

In Response to:

Hassan A, Caviness J. Slow Orthostatic Tremor – Review of the Current Evidence. *Tremor Other Hyperkinet Mov*. 2019; 9. doi: 10.7916/tohm.v0.721

Editorials

Slow Orthostatic Tremor and the Case for Routine Electrophysiological Evaluation of All Tremors

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Citation: Torres-Russotto D, Elble RJ. Slow orthostatic tremor and the case for routine electrophysiological evaluation of all tremors. *Tremor Other Hyperkinet Mov*. 2019; 9. doi: 10.7916/tohm.v0.740

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Editor: Elan D. Louis, Yale University, USA

Received: October 14, 2019; **Accepted:** October 23, 2019; **Published:** November 26, 2019

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Funding: None.

Financial Disclosures: None.

Conflicts of Interest: The authors report no conflicts of interest.

Ethics Statement: Not applicable for this category of article.

In this issue of the journal, Hassan and Caviness reviewed the controversial topic of slow orthostatic tremor (OT).¹ Based on their review of the relevant literature, Hassan and Caviness concluded that “multiple lines of evidence separate slow OT from classical OT,” but they also noted that “clinical and electrophysiologic overlap may occur.” We were invited to discuss the significance of this overlap within the context of tremor classification.

The Task Force on Tremor of the International Parkinson and Movement Disorder Society (MDS) recently recommended that classical or so-called primary OT be clearly distinguished from OTs with frequencies less than 13 Hz.² Primary OT is a generalized high-frequency 13–18 Hz isolated tremor syndrome that becomes symptomatic upon standing. Confirmation of the tremor frequency is typically accomplished with electromyography (EMG), using skin electrodes. Spectral analysis of motion transducer recordings and low-pass-filtered rectified EMG reveals a narrow peak at 13–18 Hz, an occasional subharmonic peak at one-half or one-third the fundamental frequency, and occasional superharmonic peaks at integer multiples of the fundamental frequency. Coherence analysis reveals uniquely high coherence (linear correlation squared) of 0.9–1 between muscles of opposite sides of the body (Figure 1). This bilateral EMG coherence at 13–18 Hz is not seen in other forms of tremor.³

The electrophysiologic overlap between slow and primary OT, noted by Hassan and Caviness, seems largely based on their observation that 5 of 70 reported patients with slow OT also had classic 13–18 Hz OT. However, these five patients actually exhibited classic high-frequency primary OT with intermittent subharmonic oscillation at one-half or one-third the fundamental frequency. For example, the patient described by Thompson and coworkers⁴ clearly exhibited a 16-Hz OT that intermittently shifted to a subharmonic 8-Hz frequency. This is not the same as true low-frequency OT in which the fundamental frequency is less than 13 Hz, and Thompson and coworkers did not refer to the subharmonic 8-Hz oscillation as slow OT. Similar one-half or one-third subharmonic oscillation occurred in the cases of Deuschl, Cano, and Setta (see Table 1 of Hassan and Caviness). These cases are not examples of slow OT, which has a fundamental frequency less than 13 Hz. All pathologic tremors emerge from nonlinear oscillatory behavior of neural networks, and subharmonic and superharmonic oscillation is a common characteristic of non-linear oscillators.⁵ Computer models of thalamocortical oscillation are conducive to subharmonic and superharmonic oscillation.^{5,6} Slow OT must be distinguished from subharmonic oscillation of classic OT. Subharmonics in primary OT are clinically important because the lower frequencies of oscillation produce a more visible and symptomatic

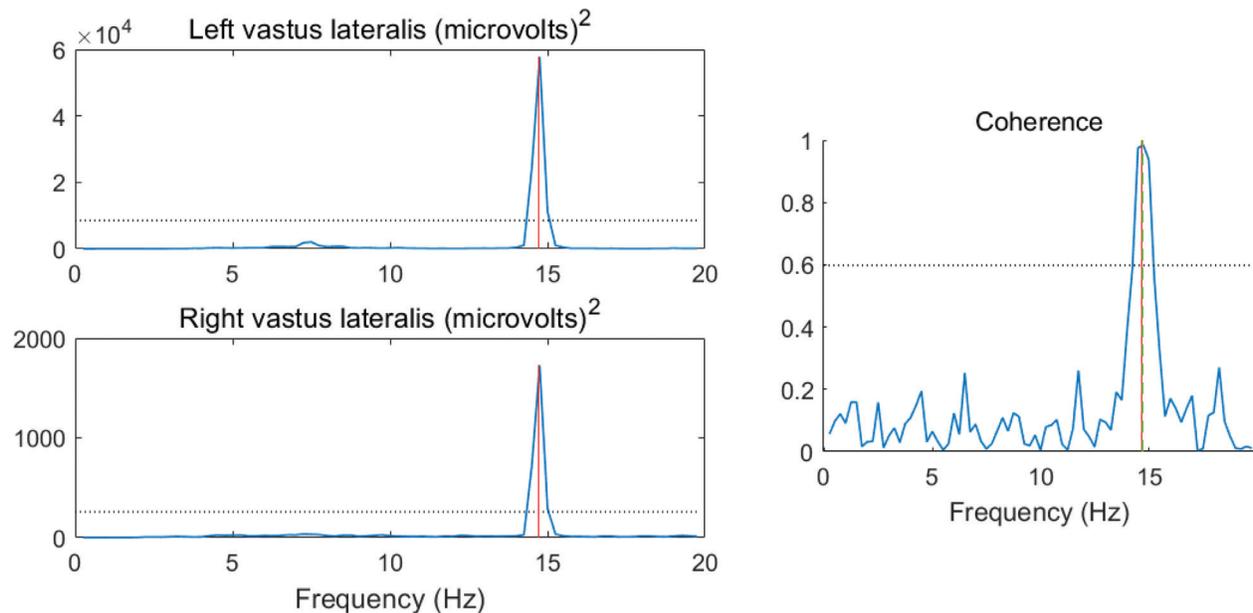


Figure 1. Primary Orthostatic Tremor in a 62-Year-Old Man with a 14-Year History of Unsteadiness and Shakiness in the Lower Limbs When Standing. Full-wave rectified, low-pass-filtered (-3 dB at 50 Hz) EMG of the right and left vastus lateralis was recorded with skin electrodes in a bipolar configuration, and the recordings were analyzed with Fourier spectral and coherence analysis. The power spectra of the two muscles contain a single narrow spectral peak at 14.7 Hz, and the coherence is nearly 1 at this frequency. However, there was a 70° phase difference in the tremors of the two limbs. The horizontal dashed lines are the 95% confidence limits for statistically significant spectral power and coherence.

tremor due to less attenuation by the low-pass filtering properties of skeletal muscle.⁴

The clinical overlap discussed by Hassan and Caviness is based largely on the observations that slow OT can occur as an isolated tremor syndrome and that tremor with the characteristics of primary OT has occurred in conjunction with various other conditions, such as dementia, Parkinson disease, and hereditary ataxia. The combination of classic OT with other neurologic signs or conditions is called primary OT plus.² The pathophysiologic role of the associated conditions is unclear. However, there is noteworthy evidence that 13–16 Hz lower limb EMG bursts can be induced in normal people in whom balance is threatened by vestibular galvanic stimulation or by leaning backward.⁷ Thus, many conditions conceivably could affect the clinical expression of primary OT simply by affecting balance. In most instances, primary (classic) OT is an isolated tremor syndrome,⁸ and slow OT is typically a combined tremor syndrome that is pathophysiologically related to a variety of specific neurologic conditions.⁹ Virtually, all cases of “isolated” slow OT in Table 1 of Hassan and Caviness have atypical tremor characteristics that do not resemble primary OT. For example, the EMG discharges in Figure 1 of Coffeng et al.¹⁰ are not convincingly coherent and are clearly arrhythmic.

Hassan and Caviness object to the MDS task force terminology of pseudo-OT instead of slow OT. Pseudo-OT emphasizes the distinction from primary OT. Slow OT emphasizes the frequency of tremor. Neither term does a good job of emphasizing the clinical and

electrophysiologic heterogeneity of slow (pseudo-) OT. The new MDS tremor classification system encourages precise axis 1 definitions of tremor syndromes, with no assumption of underlying etiology or pathophysiology.² Axis 1 syndromes are defined in terms of historical features, associated physical and neurological signs, distribution of tremor, tremor activation conditions, tremor frequency, and laboratory tests. Primary OT is the only tremor syndrome that is defined in terms of clinical and electrophysiologic properties because the electrophysiologic properties of primary OT are unique.² Given the obvious clinical and electrophysiologic heterogeneity of slow (pseudo) OT, there is an obvious need for carefully defined syndromic subtypes.

In the absence of a well-designed multicenter trial, one could argue that the defined 13–18 Hz frequency range for primary OT may be biased. One reason for this concern is that 10–13-Hz OT has characteristics that overlap with primary OT.¹¹ However, it is clear that very few cases fall in the 10–13 Hz frequency range, and at least some of these cases have features that are not consistent with primary OT.¹¹ It is important to remember that axis 1 tremor syndromes are merely clinical classifications that will hopefully lead to effective treatment and identification of the axis 2 etiology for a particular patient. An axis 1 syndrome may not be and need not be comprehensive in its characterization of all patients with a specific axis 2 etiology. Primary OT is arguably the most rigorously defined axis 1 tremor syndrome. Therefore, one would hope that the consistent use of this syndrome will facilitate the discovery of effective treatment, underlying pathophysiology, and etiology.

Most clinicians do not use electrophysiology routinely in the assessment of other tremor disorders even though tremor frequency is now easily measured at the bedside with portable transducers and smartphones.^{12,13} Tremor frequency is often categorized as <4, 4–8, 8–12, and >12 Hz.² The frequency of most pathologic tremors (e.g., essential tremor, Parkinson tremor, and dystonic tremor) falls between 4 and 8 Hz. Myorhythmia is defined in terms of its unusually low-frequency range of less than 4 Hz. Enhanced physiologic tremor, rhythmic cortical myoclonus (also known as cortical tremor), and slow OT commonly have a frequency range of 8–12 Hz. Functional (psychogenic) tremor typically has a variable frequency that can be altered or entrained by voluntary rhythmic movement of the contralateral limb.¹⁴ There is considerable overlap in tremor frequencies among various tremor syndromes.¹⁵ Tremor frequency has not been prospectively, longitudinally, and objectively measured in most tremor syndromes, but studies of this type have revealed a very slow decline in tremor frequency in essential tremor¹⁶ and no frequency change in primary OT.⁸

The fairly routine performance of electrophysiological tests in patients with orthostatic shakiness has led to the discovery of slow OT and orthostatic myoclonus, which also have been reviewed by Hassan and Caviness.^{1,17,18} Tremor frequency and coherence are only two of many measures that could prove useful in the characterization of other tremor syndromes. For example, tremor rhythmicity and frequency stability may be useful in distinguishing Parkinson tremor from essential tremor,¹⁹ and many other electrophysiologic properties of tremor are being explored for their utility in tremor classification.¹⁴ Ultimately, the sensitivity and specificity of each electrophysiologic test should be confirmed in multiple patient populations and by multiple investigators. Ideally, this should be accomplished with a well-designed multicenter trial, and such validity studies are an expressed mission of the MDS Tremor Study Group (<https://www.movementdisorders.org/MDS/About/Study-Groups/MDS-Task-Forces/Task-Force-on-Tremor.htm>). The tremor frequency and coherence properties of primary OT have been reproduced by many investigators, as reviewed by Hassan and others.^{1,17} However, there has been no attempt to standardize the methods of recording and analysis, and the range of acceptable contralateral limb coherence has not been specified, although published reviews suggest that 0.8 is the lower limit for EMG coherence in the lower limbs.

Most smartphones contain motion transducers (inertial measurement units) that are capable of recording pathologic tremor. Tremor amplitude and frequency can be measured from any body part that is amenable to secure attachment of a smartphone in a manner that does not impede or otherwise alter the mechanics of movement. The limitations of smartphones in measuring tremor amplitude have been discussed and reviewed in this journal.¹² Nevertheless, tremor frequency can be measured reliably with these devices, and this has been demonstrated for OT in the lower limbs.¹³ Simultaneous EMG recordings from skin electrodes on contralateral lower limb muscles are needed to demonstrate the characteristic high coherence and motor unit entrainment at 13–18 Hz. These recordings are easily obtained with most EMG machines used in the clinic. Coherence analysis of the digitized

recordings can be accomplished with computer programs written in MATLAB or Python, and commercially available software is also available (e.g., www.sigview.com). Coherence is a statistical estimate of the squared linear correlation between two signals at a particular frequency. A significant coherence occurs when the two signals have a fixed-phase relationship, which is not necessarily synchronous. The coherent EMG recordings in primary OT are typically not synchronous (i.e., phase = 0), as illustrated in Figure 1, and the significance of this has not been studied. As in all statistical tests, caution and knowledge are required to compute and interpret coherence correctly.²⁰ Visual estimates of coherence (i.e., synchrony) between EMG recordings are not reliable. The use of motion sensors to examine bilateral coherence could be influenced by tremor from one side of the body being mechanically transmitted to the other side.

Primary OT has been well defined for more than 20 years, and while this condition is rare, it is no longer reportable unless it is observed in an unusual clinical context (e.g., in association with some other neurological condition). This leads to substantial reporting bias, making literature reviews difficult to interpret from an epidemiologic standpoint. There has never been a cohort or case-control epidemiologic study of primary OT. Electrophysiology would be needed to search for this tremor because it is typically not visible and conceivably could be asymptomatic in some people.

In conclusion, primary OT is now by definition an isolated tremor syndrome, and electrophysiologic methods are necessary for a rigorous diagnosis.² We suspect that electrophysiologic methods will become increasingly valuable in the axis 1 definition of other tremor syndromes. The more rigorously we define axis 1 syndromes, the easier it will be to compare and interpret studies of treatment, pathophysiology, and etiology. Evidence-based guidelines are needed for all electrophysiologic tests that are used in this manner. Standardized software and assessment protocols would be very useful to clinicians who are attempting to decipher the complexities of tremor disorders.

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