



## Commentary

## The many roads to tremor

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## ABSTRACT

Tremor represents one of the most prominent examples of aberrant synchronisation within the human motor system, and Essential Tremor (ET) is by far the most common tremor disorder. Yet, even within ET there is considerable variation, and patients may have contrasting amounts of postural and intention tremor. Recently, Pedrosa et al. (2013) challenged tremor circuits in a cohort of patients presenting with ET, by applying low-frequency deep brain stimulation within thalamus. This interventional approach provided strong evidence that distinct (yet possibly overlapping) neural substrates are responsible for postural and intention tremor in ET. Intention tremor, and not postural tremor, was exacerbated by low frequency stimulation, and the effect was localised in the region of the ventrolateral thalamus in such a way as to implicate cerebello-thalamic pathways. These results, taken in conjunction with the contemporary literature, reveal that pathological changes exaggerate oscillatory synchrony in selective components of an extensive and distributed motor network, and that synchronisation within these networks is further regulated according to motor state. Through a combination of pathological and more dynamic physiological factors, activity then spills out into the periphery in the form of tremor. The findings of Pedrosa et al. (2013) are timely as they coincide with an emerging notion that tremor may result through selective dysregulation within a broader tremorgenic network.

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## Introduction

Ever since the first electrical recordings were made from the brain it has been clear that oscillations play a central role in brain function. Nowhere is this more apparent than in pathological tremor, where aberrant oscillations overwhelm the motor network resulting in rapid alternation of one of more body parts. The prevalence of tremor is matched only by its heterogeneity. But for such an apparently simple clinical phenomenon, a lucid view of tremor is, perhaps surprisingly, still very much lacking.

Essential tremor (ET) is the most common movement disorder. The ideal that ET represents a single homogeneous clinical entity has however long been superseded (Arkadir and Louis, 2013). In particular, ET patients vary in the severity of postural and intention (end-goal dysmetria) tremor elements. This phenotypic variability may afford particular insight into brain function and dysregulation. Thus cerebellar signs are more common in ET patients with prominent intention tremor (Koster et al., 2002), hinting at the idea developed by Pedrosa et al. (2013), that intention tremor may be more dependent on cerebello-thalamic involvement (see also Herzog et al., 2007).

Specifically, Pedrosa et al. (2013) provide strong evidence that distinct (yet possibly overlapping) neural substrates are responsible for producing postural versus intention tremor within a cohort of 16 ET

patients. The authors take advantage of the presence of deep brain stimulation electrodes, implanted in and just below the ventrolateral thalamus for the treatment of tremor. They demonstrate that low-frequency stimulation at 10 Hz can increase clinical rating scores of tremor beyond levels observed in the unstimulated state. Kinematic analysis further suggests that this worsening with low-frequency stimulation was due to a deleterious effect on intention tremor rather than postural tremor, and co-registration of stimulation site with pre-operative imaging and the Atlas of the Human Brain (Mai et al., 2008) showed that the exacerbation of intention tremor was greatest when low-frequency stimulation was delivered ventrally in the ventrolateral thalamus or just inferior to this, a region which the authors suggest may have more concentrated cerebello-thalamic axons. This topographic response to low-frequency stimulation was not evident for postural tremor in the same patients.

The study demonstrates the strength of interventional techniques in probing, rather than passively observing, tremor phenomena. Pedrosa et al. (2013) challenged tremor circuits by stimulating the thalamus at 10 Hz, thus exposing the partly independent neural substrates of postural and intention tremors in ET. The worsening of ET during stimulation of the thalamus at low frequencies has previously been reported (Kuncel et al., 2007). Presumably, such low frequency stimulation leads to resonance phenomena in tremor circuits. Other recent work indicates that the effect of stimuli delivered to the ventrolateral thalamus at tremor frequency is dependent on their precise timing with respect to the tremor cycle, so that the amplitude of the tremor in the subsequent

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cycle can be suppressed as well as increased in ET (Cagnan et al., 2013). This amplitude modulation was accompanied by partial entrainment, whereby tremor tended to become in-step with the stimulation pulse train. Both the amplitude modulation and entrainment suggest that the ventrolateral thalamus and its connections play a key role in the production of tremor, although only postural tremor was tested. It would be interesting to follow-up the current findings by Pedrosa et al. (2013) by determining whether postural and intention tremors in ET have different susceptibilities to amplitude modulation and entrainment, and differences in how well tuned stimulation frequencies have to be to elicit these effects.

Indeed, the dependence of stimulation responses on the precise timing (phase) of stimuli with respect to the underlying tremor cycle may be a general feature of tremor, albeit with variations in the phase and frequency that optimally elicits this phenomenon. In the rest tremor of Parkinson's Disease (PD), for example, the phase-alignment between transcranial alternating current stimulation and the incumbent tremor has proven critical in determining the extent of amplification or suppression of tremor, though there was little sign of entrainment in this case (Brittain et al., 2013).

### Pathological underpinnings of different tremors

Pedrosa et al. (2013) stress the distinct origin of intention tremor in ET. Elsewhere, it has been hypothesised that loss of GABAergic tone in the locus coeruleus and deep cerebellar nuclei could upregulate cerebellar networks, leading to the emergence of tremor-frequency activity during movement (Helmich et al., 2013; Paris-Robidas et al., 2012).

The basis of the postural tremor in ET is even less well defined, but in PD the independent origins of different tremor expressions are becoming more firmly established. Recently, Loane et al. (2013) reported that action and postural tremors observed in PD, but crucially not rest tremor, correlate with serotonergic loss across the striatum and raphe nuclei, as measured by  $^{11}\text{C}$ -DASB PET. In contrast, dominance of rest tremor has been associated with degeneration of midbrain dopaminergic area A8 (retrosubthalamic area). Some postural tremors in PD seem closely related to rest tremor and have been termed re-emergent as the tremor begins a few seconds after resumption of a posture. It would therefore be of great interest to further ascertain whether re-emergent tremor is, like rest tremor, associated with degeneration of A8 rather than serotonergic loss across the striatum and raphe nuclei. The dominance of rigidity and bradykinesia meanwhile has long been associated with degeneration of area A9 (substantia nigra pars compacta; SNc; see Helmich et al., 2012). Accordingly, dopamine expression in striatum (recipient of SNc efferents) correlates with bradykinesia but fails to show any relationship with rest tremor (Pirker, 2003). This relationship instead emerges when considering dopamine in the pallidum (Pirker, 2003), a recipient of A8 efferents (see Helmich et al., 2012 for further discussion).

The above assumes that both pathological and phenomenological tremor types have distinct pathophysiological bases. However, this may be overly simplistic. An alternative view was recently proposed in relation to tremor in PD, which allows for the interplay between different systems in the genesis of tremor. The dimmer-switch hypothesis principally emerged following correlational studies between brain networks identified through functional magnetic resonance imaging and spontaneous fluctuations in resting tremor (Helmich et al., 2012). The amplitude of tremor was shown to correlate with activation in cerebello-thalamo-cortical pathways, whereas the timing of the onset of periods of prominent tremor was associated with activation of basal-ganglia networks. The implication in PD is that the dopamine deficient basal ganglia dysregulates, or unmasks, cerebello-thalamo-cortical networks, permitting the emergence of tremor at rest. The identification of a loss of serotonergic tone may offer a similar mechanism during motor engagement, permitting the emergence of action and postural

tremor in PD. Essentially this new view allows for a more extensive, multisystem, circuit underpinning of tremor.

### Task-related effects on tremor manifestation

But, as intimated above, tremor expression is not just the product of fixed, albeit possibly multiple circuit changes, but is also crafted by motor state or set, i.e. whether the motor system is partially disengaged at rest, or engaged in posture or movement. Here it is envisaged that different motor states up- and down-regulate subcircuits of the motor networks involved in tremor production. This results in a change of network balance, biasing contributions towards the active subsystems. In ET, for instance, engagement of cerebellar circuits during movement may heighten the contribution of these circuits during periods of intention tremor. Likewise, cerebellar circuits may be downregulated during postural tremor when the rapid update of feedforward models from the cerebellum is no longer required. In this way, a fixed pattern of pathological network change can result in different tremor manifestations according to the nature of the current motor state. In short, the various manifestations of tremor can be viewed as dysregulated, or unmasked circuits which are engaged and disengaged in task-specific fashion. The important notional concept being that manifestation may rely on activation biases within a broader tremorigenic network.

### Are tremor circuits per se pathological?

The growing evidence for relatively focal or multifocal deficits in selected neurotransmitter systems in different tremors raises the question of whether tremor circuits are primarily pathological or just dysregulated physiological phenomena, still malleable by variation in motor state. Here, it is interesting to note that activity about the usual tremor frequency (around 5 Hz) and its first harmonic (about 10 Hz) have regularly been observed in subcortical structures, often despite the complete absence of tremor (Brittain and Brown, *in press*).

In an earlier study, Pedrosa et al. (2012) reported the presence of multiple distinct tremor-clusters in ventrolateral thalamus, a finding that proved consistent across both ET and PD cohorts. A similar organisational topography was also reported in the subthalamic nucleus of patients with PD (Reck et al., 2009, 2010). These findings are interesting not only because they suggest that multiple and distributed clusters of neurons synchronised at tremor frequency form a general organisational principle of tremor, but also because they raise the intriguing possibility that multifocal nuclei of synchronised neurones are, in fact, a physiological feature of the healthy motor network, exposed when different pathological triggers and task requirements drive exaggerated oscillatory synchronisation and overflow to the periphery in the form of tremor. The degree of synchronisation between nuclei (as opposed to within a nucleus) then dictates how phase-coupled tremor is between body parts. Only in orthostatic tremor is this pronounced (Lauk et al., 1999); both ET and PD tremors are poorly synchronised across body parts (Raethjen et al., 2000; Ben-Pazi et al., 2001), suggesting that there is relatively little synchronisation between nuclei in the basal ganglia and thalamus. It remains to be seen if these foci also extend to motor cortical areas. Superimposed upon this is a temporal fluctuation in the degree of synchronisation between tremor and nuclei, with evidence that tremor can form transient periods of coupling with neural subpopulations (Hurtado et al., 2005; Moran et al., 2008). The implication is that for a given body part, tremor sometimes involves more than one nucleus, with their contribution ebbing and flowing over time.

A picture emerges in which pathological changes exaggerate oscillatory synchrony in selective components of an extensive and distributed motor network, but in which synchronisation within these components is further up and down-regulated from moment to moment according to motor state. Activity then spills out in the periphery in the form of tremor when synchronisation, through a combination of pathological and more dynamic physiological factors, reaches a particular intensity.

The central tremor-frequency correlates of EMG activity need not therefore represent a wholly pathological entity, but rather the dysregulation of a healthy motor network.

Although oscillatory synchronisation can be a feature of normal motor systems, such as the beta activity expressed in the cortico-muscular system, dysregulation does not necessarily have to involve physiologically oscillatory substrates within the healthy motor network to generate tremor. A shift in excitability, or an imbalance in network cooperation including that at the spinal level, can just as easily result in resonance phenomena (Elble, 1996; Lakin et al., 2012; McAuley and Marsden, 2000). In the presence of mechanical resonance and reafferent entrainment the precise origins of tremor may yet prove even more elusive.

### Clinical implications

These emerging views of tremor have clinical implications too. First, the acknowledgement that different distributions of pathological change can contribute to different tremor phenotypes, in turn implies different topographies for the consequent functional disturbances, opening up the possibility of surgical targeting based on patient specific tremor characteristics. For example, the work of Pedrosa et al. (2013) raises the possibility that the selection of the precise surgical target should take into account whether the amelioration of the intention or postural element of ET is the principal therapeutic objective in an individual patient. Perhaps in time a similar patient specific approach might be possible with pharmacological treatments as well.

Second, in understanding the nature of underlying circuit activities, more specific treatments for tremor can be developed. In the field of deep brain stimulation, two related approaches are being pursued. As mentioned earlier, evidence suggests that particular phase relationships can be selected between electrical stimuli and peripheral tremor that promote the amplitude attenuation of the subsequent tremor cycle, based on the assumption that these tremor bursts reflect threshold and subthreshold alternating cycles of depolarisation and hyperpolarisation of neuronal populations at the site of stimulation (Brittain et al., 2013; Cagnan et al., 2013). The utility of this approach may well be heightened by the harnessing of spike-timing dependent forms of plasticity through persistent stimulation at the optimal phase of tremor. The latter requires the tracking of tremor phase and stimulation in a closed loop mode. The other development is coordinated reset neuromodulation, which uses the phase-resetting properties of a stimulus (single pulse or high frequency pulse train) in order to decouple populations of locally synchronised neurons. The phase-reset of these neural populations, which are presumed to be spatially distributed within the stimulation target, is accomplished by applying pulses through different DBS electrode contacts at different times (Tass et al., 2012). This can be achieved open-loop without specifying the phase relationship between the stimulation and the underlying oscillations (Popovych and Tass, 2012). The therapeutic benefit of this technique may also potentially be promoted through the engagement of plasticity. In particular, a recent study in a non-human primate model of PD has suggested that coordinated reset neuromodulation can have pronounced and long-term plastic effects (Tass et al., 2012). Still, one of the major challenges for these more sophisticated and biologically informed interventions is to scale them so that they can, if necessary, control multiple *nidi*, themselves poorly coupled.

### Conclusions

The demonstration by Pedrosa et al. (2013) that one tremor manifestation can be selectively altered over another within the same individual has important inferences with regard to the underlying substrate responsible for tremor. Their work is timely as it coincides with an emerging notion that tremor may result through selective dysregulation within a broader tremorigenic network (Helmich et al., 2012). To this

pathological dysregulation we would add the possibility that the physiological motor state or set also alters the bias of subcircuits in the more widespread tremor network. As we have already alluded to, the putative presence of a broader tremorigenic network need not necessarily require that network per se to be pathological, just pathologically regulated.

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