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Tracking the central and peripheral origin of tremor

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Human motor control is a highly complex process that requires extraordinary precision to achieve optimal speed and accuracy of each movement. The dysfunction of the motor control system leads to a variety of movement disorders such as parkinsonism, dystonia, and ataxia. How the nervous system governs the movements in both physiological and pathological conditions in real time remains unclear, partly due to the rather complex nature of movements and the corresponding neurophysiology. Tremor is a type of movement with enriched information (phase, frequency, and amplitude) that can be tracked in real time to correlate with oscillatory neuronal activities in the brain, providing a very unique platform to study human motor control (McAuley and Marsden, 2000). In addition, the distinct frequencies of different types of tremor can allow to separate each component of movements derived from diverse sources.

Normally, human limbs have naturally-occurring tremor, called “physiological tremor”, which is originated from the unique motor unit firing properties and the mechanical and reflex resonance in the sensori-motor loop (McAuley and Marsden, 2000). Physiological tremor is thus considered “peripheral” in origin, and weight loading will decrease the tremor frequency by altering the biophysical property of the reflex loop (Raethjen et al., 2004; Lakie et al., 2015). On the other hand, essential tremor (ET), the most common movement disorder (Louis and Ferreira, 2010), is thought to be generated from the cerebello-thalamo-cortical loop, possibly related to the abnormal Purkinje cell synaptic organization (Lin et al., 2014), and could be modulated by GABAergic neurotransmission because a subset of ET patients responds to alcohol (Lou and Jankovic, 1991). Thus, ET is considered “central” in origin (Hellwig et al., 2001; Lu et al., 2015). Weight loading will not decrease the frequency of centrally generated tremor (Gironell et al., 2004) but rather dampen the amplitude because the central driver for tremor remains unchanged. Both types of tremor (central or peripheral in origin) are at the similar frequency; therefore, it is often difficult to distinguish one from another (Fig. 1A).

While ET has a predominant central driving component, the peripheral component at the same frequency can also contribute to the tremor. To further explore the relationship between the central and peripheral components of tremor, Cao et al., in this issue of *Clinical Neurophysiology*, conducted a study to address this important question (Cao et al., 2018). They observed that weight loading in a subset of ET patients can separate the central and peripheral components of tremor (Fig. 1B). Interestingly, octanoic acid, an analogue to alcohol, can suppress both central and peripheral components of tremor to a similar degree (Fig. 1C). Therefore, the authors concluded that these two components of tremor in ET patients are closely related and might be both modulated by the GABAergic system. They further hypothesized that the peripheral component might depend on the central component of tremor.

This discovery is important in our understanding of ET, which can constitute several different components. This notion might help to explain some degrees of clinical heterogeneity of ET (Bhatia et al., 2018) based on the preferential involvement of central vs. peripheral components. In addition, different interventions have diverse effects on each tremor component. For example, weight loading alters the tremor frequency of the peripheral component whereas the GABAergic manipulation changes the overall tremor amplitude of both the central and peripheral components. Elucidating the contribution of each component of tremor will have implications in personalized treatment for tremor disorders.

How does the current discovery help to advance our knowledge of ET pathophysiology? Since both central and peripheral components of tremor can be suppressed by octanoic acid to a similar degree, peripheral tremor can possibly be modulated by the same oscillatory source that drives central tremor. For instance, the central driver can tune the intrinsic oscillatory activities of each motor unit into more synchronized fashion, which can determine the overall amplitude of tremor. An alternative possibility is that octanoic acid can suppress tremor at the level of the spinal cord, which will affect both central and peripheral components since both types of tremor will eventually be summated at the spinal cord and/or musculature levels. Renshaw cells, the key neurons for the sensori-motor feedback loop in the spinal cord, express both glycinergic receptors and GABA_A receptors (Geiman et al., 2002). The latter are the main receptors for alcohol action in the nervous system (Davies, 2003). Therefore, octanoic acid can possibly influence both central and peripheral tremor by altering the physiology of Renshaw cells. The third possibility is that octanoic acid might exert its effects at multiple levels in the neural axis for both tremor components. Nevertheless, further dissection of central and peripheral components, as well as their interactions in ET, can be facilitated by simultaneous measurement of tremor and central oscillations (Hellwig et al., 2001; Raethjen et al., 2007). The detailed mechanism relies on adequate animal models recapitulating chronic, progressive and kinetic tremor, which remains to be established.

There are some limitations in the current study. The sample size is small for which the statistical analysis should be considered exploratory. In addition, ET patients have been pre-selected for alcohol responsiveness based on the strict selection criteria (Haubenberger et al., 2013); thus, whether this observation can be generalized to a broader population remains to

be studied. Moreover, peripheral tremor can only be detected in 22% of subject in the current study, which means that the methodology to measure tremor is insensitive to reliably detect such peripheral component or the weight loading protocol does not reliably separate out the central and peripheral components in all subjects. Nonetheless, the current study provides an important conceptual framework for the future investigation.

In summary, the present study advances our understanding of different components of tremor, which might have therapeutic implications. Future studies can focus on the effects of different interventions, such as deep brain stimulation and/or focused ultrasound for the thalamus, on these two components of tremor. Coupling with neurophysiology measurement (electroencephalogram or magnetoencephalogram) will be another powerful tool to study the relationship between oscillatory activities and tremor with these interventions. The detailed studies of each tremor component will push forward novel therapies of tremor and will likely to further our knowledge of movement control in humans.

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Fig. 1.

The central and the peripheral components of tremor cannot be distinguished at baseline (A). Upon weight loading, the peripheral tremor shifts to a lower frequency (B). Octanoic acid treatment suppresses both central and peripheral tremor amplitude to a similar degree without altering the frequencies of tremor, indicating that these two components might be closely related (C).