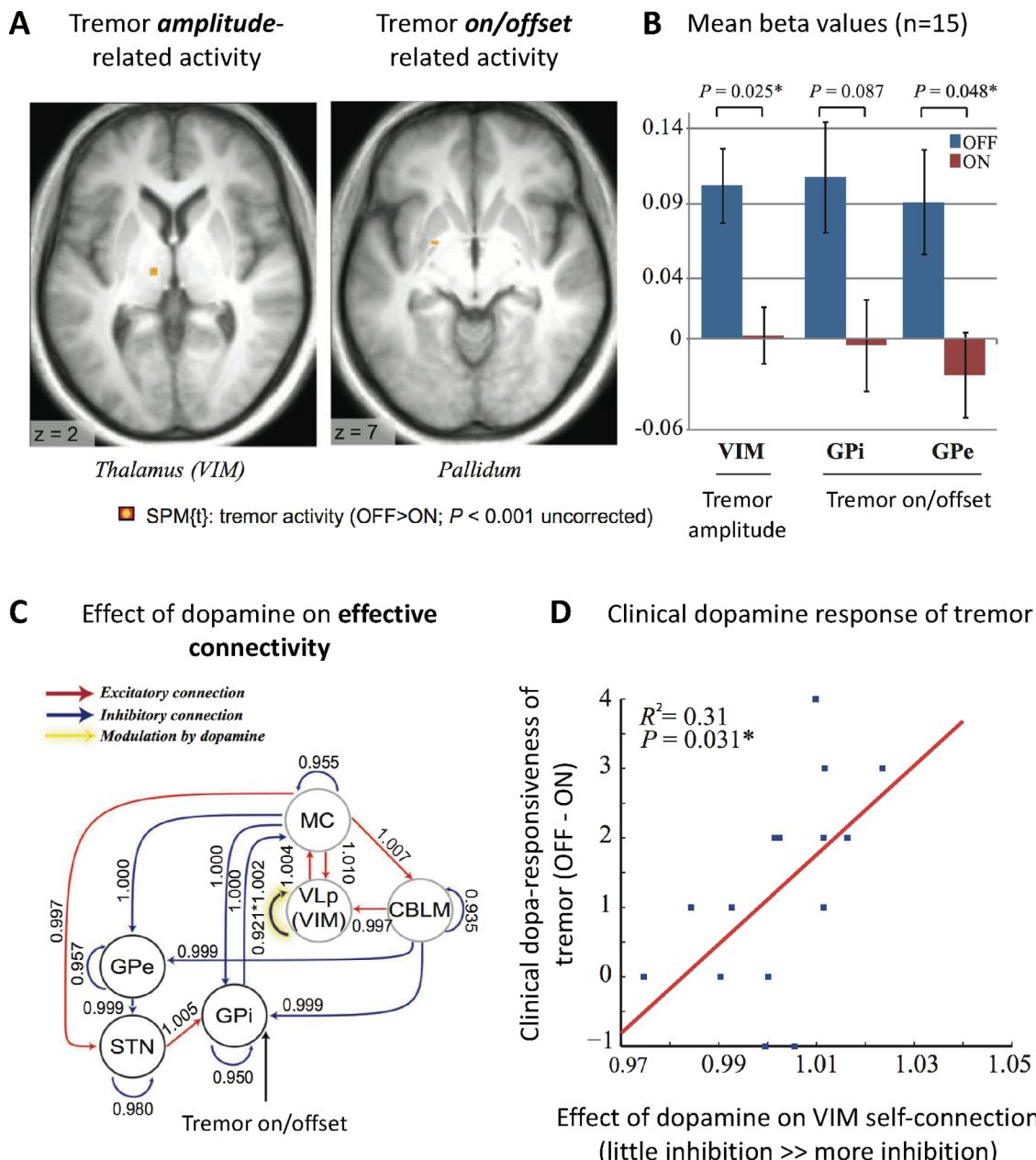


FIG. 3. The effect of dopamine on parkinsonian tremor. (A and B) The effect of dopaminergic medication on tremor amplitude-related activity in the ventrolateral posterior thalamus (VLp) and the effect on tremor on/offset related activity in the pallidum. (C) The winning model from a dynamic causal modeling analysis that compared the effect of dopamine on different nodes and connections. The model where dopamine influences the inhibitory self-connection of the VLp won. (D) The effect of dopamine on the VLp explained the clinical dopamine effect on tremor (UPDRS resting tremor score improvement). Taken from ref.²⁶ with permission. SPM, Statistical Parametric Mapping; MC, motor cortex; VIM, ventral intermediate nucleus [Color figure can be viewed at wileyonlinelibrary.com]

state, changes in network structure (intensified connectivity with the basal ganglia), and changes in neurotransmitter projections (eg, dopamine depletion), likely transform this natural oscillatory tendency into a pathological oscillatory state.

Context Matters

Parkinsonian tremor is a very variable motor sign. Not only does the expression of tremor differ between patients (eg, with respect to the body part that is

affected, its response to dopamine, its severity), but tremor also changes within patients depending on the context.¹ For example, many patients experience a dramatic increase in their tremor under emotional or cognitive stress (Fig. 4A), and tremor decreases during a voluntary movement with the tremulous limb.⁸¹ Furthermore, voluntary movements with a nontremulous limb (such as walking or tapping with the contralateral hand) increase tremor,⁸² whereas tonic contractions with the contralateral hand reduce tremor.⁸³ This suggests that there may be 2 different

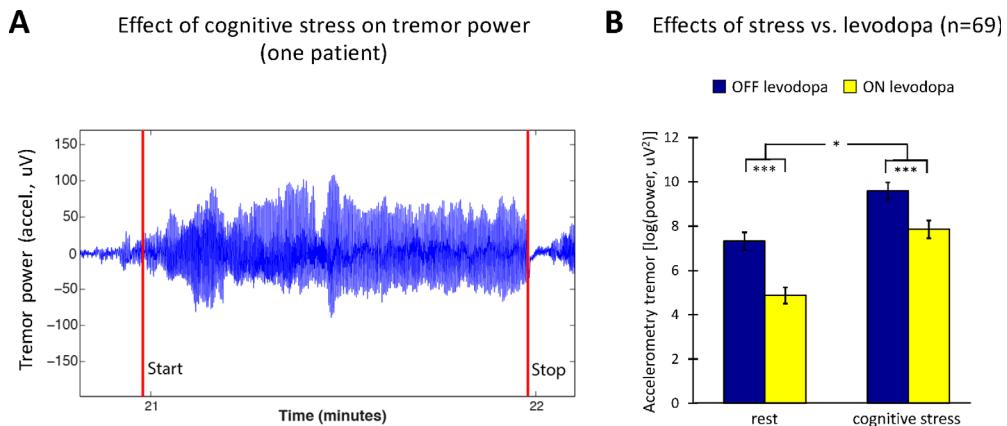


FIG. 4. The effect of cognitive stress on parkinsonian tremor. **(A)** An accelerometer trace from a patient who was asked to count back from 100 in steps of 7 during 1 minute (shown on the x-axis). This increased tremor power (shown on the y-axis). **(B)** The effect of cognitive stress (serial sevens, x-axis) and levodopa (blue and yellow columns) on tremor power (y-axis). This figure shows that levodopa reduced tremor, cognitive stress increased tremor, and the effect of levodopa were smaller during cognitive stress. Taken from ref. ⁷² with permission. [Color figure can be viewed at wileyonlinelibrary.com]

cerebral mechanisms that contribute to tremor: a pathophysiological pathway that determines whether a patient has tremor and (1 or more) modulatory mechanisms that interact with this pathophysiological pathway and determine the expression of tremor.

We have previously focused on 1 of these modulatory factors: cognitive stress. In a sample of 69 tremor-dominant PD patients, we measured resting tremor power (using accelerometry) under the following 4 conditions: OFF and ON 200/50 mg levodopa and with and without cognitive stress (subtracting 7 from 100 as fast as possible).⁷² We replicated previous findings that showed that levodopa reduced tremor overall, whereas cognitive stress increased tremor.^{82,83} In addition, we also observed that the antitremor effect of levodopa was significantly smaller during cognitive stress than during rest (Fig. 4B). This effect may be explained by a stress-related depletion of dopamine in the basal ganglia motor circuit or by the stress-related involvement of nondopaminergic mechanisms in tremor (eg, noradrenaline) or both. Because psychological stress increases rather than decreases dopaminergic transmission in the basal ganglia of healthy participants,⁸⁴ it is most likely that nondopaminergic mechanisms modulate the tremor circuitry under stressful conditions. As outlined next, a plausible explanation relates to the noradrenergic system, but other mechanisms may also be involved.

Several pieces of evidence suggest a link between the noradrenergic system and resting tremor. For instance, postmortem studies have shown that PD patients with a tremor-dominant phenotype have less degeneration of the locus coeruleus (the main source of cerebral noradrenaline) than patients with a nontremor phenotype.⁸⁵ Also, nuclear imaging has shown that noradrenaline receptor binding in the locus coeruleus is increased in PD patients versus controls,⁸⁶ particularly in tremor-dominant patients.⁸⁷ Furthermore, interventions that suppress noradrenergic

hyperactivity, both pharmacologically (beta-blockers⁸⁸⁻⁹⁰) and nonpharmacologically (guided relaxation therapy⁹¹) can reduce resting tremor. Conversely, intravenous injection of adrenaline, which activates the cerebral noradrenergic system through the vagal nerve,^{92,93} increases tremor.⁹⁴⁻⁹⁶ The cerebral mechanisms underlying worsened tremor during acute psychological stress remain very much unclear.⁹⁷ The locus coeruleus has anatomical projections to all nodes of the tremor circuit.⁹⁸ Animal studies have shown that an acute stressor produces motor hyperactivity, possibly mediated through direct effects of noradrenaline on the cerebral motor circuit.⁹⁹ Future studies may test how noradrenergic activity modulates ongoing tremulous activity in the cerebello-thalamo-cortical circuit and/or the basal ganglia, causing the salient and bothersome increase in tremor under psychological stress.

We also assessed, in a different study, how patients themselves judge the effect of levodopa and to what extent this depends on the presence or absence of cognitive stress.⁵⁸ In 43 patients, we correlated these subjective ratings on dopamine effectiveness (using a visual analogue scale) with objective tremor changes (using accelerometry), both during rest and during cognitive stress. Patient-accelerometry agreement was low during rest ($R^2 = 0.12$), but significantly higher during cognitive stress ($R^2 = 0.35$). In other words, although the antitremor effect of levodopa is reduced during cognitive stress, this effect best aligns with the patients' own impression of the antitremor effect of levodopa. This suggests that patients judge levodopa effectiveness by its ability to reduce tremor under stress. Clinicians may take this into account when evaluating the effect of levodopa on tremor in the clinic.

Translational Implications

As outlined previously, tremor has a variable expression and a variable response to dopaminergic

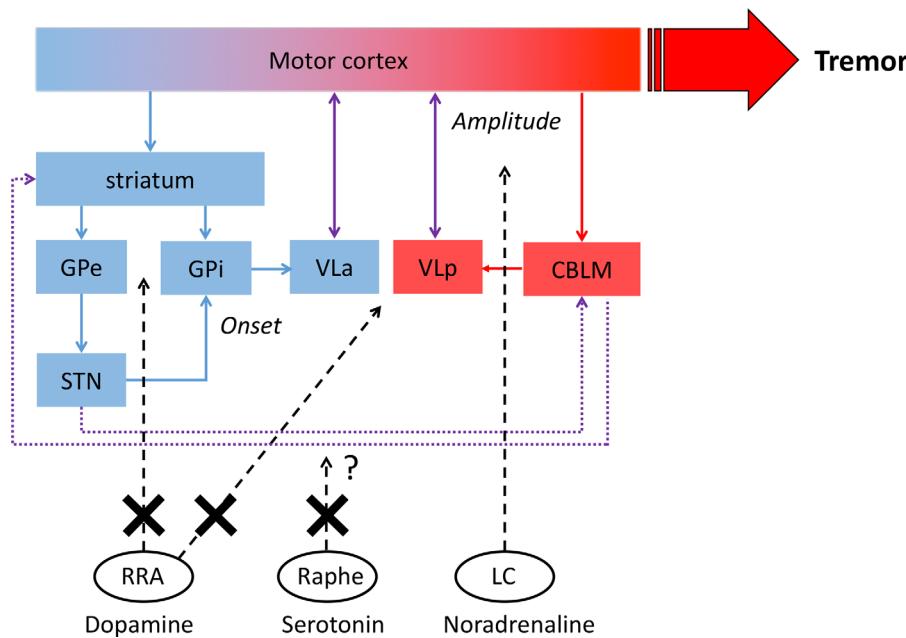


FIG. 5. The pathophysiology of parkinsonian tremor. This figure shows the hypothetical cerebral network involved in parkinsonian tremor. The basal ganglia (in blue) and the cerebello-thalamo-cortical circuit (in red) are regions where tremor-related activity has been found. Both circuits converge in the motor cortex (purple). Blue and red arrows indicate connections within each circuit; purple arrows indicate connections between the basal ganglia and cerebello-thalamo-cortical circuits. The open circles indicate neurotransmitter systems that project to these circuits and where changes have been reported in tremor-dominant PD. These include reduced dopaminergic projections from the RRA, reduced serotonergic projections from the raphe nuclei, and (possibly) increased noradrenergic projections from the LC. In italics, hypothesized roles of nodes of this network that trigger the onset of tremor (GPi) and maintain tremor amplitude (the cerebello-thalamo-cortical circuit). VLa, ventrolateral anterior thalamus; VLp, ventrolateral posterior thalamus; CBLM, cerebellum; RRA, retrorubral area; LC, locus coeruleus. [Color figure can be viewed at wileyonlinelibrary.com]

medication depending on the patient and on the prevailing context. This suggests that there is considerable between-subject variability in the neurobiology of tremor. Biological differences between patients may not always be visible on the outside, or only emerge after detailed clinical testing. For example, it is not possible to clinically predict whether resting tremor in a particular patient will respond to dopaminergic medication. It is clear that single clinical or biological tremor characteristics may explain some of the variance, but they are insufficient to understand tremor in its entirety. To do so, complex biological models are needed that incorporate several sources of information, such as patterns of neuronal loss (eg, the topography of dopaminergic cell death in the mesencephalon), the projection of neurotransmitter systems onto tremor-related brain areas (eg, dopaminergic projections onto the pallidum or VLp), the architecture of the cerebral tremor network (eg, connectivity within and between the basal ganglia and the cerebello-thalamo-cortical circuit), and the influence of modulatory factors on the tremor network (eg, noradrenergic, stress-related influences on the cerebello-thalamo-cortical circuit; Fig. 5). This is not only useful for understanding tremor but also to provide optimal treatments in individual patients. Neuroimaging techniques (such as diffusion tensor imaging and fMRI) may offer this information, provided that it is reliable (or replicable) and that it gives an individual

fingerprint of the cerebral tremor circuit. Recent findings suggest that this type of cerebral fingerprinting in individuals is feasible.¹⁰⁰⁻¹⁰² It has not been determined whether the use of individual neuroimaging in the clinic has sufficient predictive power to replace medication trials (which is current practice).

In recent years, there has been a great interest in precision medicine approaches. Precision medicine involves biologically based disease subtyping, which may or may not coincide with clinical subtyping. For instance, it has been suggested that PD should be “split” into different subtypes, integrating clinical, genetic, and patho-(physio)logical data.¹⁰³ Each subtype should be recognized as a distinct form of PD, requiring its own treatment tailored to the individual biology. The development of systems neuroscience, such as computational neurology (or psychiatry), can be a useful tool for precision medicine.¹⁰⁴ Network approaches such as DCM allow integration of different neural sources (eg, brain activity, connectivity, modulatory input) into cerebral models with a particular output (eg, tremor).¹⁰⁵ As we have recently shown, these models are better able to explain clinical variability (such as the clinical dopamine response of tremor; Fig. 3D) than a single brain region in isolation.²⁶ Future approaches may use these models based on neuroimaging and clinical data to predict the response to treatment and ultimately form the basis for rational treatment choices.¹⁰⁶ ■

Acknowledgments: This work was supported by the Dutch Brain Foundation Grant F2013(1)-15 and by the Netherlands Organization for Scientific Research NWO VENI Grant 91617077.

References

1. Zach H, Dirkx M, Bloem BR, Helmich RC. The clinical evaluation of Parkinson's tremor. *J Parkinsons Dis* 2015;5(3):471-474.
2. Hallett M. Tremor: pathophysiology. *Parkinsonism Relat Disord* 2014;20(Suppl 1):S118-S22.
3. Helmich RC, Hallett M, Deuschl G, et al. Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? *Brain* 2012;135(Pr 11):3206-3226.
4. Hallett M, Deuschl G. Are we making progress in the understanding of tremor in Parkinson's disease? *Ann Neurol* 2010;68(6):780-781.
5. Louis ED, Levy G, Côte LJ, et al. Clinical correlates of action tremor in Parkinson disease. *Arch Neurol* 2001;58(10):1630-1634.
6. Louis ED, Tang MX, Cote L, et al. Progression of parkinsonian signs in Parkinson disease. *Arch Neurol* 1999;56(3):334.
7. Lees AJ. Unresolved issues relating to the shaking palsy on the celebration of James Parkinson's 250th birthday. *Mov Disord* 2007;22(S17):S327-S334.
8. Koh S-B, Kwon D-Y, Seo W-K, et al. Dissociation of cardinal motor signs in Parkinson's disease patients. *Eur Neurol* 2010;63(5):307-310.
9. Pirker W. Correlation of dopamine transporter imaging with parkinsonian motor handicap: how close is it? *Mov Disord* 2003;18(S7):S43-S51.
10. Nonnikes J, Timmer MHM, de Vries NM, et al. Unmasking levodopa resistance in Parkinson's disease. *Mov Disord* 2016;31(11):1602-1609.
11. Timmermann L, Gross J, Dirks M, et al. The cerebral oscillatory network of parkinsonian resting tremor. *Brain* 2003;126(Pt 1):199-212.
12. Lenz FA, Tasker RR, Kwan HC, et al. Single unit analysis of the human ventral thalamic nuclear group: correlation of thalamic "tremor cells" with the 3-6 Hz component of parkinsonian tremor. *J Neurosci* 1988;8(3):754-764.
13. Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *J Neurosci* 2000;20(20):7766-7775.
14. Hurtado JM, Gray CM, Tamas LB, Sigvardt KA. Dynamics of tremor-related oscillations in the human globus pallidus: a single case study. *Proc Natl Acad Sci U S A* 1999;96(4):1674-1679.
15. Mure H, Hirano S, Tang CC, et al. Parkinson's disease tremor-related metabolic network: Characterization, progression, and treatment effects. *NeuroImage* 2011;54(2):1244-1253.
16. Krack P, Pollak P, Limousin P, et al. Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease. *Lancet* 1997;350(9092):1675.
17. Benabid AL, Pollak P, Gervason C, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 1991;337(8738):403-406.
18. Lozano AM, Lang AE, Galvez-Jimenez N, Miyasaki J. Effect of GPi pallidotomy on motor function in Parkinson's disease. *Lancet* 1995;346(8987):1383-1387.
19. Krack P, Dostrovsky J, Ilinsky I, et al. Surgery of the motor thalamus: problems with the present nomenclatures. *Mov Disord* 2002;17(S3):S2-S8.
20. Hirai T, Jones EG. A new parcellation of the human thalamus on the basis of histochemical staining. *Brain Res Brain Res Rev* 1989;14(1):1-34.
21. Magnin M, Morel A, Jeanmonod D. Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. *Neuroscience* 2000;96(3):549-564.
22. Fiechter M, Nowacki A, Oertel MF, et al. Deep brain stimulation for tremor: is there a common structure? *Stereotact Funct Neurosurg* 2017;95(4):243-250.
23. Coenen VA, Allert N, Paus S, et al. Modulation of the cerebello-thalamo-cortical network in thalamic deep brain stimulation for tremor. *Neurosurgery* 2014;75(6):657-670.
24. Helmich RC, Janssen MJR, Oyen WJG, et al. Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. *Ann Neurol* 2011;69(2):269-281.
25. Dirkx MF, Ouden den H, Aarts E, et al. The cerebral network of parkinson's tremor: an effective connectivity fMRI study. *J Neurosci* 2016;36(19):5362-5372.
26. Dirkx MF, Ouden den HEM, Aarts E, et al. Dopamine controls Parkinson's tremor by inhibiting the cerebellar thalamus. *Brain* 2017;140(3):721-734.
27. Helmich RC, Bloem BR, Toni I. Motor imagery evokes increased somatosensory activity in Parkinson's disease patients with tremor. *Human Brain Mapping* 2012;33(8):1763-1779.
28. Raz A, Vaadia E, Bergman H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. *J Neurosci* 2000;20(22):8559-8571.
29. Lenz FA, Kwan HC, Martin RL, et al. Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. *Brain* 1994;117(Pt 3):531-543.
30. Rivlin-Etzion M, Marmor O, Saban G, et al. Low-pass filter properties of basal ganglia cortical muscle loops in the normal and mptp primate model of parkinsonism. *J Neurosci* 2008;28(3):633-649.
31. Cagnan H, Little S, Foltyne T, et al. The nature of tremor circuits in parkinsonian and essential tremor. *Brain* 2014;137(Pt 12):3223-3234.
32. Brittain JS, Cagnan H, Mehta AR, et al. Distinguishing the central drive to tremor in Parkinson's disease and essential tremor. *J Neurosci* 2015;35(2):795-806.
33. Hirschmann J, Schoffelen JM, Schnitzler A, van Gerven MAJ. Parkinsonian rest tremor can be detected accurately based on neuronal oscillations recorded from the subthalamic nucleus. *Clin Neurophysiol* 2017;128(10):2029-2036.
34. Hirschmann J, Hartmann CJ, Butz M, et al. A direct relationship between oscillatory subthalamic nucleus-cortex coupling and rest tremor in Parkinson's disease. *Brain* 2013;136(Pt 12):3659-3670.
35. Nambu A, Tokuno H, Takada M. Functional significance of the cortico-subthalamo-pallidal "hyperdirect" pathway. *Neurosci Res* 2002;43(2):111-117.
36. Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. *Proc Natl Acad Sci U S A* 2010;107(18):8452-8456.
37. Rico AJ, Barroso-Chinea P, Conte-Perales L, et al. A direct projection from the subthalamic nucleus to the ventral thalamus in monkeys. *Neurobiol Dis* 2010;39(3):381-392.
38. Kumar R, Lozano AM, Sime E, et al. Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. *Neurology* 1999;53(3):561-566.
39. Patel NK, Heywood P, O'Sullivan K, et al. Unilateral subthalamotomy in the treatment of Parkinson's disease. *Brain* 2003;126(5):1136-1145.
40. Plenz D, Kitai ST. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. *Nature* 1999;400(6745):677-682.
41. Kang G, Lowery MM. Effects of antidromic and orthodromic activation of STN afferent axons during DBS in Parkinson's disease: a simulation study. *Front Comput Neurosci* 2014;8(35):32.
42. Britton TC, Thompson PD, Day BL, et al. Modulation of postural tremors at the wrist by supramaximal electrical median nerve shocks in essential tremor, Parkinson's disease and normal subjects mimicking tremor. *J Neurol Neurosurg Psychiatr* 1993;56(10):1085-1089.
43. Lee RG, Stein RB. Resetting of tremor by mechanical perturbations: a comparison of essential tremor and parkinsonian tremor. *Ann Neurol* 1981;10(6):523-531.
44. Rack PM, Ross HF. The role of reflexes in the resting tremor of Parkinson's disease. *Brain* 1986;109 (Pt 1):115-141.
45. Walshe F. Observations on the nature of the muscular rigidity of paralysis agitans, and on its relationship to tremor. *Brain* 1924.
46. Volkmann J, Joliot M, Mogilner A, et al. Central motor loop oscillations in parkinsonian resting tremor revealed magnetoencephalography. *Neurology* 1996;46(5):1359-1359.
47. Wang Z, Chen H, Ma H, et al. Resting-state functional connectivity of subthalamic nucleus in different Parkinson's disease phenotypes. *J Neurol Sci* 2016;371(C):137-147.

48. Baudrexel S, Witte T, Seifried C, et al. Resting state fMRI reveals increased subthalamic nucleus-motor cortex connectivity in Parkinson's disease. *NeuroImage* 2011;55(4):1728-1738.
49. Zhang J-R, Feng T, Hou Y-N, et al. Functional connectivity of vim nucleus in tremor- and akinetic-/rigid-dominant Parkinson's disease. *CNS Neurosci Ther* 2016;22(5):378-386.
50. Friston KJ, Harrison L, Penny W. Dynamic causal modelling. *NeuroImage* 2003;19(4):1273-1302.
51. Caligiore D, Pezzulo G, Baldassarre G, et al. Consensus paper: towards a systems-level view of cerebellar function: the interplay between cerebellum, basal ganglia, and cortex. *Cerebellum* 2017; 16(1):203-229.
52. Hoover JE, Strick PL. The organization of cerebellar and basal ganglia outputs to primary motor cortex as revealed by retrograde transneuronal transport of herpes simplex virus type 1. *J Neurosci* 1999;19(4):1446-1463.
53. Rüb U, Del Tredici K, Schultz C, Ghebremedhin E. Parkinson's disease: the thalamic components of the limbic loop are severely impaired by α -synuclein immunopositive inclusion body pathology. *Neurobiol Aging* 2002.
54. Helmich RC, Toni I, Deuschl G, Bloem BR. The pathophysiology of essential tremor and Parkinson's tremor. *Curr Neurol Neurosci Rep* 2013;13(9):378.
55. Hopfner F, Haubenberger D, Galpern WR, et al. Knowledge gaps and research recommendations for essential tremor. *Parkinsonism Relat Disord* 2016;33(C):27-35.
56. Buijink AWG, van der Stouwe AMM, Broersma M, et al. Motor network disruption in essential tremor: a functional and effective connectivity study. *Brain* 2015;138(Pt 10):2934-2947.
57. Gallea C, Popa T, Garcia-Lorenzo D, et al. Intrinsic signature of essential tremor in the cerebello-frontal network. *Brain* 2015; 138(Pt 10):2920-2933.
58. Zach H, Dirkx M, Pasman JW, et al. The patient's perspective: the effect of levodopa on Parkinson symptoms. *Parkinsonism Relat Disord* 2017;35:48-54.
59. Jellinger KA. Neuropathology of sporadic Parkinson's disease: Evaluation and changes of concepts. *Mov Disord* 2012;27(1):8-30.
60. Isaías IU, Benti R, Cilia R, et al. [123I]FP-CIT striatal binding in early Parkinson's disease patients with tremor vs. akinetic-rigid onset. *NeuroReport* 2007;18(14):1499-1502.
61. Selikhova M, Williams DR, Kempster PA, et al. A clinicopathological study of subtypes in Parkinson's disease. *Brain* 2009; 132(11):2947-2957.
62. Hirsch EC, Mouatt A, Faucheuix B, et al. Dopamine, tremor, and Parkinson's disease. *Lancet* 1992;340(8811):125-126.
63. François C, Yelnik J, Tandé D, et al. Dopaminergic cell group A8 in the monkey: anatomical organization and projections to the striatum. *J Comp Neurol* 1999;414(3):334-347.
64. Jan C, François C, Tandé D, et al. Dopaminergic innervation of the pallidum in the normal state, in MPTP-treated monkeys and in parkinsonian patients. *Eur J Neurosci* 2000;12(12):4525-4535.
65. Sánchez-González MA, García-Cabezas MA, Rico B, Cavada C. The primate thalamus is a key target for brain dopamine. *J Neurosci* 2005;25(26):6076-6083.
66. Qamhawi Z, Towey D, Shah B, et al. Clinical correlates of raphe serotonergic dysfunction in early Parkinson's disease. *Brain* 2015; 138(10):2964-2973.
67. Loane C, Wu K, Bain P, et al. Serotonergic loss in motor circuitries correlates with severity of action-postural tremor in PD. *Neurology* 2013;80(20):1850-1855.
68. Doder M, Rabiner EA, Turjanski N, et al. Tremor in Parkinson's disease and serotonergic dysfunction: an ^{11}C -WAY 100635 PET study. *Neurology* 2003;60(4):601-605.
69. Podurgiel SJ, Milligan MN, Yohn SE, et al. Fluoxetine administration exacerbates oral tremor and striatal dopamine depletion in a rodent pharmacological model of parkinsonism. 2015;40(9): 2240-2247.
70. García-Cabezas MA, Rico B, Sánchez-González MA, Cavada C. Distribution of the dopamine innervation in the macaque and human thalamus. *NeuroImage* 2007;34(3):965-984.
71. García-Cabezas MA, Martínez-Sánchez P, Sanchez-Gonzalez MA, et al. Dopamine Innervation in the thalamus: monkey versus rat. *Cereb Cortex* 2009;19(2):424-434.
72. Zach H, Dirkx MF, Pasman JW, et al. Cognitive stress reduces the effect of levodopa on Parkinson's resting tremor. *CNS Neurosci Ther* 2017;23(3):209-215.
73. Rajput AH, Sitte HH, Rajput A, et al. Globus pallidus dopamine and Parkinson motor subtypes: clinical and brain biochemical correlation. *Neurology* 2008;70(16 Pt 2):1403-1410.
74. Prodoehl J, Planetta PJ, Kurani AS, et al. Differences in brain activation between tremor- and nontremor-dominant Parkinson disease. *JAMA Neurol* 2013;70(1):100-106.
75. Yin HH. The basal ganglia in action. *Neuroscientist* 2017;23(3): 299-313.
76. Houk JC, Wise SP. Distributed modular architectures linking basal ganglia, cerebellum, and cerebral cortex: their role in planning and controlling action. *Cereb Cortex* 1995;5(2):95-110.
77. Hoshi E, Tremblay L, Féger J, et al. The cerebellum communicates with the basal ganglia. *Nat Neurosci* 2005;8(11):1491-1493.
78. Schweighofer N, Doya K, Kuroda S. Cerebellar aminergic neuro-modulation: towards a functional understanding. *Brain Res Rev* 2004;44(2-3):103-116.
79. Gross J, Timmermann L, Kujala J, et al. The neural basis of intermittent motor control in humans. *Proc Natl Acad Sci U S A* 2002;99(4):2299-2302.
80. Marsden JF, Ashby P, Limousin-Dowsey P, et al. Coherence between cerebellar thalamus, cortex and muscle in man: cerebellar-thalamus interactions. *Brain* 2000;123(Pt 7):1459-1470.
81. Papengut F, Raethjen J, Binder A, Deuschl G. Rest tremor suppression may separate essential from parkinsonian rest tremor. *Parkinsonism Relat Disord* 2013;19(7):693-697.
82. Raethjen J, Austermann K, Witt K, et al. Provocation of parkinsonian tremor. *Mov Disord* 2008;23(7):1019-1023.
83. Sturman MM, Vaillancourt DE, Metman LV, et al. Deep brain stimulation and medication for parkinsonian tremor during secondary tasks. *Mov Disord* 2007;22(8):1157-1163.
84. Pruessner JC, Champagne F, Meaney MJ, Dagher A. Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using $[11\text{C}]$ raclopride. *J Neurosci* 2004;24(11): 2825-2831.
85. Paulus W, Jellinger K. The neuropathologic basis of different clinical subgroups of Parkinson's disease. *J Neuropathol Exp Neurol* 1991;50(6):743-755.
86. Lewis SJ, Pavese N, Rivero-Bosch M, et al. Brain monoamine systems in multiple system atrophy: A positron emission tomography study. *Neurobiol Dis* 2012;46(1):130-136.
87. Isaías IU, Marotta G, Pezzoli G, et al. Enhanced catecholamine transporter binding in the locus coeruleus of patients with early Parkinson disease. *BMC Neurol* 2011;11(1):88.
88. Kissel P, Tridon P, André JM. Letter: levodopa-propranolol therapy in parkinsonian tremor. *Lancet* 1974;1(7854):403-404.
89. Henderson JM, Yiannikas C, Morris JG, et al. Postural tremor of Parkinson's disease. *Clin Neuropharm* 1994;17(3):277-285.
90. Abramsky O, Carmon A, Lavy S. Combined treatment of parkinsonian tremor with propranolol and levodopa. *J Neurol Sci* 1971; 14(4):491-494.
91. Schlesinger I, Benyakov O, Erikh I, et al. Parkinson's disease tremor is diminished with relaxation guided imagery. *Mov Disord* 2009;24(14):2059-2062.
92. Tank AW, Wong DL. Peripheral and central effects of circulating catecholamines. *Compr Physiol* 2015;5(1):1-15.
93. Hermans EJ, Henckens MJAG, Joëls M, Fernández G. Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends Neurosci* 2014;37(6):304-314.
94. Marshall J, Schnieden H. Effect of adrenaline, noradrenaline, atropine, and nicotine on some types of human tremor. *J Neurol Neurosurg Psychiatr* 1966;29(3):214-218.
95. Constanas C. The effects of adrenaline, noradrenaline, and isoprenaline on parkinsonian tremor. *J Neurol Neurosurg Psychiatr* 1962; 25:116-121.
96. Barcroft H, Peterson E, Schwab RS. Action of adrenaline and noradrenaline on the tremor in Parkinson's disease. *Neurology* 1952;2(2):154-160.

97. Hemmerle AM, Herman JP, Seroogy KB. Stress, depression and Parkinson's disease. *Exp Neurol* 2012;233(1):79-86.
98. Delaville C, Deurwaerdère PD, Benazzouz A. Noradrenaline and Parkinson's disease. *Front Syst Neurosci* 2011;5:31.
99. Metz GA. Stress as a modulator of motor system function and pathology. *Rev Neurosci* 2007;18(3-4):209-222.
100. Wang D, Buckner RL, Fox MD, et al. Parcellating cortical functional networks in individuals. *Nat Neurosci* 2015;18(12):1853-1860.
101. Drysdale AT, Gosenick L, Downar J, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med* 2016;23(1):28-38.
102. Finn ES, Shen X, Scheinost D, et al. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. *Nat Neurosci* 2015;18(11):1664-1671.
103. Espay AJ, Brundin P, Lang AE. Precision medicine for disease modification in Parkinson disease. *Nat Rev Neurol* 2017;13(2):119-126.
104. Stephan KE, Iglesias S, Heinze J, Diaconescu AO. translational perspectives for computational neuroimaging. *Neuron* 2015; 87(4):716-732.
105. Rigoux L, Daunizeau J. Dynamic causal modelling of brain-behaviour relationships. *NeuroImage* 2015;117(C):202-221.
106. Caligiore D, Helmich RC, Hallett M. Parkinson's disease as a system-level disorder. *NPJ Park Dis* 2016;2(1):16025.