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Are we making progress in the understanding of tremor in Parkinson's disease?

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In his essay on the Shaking Palsy,[1] James Parkinson noted the presence of tremor as a cardinal feature: "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported." While superficially, tremor might seem to be a simple aspect of Parkinson's disease, it has actually turned out to be rather difficult to understand. One issue is that there is clearly more than one type of tremor. The classic" tremor is tremor-at-rest; as Parkinson put it: "in parts not in action". The classic tremor might also be present in posture, although there might well be a pause in it during the transition from rest to posture. This has been called re-emergent tremor. Many patients, however, have a distinct postural tremor clearly different from re-emergent tremor. The distinction can come from the frequency which is often faster than tremor-at-rest or it can be present in some patients who lack tremor-at-rest. To be fair, however, sometimes it is difficult to tell whether it is truly different. A third postural tremor can be an essential tremor. There is sometimes a co-existence of essential tremor and Parkinson's disease, and, in this regard, it is now established that patients with essential tremor have a slightly higher chance of developing Parkinson's disease. Parkinson "postural" tremor and essential tremor can appear clinically very similar. Given that there are sometimes dystonic elements in Parkinson's disease, yet another possibility is a dystonic tremor, and, if present, it would also look similar to "postural" tremor and essential tremor. In this regard, recently it has been suggested that the SWEDD (scans without evidence of dopamine deficiency) patients have dystonic tremor.[2] Moreover, any patient can have an exaggerated physiological tremor. Hence, there are at least five possible postural tremor types in patients. In order to understand the pathogenesis of postural tremor in Parkinson's disease, the first step should be a clear clinical characterization.

The origins of the tremors in Parkinson disease are not at all clear, and almost all attention has been paid to the tremor-at-rest. In regard to the tremor-at-rest, it is not closely tied to the dopaminergic deficit. Bradykinesia and rigidity are strongly related to dopamine and are typically responsive to dopamine replacement. Tremor-at-rest may improve with dopamine, but this may not be the case and can even worsen. Positron emission tomography (PET) imaging shows a possible relationship of tremor-at-rest to serotonergic deficiency,[3] but serotonergic drugs do not clearly help. The network of active brain regions related to tremor can be determined by FDG (flurodeoxyglucose) PET or functional magnetic resonance imaging (fMRI). An early study with PET showed cerebellar hypermetabolism associated with tremor.[4] A tremor network with FDG PET was determined to be thalamus, pons, and premotor cortical regions.[5] Another study showed a negative correlation of tremor and the putamen and cerebellar vermis.[6] An magnetoencephalographic (MEG) analysis showed a

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cerebello-diencephalic-cortical network related to tremor-at-rest.[7] A voxel-based morphometry (VBM) study showed loss of cerebellar gray matter in the right quadrangular lobe and declive of the cerebellum in patients with rest tremor compared to those without.[8]

Recordings of neuronal activity or local field potentials from basal ganglia structures and thalamus show rhythmic activity related to tremor-at-rest. Coupling is strongest with recordings from the VIM (ventralis intermedius) nucleus of the thalamus, which is a cerebellar relay nucleus. VIM thalamotomy or VIM deep brain stimulation (DBS) markedly improves tremor-at-rest; indeed, it seems to improve tremors of all types. Recording of cell burst patterns in the VIM suggest that most cells are followers and not spontaneous bursters.[9] This suggests that the tremor does not originate in the VIM, and that the tremor either originates elsewhere, or that the tremor emerges as an abnormal network property. The best thinking at present is that the cerebellar networks are clearly involved in virtually all tremors, at least for the motor manifestation. Whether the origin of any tremor is in the cerebellar network or elsewhere remains uncertain.

In a paper in the current issue of *Annals of Neurology*, the authors sought to learn more about rest versus postural tremor in patients with PD.[10] They found a similar response to motor cortical stimulation resetting the tremor rhythm for rest and postural tremor in PD. This is similar to their earlier results in essential tremor, another form of postural tremor[11] and is also consistent with the coherence of almost all tremors with the motor cortex.[12, 13] Thus, cortical involvement seems to be a common feature in tremor and the present finding extends this observation to motor cortical resettability of Parkinson rest tremor. In contrast, cerebellar stimulation reset Parkinsonian postural but not rest tremor, and contrasts with the lack of resettability in essential tremor.[11] They conclude that the Parkinson rest and postural tremors are mediated by different neural networks and that only the postural tremor utilizes the cerebellothalamocortical network. The conclusion should be accepted only very cautiously since there is so much other evidence that the cerebellum is involved in the rest tremor.

The decrease in resetting is correlated with the decrease in cerebellar inhibition. The authors described this decrease in cerebellar inhibition previously in Parkinson's disease[14] and reproduce their finding here. This too has to be accepted only cautiously. While there is a group effect and inter-stimulus interval effect, the interaction is not significant. This means that there is some general effect of the cerebellar stimulation and not necessarily involvement of the specific cerebellothalamocortical pathway. Moreover, Ugawa and colleagues reported normal cerebellar inhibition using transcranial electrical stimulation rather than magnetic stimulation,[15] and this suggests that any deficiency may only be relative since electrical stimulation is more potent than magnetic. In any resetting experiment, the reset depends on the relative strength of the tremor generator and the resetting stimulus. If the rest tremor generator is stronger than the postural tremor generator, there could well be an effect only on the postural generator even if similar networks are involved. There is some evidence for this since there is also less resetting of the rest tremor with M1 stimulation.

This paper adds to our knowledge, but the conclusions are limited, and the pathophysiology of tremors in Parkinson's disease remains mysterious. We would not suggest giving up yet on the idea of involvement of cerebellar pathways in tremor-at-rest, and there is still room for further discoveries.

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