In quest of the oscillator(s) in tremor: are we getting closer?

This scientific commentary refers to ‘The nature of tremor circuits in parkinsonian and essential tremor’ by Cagnan et al. (10.1093/brain/awu250).

Periodic oscillatory activity is abundant in the nervous system (Gray, 1994), both in health and in disease. Ion channels, membrane potentials, action potentials of single neurons and macroscopic brain regions all show periodic oscillations (hereafter ‘oscillations’). Within this framework, the neuronal oscillators that generate tremor, an oscillatory phenomenon in its own right, are being sought. However, attempts to define the neuronal substrate/s that generate rest and postural tremors in Parkinson’s disease and essential tremor face a number of conceptual difficulties. Correlation does not imply causality, thus strong coherence between tremor and neuronal oscillations could be the result of peripheral feedback to the nervous system. Many researchers have therefore focused on active manipulation of tremor phenomena. However, the ability to attenuate or modulate tremor by stimulating a certain brain structure does not necessarily prove that this locus is the tremor generator. What features can be used to distinguish between the tremor generator and the downstream neuronal pathways that transmit the oscillatory signal? In this issue of Brain, Cagnan et al. (2014) address this question and others by testing the effect of electric stimulation on tremor in patients who underwent deep brain stimulation (DBS) surgery.

Cagnan et al. compared three group of patients—individuals with Parkinson’s disease and chronically implanted electrodes in either the subthalamic nucleus (n = 7) or the ventrolateral thalamus (n = 8), and patients with essential tremor and electrodes in the ventrolateral thalamus (n = 10). Stimulation was applied for each individual at a frequency that was close to, but not identical to, that of the patient’s own tremor. Small differences between the frequencies of tremor and stimulation unlocked these two oscillatory processes. Therefore, in each tremor cycle, stimulation was applied at a slightly different phase. This enabled the researchers to test stimulation-induced phase locking and the effects on tremor amplitude of stimulation in different phases.

Recording limb tremor with accelerometers revealed stimulus-induced entrainment of tremor in all three groups, even though strong phase-locking was not observed. The tremor frequency per se did not change. While entrainment did not distinguish Parkinson’s disease from essential tremor, the precise timing of stimulation relative to the phase of tremor did separate these two diseases. In essential tremor, the stimulus modulated the amplitude of tremor differently when applied in different phases of the tremor cycle. This phase-dependent modulation was not observed in Parkinson’s disease, whether the ventrolateral thalamus or the subthalamic nucleus was stimulated.

Cagnan and colleagues’ work may be approached in the context of previous studies that have used phase resetting to look for tremor generators. In phase resetting a perturbation that is delivered to an oscillatory system changes the timing of the following cycles (Fig. 1). It has generally been assumed that only perturbations applied to the oscillator itself, and not to other downstream

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structures, will have this effect. Early work in the field applied either mechanical (Lee and Stein, 1981; Britton et al., 1992) or electrical (Hufschmidt, 1963; Britton et al., 1993a) perturbations to the tremulous limb of patients with Parkinson’s disease or essential tremor. Phase resetting of tremor in these studies was considered as evidence for the involvement of peripheral feedback mechanisms in generating these tremors. Transcranial magnetic stimulation was later used to test phase resetting by stimulating the cerebral cortex (Britton et al., 1993b; Pascual-Leone et al., 1994; Ni et al., 2010) or the cerebellum (Ni et al., 2010) and served as evidence for the presence of central generators.

The results presented in all of the above studies are intriguing but their interpretation is not straightforward. Coupling of interconnected oscillators and multiple feedback loops can yield complex oscillations. Perturbing any one of these oscillators or their reciprocal connections with the periphery (muscles and joints) can lead to phase resetting of the entire system. This is highly relevant to neuronal systems in which a high degree of connectivity exists. It is thus reasonable to assume that tremor results from coupling of oscillators in different sites, both in the peripheral and CNS (Lee and Stein, 1981). Moreover, while to the naked eye it often seems as if the frequency of tremor in a given Parkinsonian patient is remarkably similar in different muscles of the extremities and trunk, coherence analysis reveals this not to be the case. Tremor in different extremities, even on the same body side, is not coherent (Raethjen et al., 2000). This indicates that searching for a single generator may be fruitless.

However, while the search for the neuronal networks that generate tremor is still on, the clinical implications of Cagnan and colleagues’ findings are already apparent. Today, deep brain stimulation devices that are used to treat Parkinson’s disease or essential tremor are not closed by a feedback loop. The neurologist programs the stimulation parameters of these devices and adjusts them from time to time. Minute-to-minute fluctuations in tremor severity, however, may benefit from a closed loop device that can optimize performance, minimize side effects of stimulation and prolong battery life (Little et al., 2013). The work of Cagnan et al. suggests that the optimal feedback algorithm may differ between Parkinson’s disease and essential tremor. Whereas in essential tremor a strategy to lock the deep brain electrical stimulation to a certain phase of the tremor is potentially beneficial, in Parkinson’s disease this strategy would probably fail.

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Figure 1 Application of a perturbation (red line) at a random time to an oscillatory process represented on recurrent trials by black dots. This perturbation can either have no effect on the oscillatory process (A) or can reset the following cycles (B). These two scenarios represent the extremes of a spectrum of results of phase resetting tests.