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Review

The clinical and electrophysiological investigation of tremor

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HIGHLIGHTS

- This chapter provides an overview of clinical and electrophysiological tools for measuring and classifying tremor.
- The distinguishing clinical and electrophysiologic features of the different forms of tremor are explained.
- The pathophysiology of the different tremors is reviewed with an emphasis on electrophysiological methods.

ABSTRACT

The various forms of tremor are now classified in two axes: clinical characteristics (axis 1) and etiology (axis 2). Electrophysiology is an extension of the clinical exam. Electrophysiologic tests are diagnostic of physiologic tremor, primary orthostatic tremor, and functional tremor, but they are valuable in the clinical characterization of all forms of tremor. Electrophysiology will likely play an increasing role in axis 1 tremor classification because many features of tremor are not reliably assessed by clinical examination alone. In particular, electrophysiology may be needed to distinguish tremor from tremor mimics, assess tremor frequency, assess tremor rhythmicity or regularity, distinguish mechanical-reflex oscillation from central neurogenic oscillation, determine if tremors in different body parts, muscles, or brain regions are strongly correlated, document tremor suppression or entrainment by voluntary movements of contralateral body parts, and document the effects of voluntary movement on rest tremor. In addition, electrophysiologic brain mapping has been crucial in our understanding of tremor pathophysiology. The electrophysiologic methods of tremor analysis are reviewed in the context of physiologic tremor and pathologic tremors, with a focus on clinical characterization and pathophysiology. Electrophysiology is instrumental in elucidating tremor mechanisms, and the pathophysiology of the different forms of tremor is summarized in this review.

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Contents

1. Definition and measurement of tremor

1.1. Definition of tremor and tremor syndromes

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part (Bhatia et al., 2018). This is a general definition that covers all forms of tremor including normal physiologic tremor. While the focus of this review is pathologic tremor, it is important for the clinical neurophysiologist to understand the distinguishing features of normal tremor, which are reviewed in Section 2.

The full spectrum of tremors was described in a consensus statement of the Movement Disorder Society in 1998 (Deuschl et al., 1998a), and this statement was revised in 2018 (Bhatia et al., 2018). The new classification consists of two axes: clinical features in axis 1 and etiology in axis 2. The clinical features include medical history (age at onset, evolution, past medical and family history, and alcohol and drug sensitivity), tremor characteristics (body distribution, activation conditions, and tremor frequency), associated signs (signs of systemic illness and neurologic signs), and laboratory tests (electrophysiological tests, structural and receptor imaging, serum biomarkers). The clinical features often constitute a tremor syndrome (Fig. 1). If a specific axis 2 etiology (e.g., specific genetic mutations, systemic illnesses) is not known, the axis 2 classification defaults to idiopathic acquired or heredofamilial.

Rhythmicity varies among tremors, and there is no accepted minimum rhythmicity for tremor. Rhythmicity decreases with successful treatment and tends to increase with increasing severity, likely reflecting greater entrainment of motor pathways (Vaillancourt et al., 2001, Vaillancourt et al., 2003). However, there is also an impression that some forms of tremor (e.g., dystonic tremor) are less rhythmic than others. Entrainment of motor pathways can be assessed by coherence analysis between peripheral tremor recordings (transducer or EMG) and EEG or MEG. This approach has demonstrated pathophysiologic involvement of the

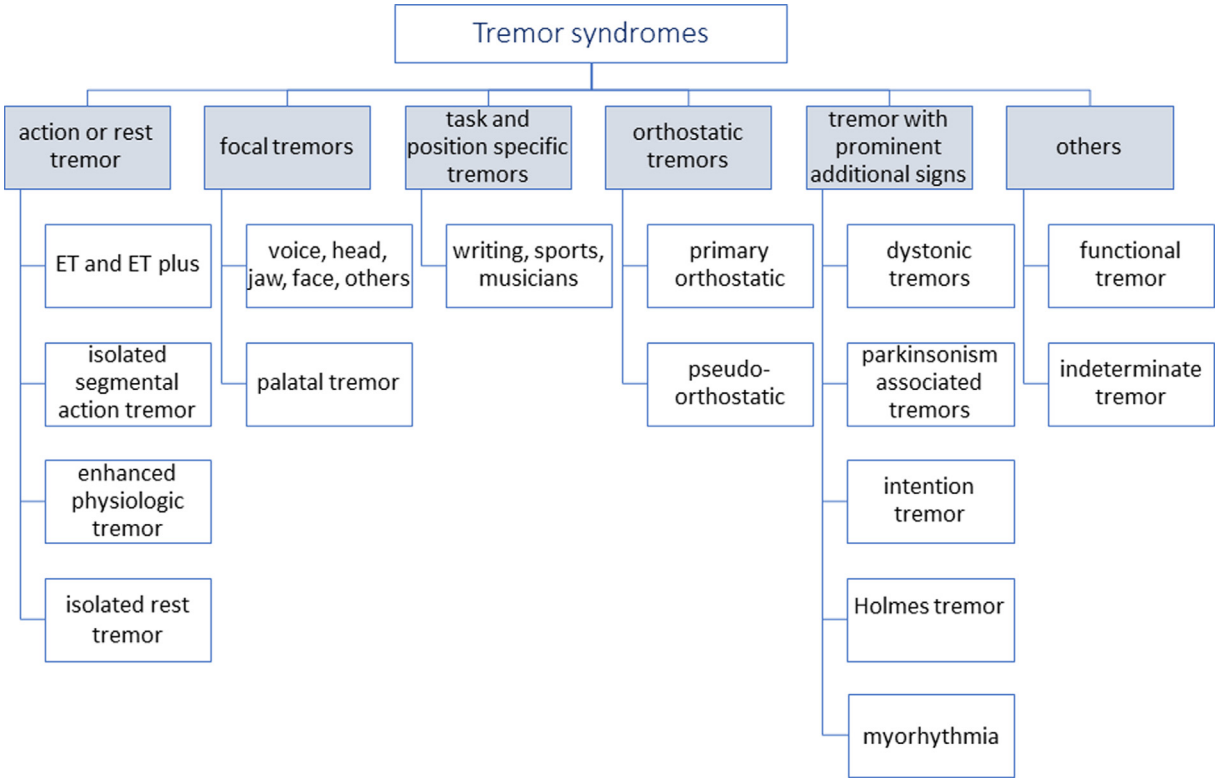

Fig. 1. The tremor syndromes based on clinical criteria according to the most recent tremor classification (Bhatia et al., 2018).

cerebellothalamocortical pathway in all forms of tremor, including physiologic tremor and voluntarily mimicked tremor (Muthuraman et al., 2018, Schnitzler and Gross, 2005). An unsolved issue is whether rhythmic cortical myoclonus or rhythmic asterixis should be regarded as a tremor (Latorre et al., 2020, van Rootselaar et al., 2020). Thus, the definition of tremor is clinical and is unsettled with respect to the degree of rhythmicity required.

1.2. The measurement of tremor

1.2.1. The clinical measurement of tremors

The clinical rating scales for tremor have been reviewed extensively (Elble et al., 2013). The Fahn-Tolosa-Marin scale (Fahn et al., 1993) is validated and commonly used for all tremors. The Essential Tremor Rating Assessment Scale (TETRAS) is a well validated scale designed specifically for essential tremor and has the advantage of better resolution for high amplitude tremors (Ondo et al., 2018). However, TETRAS has no assessment of rest tremor. Subscores of the Unified Parkinson Disease Rating Scale (UPDRS) have been used for tremor in Parkinson disease (Forjaz et al., 2015), but the Fahn-Tolosa-Marin scale seems to outperform them (Pinter et al., 2020). Subtle clinical signs (e.g., unusual posturing of the limbs or head, jerky tremors) that are suggestive of other movement disorders are important for deeper phenotyping of patients with tremor, but inter-rater reliability appears to be poor (Becktepe et al., 2021). Electrophysiologic methods are at least complementary to rating scales in the quantification of tremor, and electrophysiology is crucial to the characterization of tremor beyond what is provided by routine clinical examination (Haubenberger et al., 2016). Tremor ratings are strongly correlated with log-transformed transducer measures of tremor amplitude, consistent with the Weber-Fechner law of psychophysics (Elble, 2018, Elble et al., 2006).

1.2.2. Overview of electrophysiologic measurements of tremor

Electrophysiology is appropriately viewed as an extension of the neurological exam, and it is therefore fitting that the results of electrophysiologic tests are considered in Axis 1 classification. Validated electrophysiologic tests are diagnostic of physiologic tremor, functional tremor, and primary orthostatic tremor. However, electrophysiology is used most commonly to quantify tremor amplitude and frequency and to address specific questions pertaining to tremor classification and pathophysiology. These questions and required methods are summarized in Table 1 and are briefly reviewed in this section. They are subsequently discussed in the context of physiologic and pathologic tremors

Table 1
Electrophysiologic methods for tremor classification and pathophysiologic studies.

Clinical question	Electrophysiologic tools	Electrophysiologic results
Is the movement a tremor?	Motion transducers Surface EMG	Spectral analysis demonstrating a spectral peak with narrow bandwidth
How rhythmic or regular is tremor?	Motion transducers Surface EMG	Bandwidth of spectral peak Cycle-to-cycle frequency variability Entropy
Is the tremor abnormal?	Motion transducers Surface EMG	Amplitude exceeding control values and rhythmic EMG that is coherent with tremor.
Does tremor emerge primarily from stretch reflex pathways?	Motion transducers Surface EMG	Tremor frequency is a function of reflex arc length, joint stiffness, and joint inertia
Does tremor emerge primarily from central neural networks?	Motion transducers Surface EMG	Tremor frequency does not vary significantly with reflex arc length, joint stiffness, or joint inertia
Is tremor in different body parts linearly correlated?	Motion transducers Surface EMG	Statistically significant coherence at tremor frequency among body parts.
Does rest tremor exist, and how is it affected by voluntary muscle activation?	Motion transducers Surface EMG	Tremor is present during relaxation. Tremor may be suppressed with voluntary muscle activation.
Is tremor suppressed or entrained by voluntary movements of contralateral body parts?	Motion transducers Surface EMG	Tremor frequency shifts to the frequency of voluntary movement. Tremor is suppressed by movement of other body parts
What is the significance of rhythm resetting in response to external stimuli?	Motion transducers Surface EMG Mechanical, electrical, or magnetic stimulator.	The phase of the tremor rhythm is permanently shifted.
Is tremor linearly correlated with rhythmic brain activity?	Motion transducers Surface EMG EEG MEG	Statistically significant coherence between tremor recordings and EEG or MEG source analysis
Is tremor non-linearly correlated between muscles	Motion transducers Surface EMG	Statistically significant cross-frequency coupling between muscles

1.2.3. Is the movement a tremor?

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part (Bhatia et al., 2018). Rhythmic movements are easily recorded with a motion or force transducer, and associated motor unit activity is recorded with needle or wire electrodes or, more commonly, with surface EMG (sEMG) electrodes. Rhythmicity in these recordings can be quantified with frequency analysis methods such as half-power bandwidth of the Fourier analysis (Elble and McNames, 2016) and with measures of cycle-to-cycle variability, referred to as the tremor stability index (TSI) (di Biase et al., 2017). Unfortunately, the degree of rhythmicity required for classification as tremor has never been specified. No tremor is perfectly rhythmic, and rhythmicity varies among tremors. Therefore, the definition of tremor contains an ambiguity that needs to be addressed by quantitative electrophysiology, which will possibly provide a better definition.

At a minimum, there must be a statistically significant spectral peak because if there is no spectral peak, there is no tremor (i.e., rhythmic oscillation). In most instances, the presence of a spectral peak will be obvious by visual inspection and can be tested statistically when a peak is in doubt (Elble and McNames, 2016). The half-power bandwidth of the spectral peak typically will be 2 Hz or less (Fig. 2), which is considered a narrow bandwidth and therefore a high rhythmicity.

A power spectrum is the average distribution of signal (tremor) power (variance) over frequency. Tremor may be very intermittent or transient during a long recording, and the presence of tremor can therefore be obscured by other signal variation. Time-frequency spectral plots (spectrograms) are used to detect transient tremor activity (Elble and McNames, 2016).

1.2.4. How rhythmic or regular is tremor?

The half-power bandwidth is a well-known measure of rhythmicity. The half-power bandwidth becomes increasingly narrow as the oscillation becomes finely “tuned” to a single frequency. An oscillation at one frequency produces a single spike in the Four-

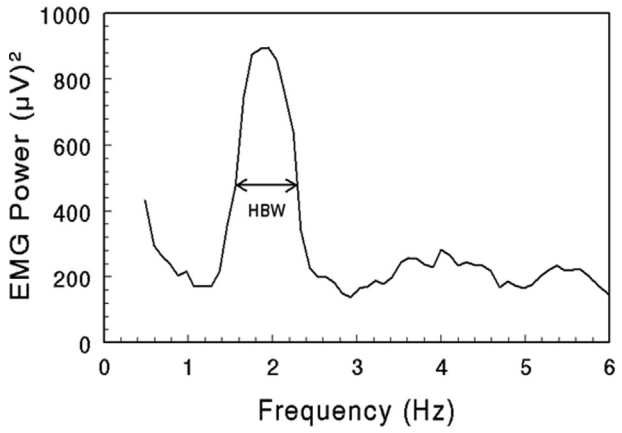

Fig. 2. Fourier power spectrum of rectified-filtered surface EMG recorded with nasopharyngeal electrodes from a patient with the syndrome of progressive ataxia with palatal tremor. Palatal tremor was previously called palatal myoclonus but was renamed palatal tremor because of its rhythmicity. The half-power bandwidth (HBW) is 0.88 Hz.

ier spectrum (Elble and McNames, 2016). Mechanical oscillators, for example, become increasingly finely tuned with reductions in viscous damping, which can be estimated with half-power bandwidth (Papagiannopoulos and Hatzigeorgiou, 2011).

It is also possible to measure cycle-to-cycle frequency variability in the time domain. This approach is particularly useful in documenting abrupt or transient changes in rhythmicity that are associated with specific events such as an external mechanical or electromagnetic stimulus or a voluntary movement. For example, this approach is useful quantifying the effects of rhythmic voluntary tapping or ballistic movement of a contralateral limb in functional tremor (O'Suilleabhain and Matsumoto, 1998). The interquartile range of cycle-to-cycle frequency variability has been called the Tremor Stability Index (TSI), referring of course to frequency stability (di Biase et al., 2017). The TSI is the interquartile range of frequency variability over a specific recording time and therefore assumes that the time series is statistically stationary.

Yet another measure of regularity (rhythmicity) is entropy. Entropy is greater when tremor is less rhythmic. Physiologic tremor has greater entropy than pathologic tremors because physiologic tremor has multiple sources of variability (joints with differing natural frequencies, random unfused muscle contractions, variable reflex modulation of motor units, cardioballistics, and central neurogenic oscillation; see Section 2) that are not entrained into a stable limit-cycle oscillation. By contrast, pathologic tremors behave more-or-less like a limit-cycle oscillator (Elble et al., 1992, Gil et al., 2010, Vaillancourt et al., 2001). There are several mathematical algorithms for estimating entropy, sample entropy and approximate entropy being most common (Richman and Moorman, 2000), and MATLAB software for these algorithms is available (https://www.mathworks.com/help/predmaint/ref/approximateentropy.html).

Measures of regularity are not likely to be diagnostic for a particular tremor disorder unless the tremor disorder is characteristically arrhythmic (Panyakaew et al., 2020). For example, rhythmic cortical myoclonus (cortical tremor) has rhythmicity that some argue is too low for a classification as tremor (Latorre et al., 2020, van Rootselaar et al., 2020). Most tremor disorders become increasing rhythmic as severity (amplitude) increases (e.g., PD and ET) (Vaillancourt et al., 2001, Vaillancourt et al., 2003), reflecting greater entrainment of motor pathways that produces limit-cycle oscillation behavior. Not surprisingly, rhythmicity decreases with successful treatment and tends to increase with increasing severity (Vaillancourt et al., 2001, Vaillancourt et al., 2003).

1.2.5. Is the tremor abnormal?

Tremor that statistically exceeds normal amplitudes is abnormal, but mild pathologic tremor commonly fluctuates into the upper range of normal (Elble, 1986). Therefore, distinguishing mild pathologic tremor from physiologic tremor generally requires the demonstration of a tremor property that is not seen in physiologic tremor. The characteristics of physiologic tremor are reviewed in Section 2, and examples of how physiologic tremor can be replaced by pathologic tremor (i.e., essential tremor) have been published (Elble et al., 2005). Pathologic tremor, in contrast to normal physiologic tremor, is always associated with rhythmic bursts of EMG at the tremor frequency, and most pathologic tremors (e.g., essential tremor, Parkinson tremor and dystonic tremor) have a frequency that is not a function of reflex arc time or limb mechanics, as discussed throughout the remainder of this review.

It should also be noted that physiologic tremor is so low in amplitude that it cannot be detected by many motion transducers. This is true for many motion transducers in smartphones, smart devices, digitizing tablets, and tablet computers. Sensitivity to physiologic tremor can be checked by recording motion from the desired body location and performing spectral analysis on the recorded movement. Tremor is reflected by a consistent spectral peak at the tremor frequency (Section 2).

1.2.6. Does tremor emerge primarily from stretch reflex pathways?

Tremor emerging from stretch-reflex oscillation will have a frequency that is a function of reflex arc length/latency (i.e., loop time) and/or the mechanical properties of the limb, which determine the mechanical resonant frequency of the oscillating joint. These properties of "mechanical-reflex" oscillation are discussed in the context of physiologic tremor in Section 2 and are illustrated in studies of cerebellar outflow tremor in laboratory primates (Section 11) (Elble et al., 1984, Kuo et al., 2019).

The frequency of mechanical-reflex oscillation is inversely proportional to reflex loop time (i.e., reflex latency in response to electrical stimulation), proportional to the square root of joint stiffness, and inversely proportional to the square root of joint inertial mass. Motion should be restricted to one joint, such as the wrist, when assessing the effects of mechanical loads (i.e., mass or stiffness) because joints differ in their mechanical properties and reflex arc length. To study the effect of mechanical loading on wrist tremor, EMG is recorded from wrist flexors and extensors, and a motion transducer is placed on the dorsum of the carpus, over the third metacarpal. Postural tremor is measured with the forearm supported and with the hand extended horizontally with and without a mass load on the hand (Fig. 3A). EMG and accelerometry (or gyroscopy) are typically recorded for 20–60 seconds (Lauk et al., 1999b). Longer recordings are often confounded by fatigue, especially during mass loading, resulting in the appearance of enhanced mechanical-reflex tremor (Section 2.3). Therefore, the optimum recording duration will depend on the goals of measurement. One study found little advantage in recording for 16 s versus 65 s (Wastensson and Andersson, 2016), and recording times of 20–30 s are common.

The normal adult in Fig. 3B (Normal) exhibited normal mechanical resonant oscillation at the wrist with no associated EMG modulation at the tremor frequency 8 Hz. The frequency of this oscillation decreased by 3 Hz with 1 kg mass loading. The enhanced physiologic tremor in the second column of Fig. 3B is a mechanical-reflex oscillation because the frequency of tremor decreased by more than 1 Hz with mass loading and because the oscillation is associated with modulation of EMG at the tremor frequency. This phenomenon is discussed further in Section 2.

There are important caveats to this method of tremor classification. A mechanical-reflex loop theoretically can become so strongly oscillatory that it becomes a limit-cycle oscillator that is largely

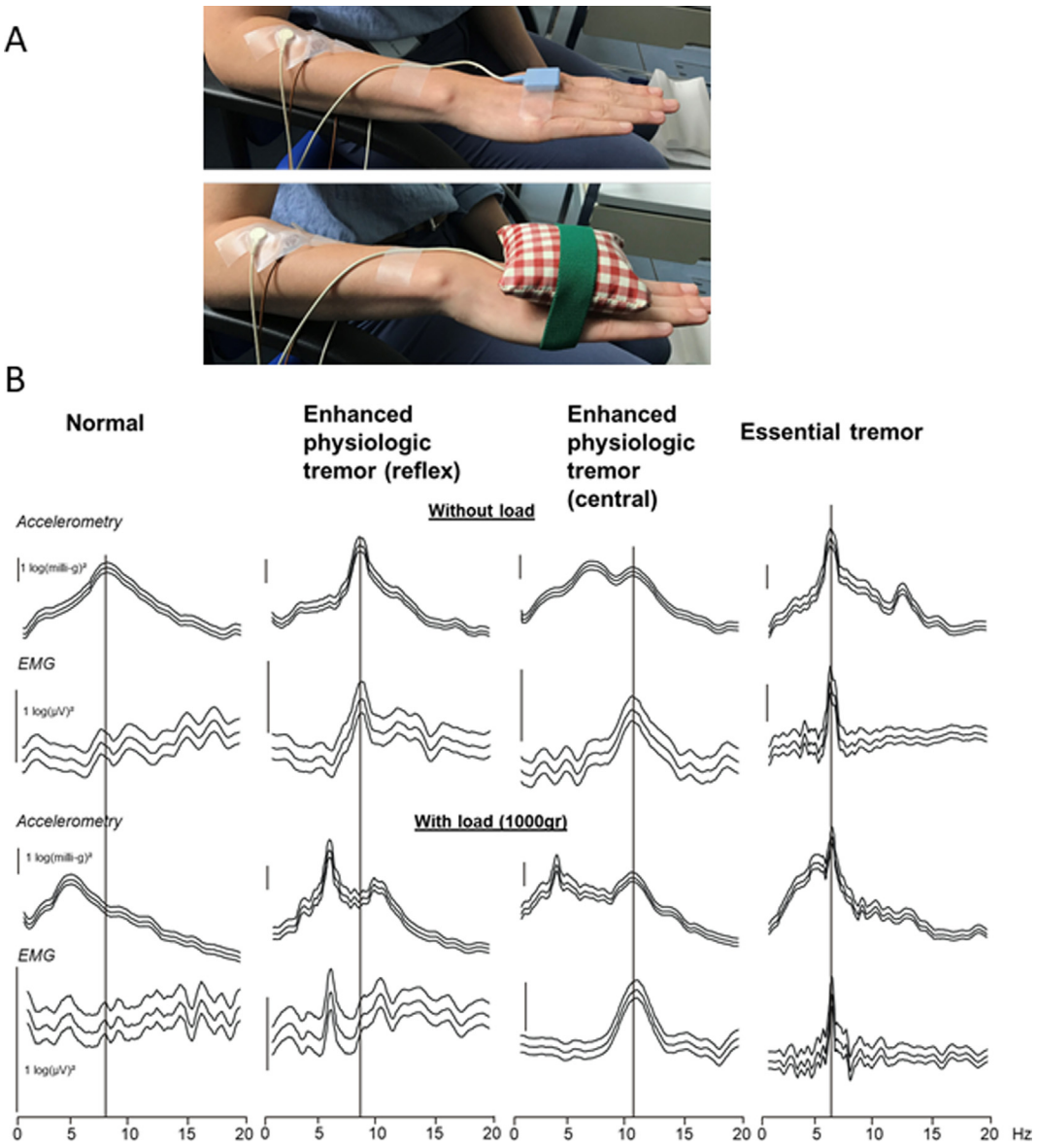

Fig 3. Tremor is recorded with an accelerometer from the dorsum of the hand and with rectified-filtered EMG of radial wrist flexors and extensors, with and without the hand loaded (1000 g) (A). Examples of Fourier power spectra of accelerometry and rectified-filtered extensor surface EMG are shown for normal physiologic tremor, enhanced mechanical-reflex physiologic tremor, enhanced physiologic 8–12 Hz central neurogenic tremor, and mild essential tremor (B). See text for interpretations.

unaffected by mechanical loads (Bock and Wenderoth, 1999). Evidence for this comes from studies of muscle fatigue tremor (Stiles, 1976). However, even in the absence of frequency change with mass loading, the frequency of mechanical-reflex oscillation should still be a function of reflex loop time (i.e., longer loop time → lower frequency) (Bock and Wenderoth, 1999).

1.2.7. Does tremor emerge primarily from central neural networks?

Tremor that emerges from central network oscillation is called central neurogenic tremor, and tremor frequency is independent of mechanical loads and reflex arc length. Examples are the 8–12 Hz central component of physiologic tremor (third column of Fig. 3B), essential tremor (fourth column in Fig. 3B), and Parkinson tremor in which joint oscillation is driven by rhythmic EMG activity at a frequency that is not decreased by mass loads. Normal mechanical oscillation is often evident in the power spectra when mass loading reduces the mechanical resonant frequency and thereby prevents resonant interaction between normal mechanical-reflex oscillation and a central neurogenic tremor (see Section 2). The general interpretation of tremor frequency response to mass loading is shown in Fig. 4. Additional applications are discussed throughout the remainder of this review.

An important caveat is that mild central neurogenic oscillation can be obscured by the stronger muscle contraction needed to maintain posture with mass loading. Another caveat is that all central anatomical pathways implicated in tremor are coupled with transcortical and segmental sensorimotor reflex loops (Elble, 1996). Consequently, it is theoretically possible for the frequency of a central neurogenic oscillator to be affected by mechanical-reflex dynamics when oscillator coupling and sensory feedback are strong and the central oscillator is relatively weak (Wenderoth and Bock, 1999). To our knowledge, there have been no conclusive demonstrations of this phenomenon. Yet another caveat is that central neurogenic oscillation can be so brief and intermittent that abnormal EMG activation or suppression provides a pulsatile perturbation to mechanical-reflex pathways,

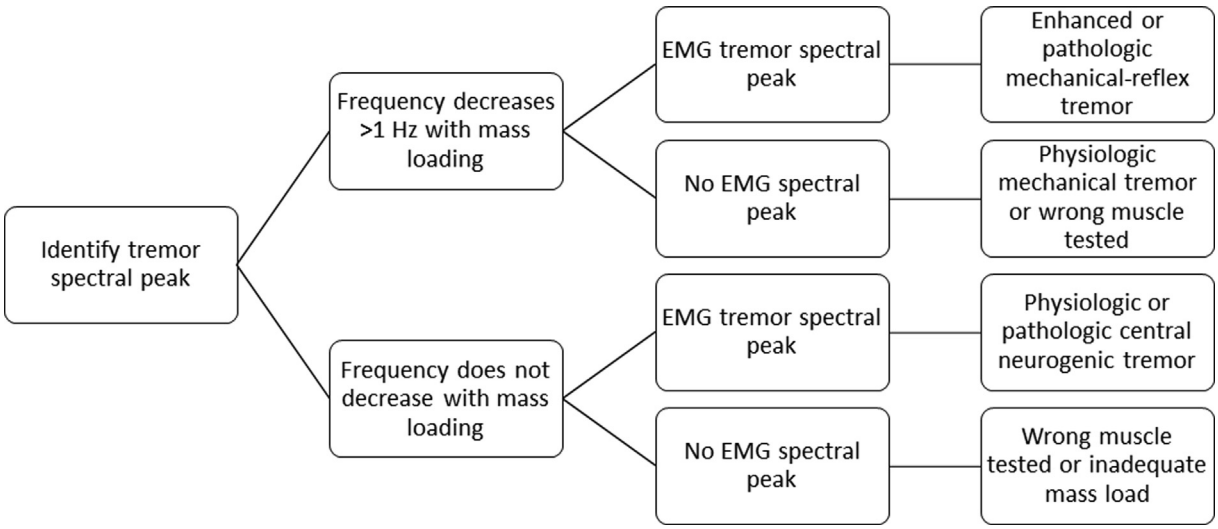

Fig. 4. Algorithm for interpreting tremor spectral peaks in motion transducer and surface EMG recordings, obtained with and without mass loading (Vial et al., 2019). Most pathological tremors have a frequency that is not reduced by mass loading. Larger mass loads are needed to change tremor frequency in large body segments (e.g., forearm versus the index finger). Care must be taken to ensure that EMG is recorded from an appropriate muscle.

resulting in oscillation with the properties of enhanced mechanical-reflex tremor. This phenomenon was demonstrated in an electrophysiologic study of palatal tremor (Elble, 1991).

1.2.8. Is tremor in different body parts linearly correlated?

It is often necessary to determine whether tremors in different muscles (e.g., antagonist muscles at a joint) or in different joints or body parts are correlated. For example, the coherence between different body parts is relevant in the diagnosis of primary orthostatic tremor and functional tremor. Irregularities and subtle differences in tremor frequency make it difficult or impossible to estimate phase and correlation visually. Therefore, coherence analysis is used to compute the frequency distribution of linear correlation squared (coherence) between the recordings. Coherence and phase are mathematically computed from auto- and cross-spectral analyses of two recordings (e.g., extensor and flexor EMG). These computations are statistical estimates with confidence limits (Benignus, 1969), and software for the computations is available for MATLAB and Python.

1.2.9. Is rest tremor present, and how is it affected by voluntary muscle activation?

Rest tremor is a cardinal feature of Parkinson disease, but it also occurs in tremor-dystonia syndromes, ET plus, Holmes tremor, and myorhythmia. In fact, all living people have rest tremor because the ejection of blood at cardiac systole produces cardioballistic oscillation throughout the body, in the absence of EMG activity (Brumlik, 1962). By contrast, pathologic rest tremor is always produced by rhythmic EMG activity at the frequency of tremor. The characteristic features of Parkinson rest tremor (i.e., suppression with voluntary muscle activation and re-emergence with sustained muscle activation) are easily demonstrated with EMG and motion transducer recordings (Dirkx et al., 2018, Jankovic et al., 1999, Mailankody et al., 2016, Papengut et al., 2013, Wilken et al., 2019). Spectral analysis is useful in determining tremor frequency before and after muscle activation.

1.2.10. Is tremor suppressed or entrained by voluntary movements of contralateral body parts?

To answer this question, sEMG electrodes and a motion transducer are mounted on a tremulous limb and on the corresponding contralateral limb. Tremor is recorded while voluntary rhythmic repetitive movements and single ballistic movements are performed with the contralateral limb, directed by the examiner. The rhythmic voluntary movements will entrain or suppress a functional tremor, and the voluntary ballistic movements will transiently suppress functional tremor (Kumru et al., 2004, McAuley et al., 1998). Coherence analysis may be needed to demonstrate entrainment (McAuley et al., 1998). It is important to explore a range of frequencies of repetitive movement to include frequencies that have no harmonic relationship to the tremor frequency. It is extremely difficult to perform rhythmic movements simultaneously with homologous body parts at frequencies that are not harmonics of each other. Functional tremor is discussed in Section 13.

1.2.11. What is the significance of rhythm resetting in response to external stimuli?

The principles of phase resetting of biological oscillators have been discussed extensively (Winfree, 2001). To summarize, all biological oscillators are nonlinear limit-cycle oscillations. The phase of oscillation can be reset (i.e., shifted) to a new steady state when a sudden perturbation (stimulus) of sufficient strength is applied to the oscillator. Resetting will not occur if the stimulus is too weak, the stimulus cannot reach the oscillator, or the oscillator is very strong (i.e., stable) relative to the stimulus. When the new phase is plotted against the old phase, the relationship has a slope of 0 if there is steady-state phase resetting (called type 0 resetting) and a slope of 1 if there is no resetting (called type 1 resetting). Alternatively, the difference between new phase and old phase (i.e., phase shift) can be plotted versus old phase, and the slope is 1 when there is type 0 phase resetting.

A reliable determination of phase resetting requires a rhythmic oscillation with a stable frequency because cycle-to-cycle variability or a small change in tremor frequency after stimulation makes the determination of new phase difficult or impossible. Stimulation may also produce a transient, and the steady-state new phase cannot be computed until the transient is over. The longer the transient, the more uncertainty there is in calculating new phase, due to the cumulative variation in tremor cycles. Plots of phase shift versus new phase rarely have a slope of 1, even when there is resetting, due to uncertainty in the calculation of new phase. Therefore, linear regression analysis is used to determine if the measured changes in phase are statistically correlated with old phase (Colebatch and Wagener, 1996). The slope of the regression

line is often referred to as the resetting index, and this index is often interpreted incorrectly as the degree of resetting (Lee and Stein, 1981), when in fact, this index is simply a measure of the degree of correlation (Colebatch and Wagener, 1996). In other words, the resetting index is a measure of the certainty that type 0 resetting occurred. There are no intermediate degrees of phase resetting; phase is either reset (type 0 resetting) or it is not (type 1 resetting) (Winfree, 2001). These caveats were illustrated in a study of essential tremor (Elble et al., 1992).

Frequency entrainment by rhythmic stimulation is essentially a frequency-domain correlate of phase resetting in which the oscillator is entrained by the rhythmic stimulus. Entrainment will not occur when the rhythmic stimulation is too weak, cannot reach the oscillator, or has a frequency that is too dissimilar from the oscillator frequency. The frequency entrainment method circumvents some of the difficulties (uncertainties) in determining new phase (Elble et al., 1992).

1.2.12. Is tremor linearly correlated with rhythmic brain activity?

This question is answered by spectral coherence analysis between peripheral tremor recordings and high-resolution EEG or MEG, using Fourier or wavelet spectral methods (Hallett et al., 2021, Liu et al., 2019). Neuroelectromagnetic source imaging is a technique that simultaneously estimates the temporal and spatial dynamics of the neuronal sources inside the brain that generate the electromagnetic fields. The current source density or activity images that neuroelectromagnetic source imaging generates are direct estimates of the electrical activity in neuronal populations. State-of-the-art source localization algorithms that are robust to noise and that are well informed about the anatomy, neurophysiology, and the realistic volume conduction physics of the brain can localize many simultaneously active sources and can even determine their variable spatial extents. The recent development of systems with the whole-head coverage offer the potential for the EEG and MEG to produce accurate estimates of the location and time course of the neuronal sources, by solving the so-called forward and inverse problems. In the context of localization of neuronal sources, the forward problem is to determine the potentials and/or magnetic fields that result from the primary current sources, and the inverse problem is to estimate the location of these primary current sources as depicted. An accurate solution of the forward problem is a prerequisite for solving the inverse problem (Muthuraman et al., 2010, Muthuraman et al., 2008). This approach has demonstrated pathophysiologic involvement of the corticobulbocerebellothalamocortical loop in the common forms of pathologic tremor and in physiologic tremor and voluntarily mimicked tremor (Muthuraman et al., 2012, Schnitzler et al., 2006). Therefore, this loop is often referred to as the "tremor network". As in all electrophysiologic studies, a carefully planned experimental design and standardized recording methods are required to maximize signal-to-noise ratios, which are characteristically low in brain-EMG coherence studies.

An ongoing goal is to discover specific differences in corticobulbocerebellothalamocortical activity that relate to different types of tremor (Muthuraman et al., 2018). Brain-EMG coherence analysis is an important method for elucidating tremor pathophysiology, as discussed in the following sections of this review.

1.2.13. Is tremor non-linearly correlated between muscles?

Most tremors emerge from nonlinear properties of neural networks. Consequently, methods of detecting nonlinear correlation are desirable for studying interaction between muscles and between muscles and central nervous system activity. Linear methods can underestimate nonlinear interactions. The three cross-frequency measures that are relevant for peripheral tremor recordings are frequency-to-frequency, power-to-power, and phase-to-phase. For all three methods, the basic tremor frequency and the first harmonic frequency (double of the tremor frequency) coupling can be investigated. This type of cross-frequency coupling gives in-depth information about the interacting muscle systems. The frequency-to-frequency coupling reflects the changes in one frequency induced by changes in another. The advantage of this method is to look at cross-frequency coupling within the same frequency band, which was not possible with traditional methods like bi-spectrum and simple coherence because of large temporal variation or jitter in phase estimation (Jirsa and Muller, 2013). The power-to-power coupling indicates how amplitude modulations at one frequency depend on amplitude modulations at another frequency (Muthuraman et al., 2020). This estimation is done by comparing the envelopes of the two signals. The phase-to-phase coupling identified by this method is a pure phase coupling, and it is amplitude independent between frequencies and within the same frequency band. It is estimated on the basis of instantaneous phases extracted from the instantaneous phases from the Hilbert-transformed raw EMG signals (Rosenblum et al., 1996). Some of the above measures and other non-linear measures like the bispectrum and bicoherence are not currently used in assessing tremor. Further research is needed to understand the importance of these measures for clinical investigation of tremor.

2. Physiologic and enhanced physiologic tremor

Physiologic tremor is an oscillatory, involuntary movement of a body part that occurs normally in living organisms. Here we discuss the neurophysiological characteristics of physiologic tremor and the peripheral (mechanical) and central mechanisms of physiologic tremor. We also explain how physiologic tremor can become enhanced and how this can be measured.

2.1. Mechanical component of physiologic tremor

Physiologic tremor is produced primarily by the underdamped inertial mass and viscoelastic properties of the musculoskeletal system. This passive mechanical system is driven by random irregularities in unfused muscle contraction (Dietz et al., 1974) and by the sudden ejection of blood in cardiac systole (Elble and Randall, 1978). These perturbations produce damped mechanical oscillations at a frequency proportional to $\sqrt{K/I}$, where K is the stiffness of the joint and I is the inertial mass of the body segment (e.g., hand). The response of somatosensory receptors (e.g., muscle spindles) to these mechanical oscillations is too weak to entrain motoneurons at the frequency of tremor (Hagbarth and Young, 1979, Young et al., 1975). Consequently, the rectified-lowpass filtered ("rectified-filtered" or "demodulated") EMG spectrum is statistically flat (Fig. 5).

Physiologic tremor is often described as a 10 Hz oscillation, but the frequency of physiologic tremor varies with the inertial mass and stiffness of joints throughout the musculoskeletal system. Thus, the 3–5 Hz frequency of normal elbow tremor (forearm tremor) is lower than the 7–10 Hz frequency of wrist tremor (hand tremor) and the 17–30 Hz frequency of metacarpophalangeal joint tremor (finger tremor), recorded with an accelerometer (Elble and Randall, 1978, Fox and Randall, 1970, Stiles, 1976, Stiles and Randall, 1967). Adding mass to a limb decreases tremor frequency, and additional stiffness K increases frequency in proportion to $\sqrt{K/I}$ (Elble and Randall, 1978, Fox and Randall, 1970, Stiles and Randall, 1967, Takanokura and Sakamoto, 2005). Similarly, voluntary co-contraction of the muscles about a joint increases tremor frequency by increasing joint stiffness, and gradual relaxation of the joint reduces the frequency (Stiles and Randall, 1967).

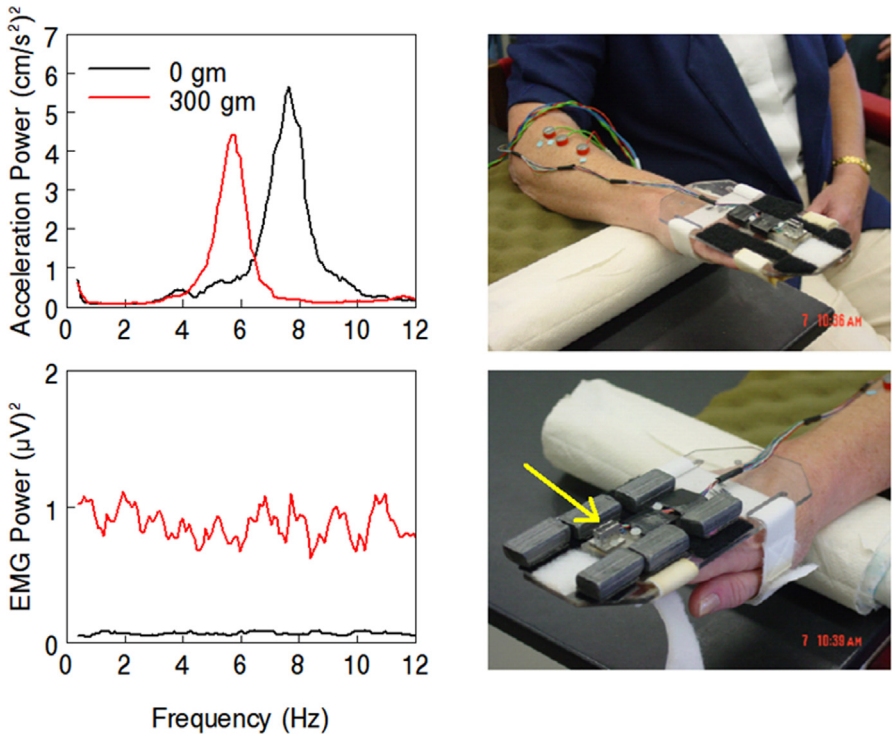

Fig. 5. Wrist tremor was recorded with and without 300-gm mass loading from a healthy person with a typical mechanical component of physiologic tremor (left side). A triaxial accelerometer (yellow arrow, lower photo) was attached to a plastic splint (right side). The splint was strapped to the hand, and the forearm was supported so that motion was restricted to the wrist. Surface EMG was recorded from the extensor carpi radialis brevis with Ag-AgCl skin electrodes (upper photo), full-wave rectified, and lowpass filtered at 30 Hz. The lead weights were attached to the splint with Velcro strips (B, lower photo). (A) Fourier spectral analysis of a 1-min recording revealed that the 300-gm load reduced the tremor frequency by 2 Hz (upper graph). The rectified-filtered EMG spectrum is statistically flat (lower graph). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

When mass is added to a joint, increased muscle contraction is needed to maintain the specified posture, and this will produce increased stiffness that reduces the impact of increased mass on tremor frequency. These opposing factors were demonstrated by Lakie and coworkers, who confirmed the $\sqrt{K/I}$ relationship for the frequency of the mechanical component of physiologic wrist tremor (Lakie et al., 2015). The magnitude of the mass load needed to demonstrate a reduction in frequency will depend on the inertial mass properties of the joint being tested. Loads of 25 gm or less are needed to reduce the frequency of finger tremor (Stiles and Randall, 1967), but more than 1000 gm is needed to significantly reduce the frequency of elbow tremor (Fox and Randall, 1970).

In the absence of muscle contraction, passive mechanical oscillation still occurs in response to the ejection of blood at cardiac systole (Brumlik, 1962, Elble and Randall, 1978, Marsden et al., 1969). This cardioballistic forcing accounts for essentially all of physiologic tremor at rest (Brumlik, 1962) but explains 10% or less of wrist postural tremor in most people (Elble and Randall, 1978).

Electrophysiological assessment of wrist (hand) tremor is performed with an accelerometer or inertial measurement unit (IMU: a combination of a triaxial accelerometer, gyroscope, and usually a magnetometer) on the hand and sEMG electrodes attached over one or more wrist extensors (e.g., extensor carpi radialis brevis, extensor carpi ulnaris) and flexors (e.g., flexor carpi ulnaris). The motion transducer can be mounted distally on a splint, as in Fig. 5, or it can be taped to the hand, as in Fig. 3A. The size of the added mass for evaluating wrist tremor can be 300 g when distributed distally on a splint (Fig. 5B) but needs to be higher (500–1000 g) when attached more proximally on the carpus (Fig. 3A). This methodology is nicely illustrated in a published video tutorial (Longardner et al., 2019).

2.2. Central neurogenic tremor component

Central neurogenic tremors have a frequency that is independent of joint inertial mass, stiffness, and reflex arc length and are therefore believed to emerge from network oscillation within central nervous system. Mass loading often increases the frequency of neurogenic oscillation slightly but never decreases the frequency more than 1 Hz (Fig. 6). Normal people exhibit central neurogenic tremor at 8–12 Hz and at 15–30 Hz (Elble and Randall, 1976, Halliday et al., 1999), but both oscillations are difficult to record except from the extended finger, which has a natural frequency of 15–30 Hz (Stiles and Randall, 1967). Less than 10% of normal adults exhibit an unequivocal central component in hand tremor assessed with standardized methodology (Raethjen et al., 2000). The contribution of motor unit entrainment to tremor in body parts with a lower natural frequency (e.g., hand, forearm) is much smaller, due to mechanical attenuation of frequencies above the natural frequency. The contribution of central neurogenic tremor to total positional error is 10% or less in most circumstances (Carignan et al., 2010).

Motor units participating in the 8–12 Hz tremor are entrained at 8–12 Hz, regardless of their mean firing frequency, and this entrainment is very intense in some people but not in most (Elble and Randall, 1976). A consistent 8–12 Hz component is evident in only 7–8% of healthy adults during routine recordings of postural wrist tremor (Elble, 2003). However, nearly all people exhibit 8–12 Hz bursts of EMG during slow voluntary movements, particularly in the wrist and finger extensor muscles during slow wrist or finger flexion (Wessberg and Vallbo, 1996). Thus, there is a tendency for 8–12 Hz motor unit entrainment to occur in everyone, but this tendency is too weak in most healthy adults

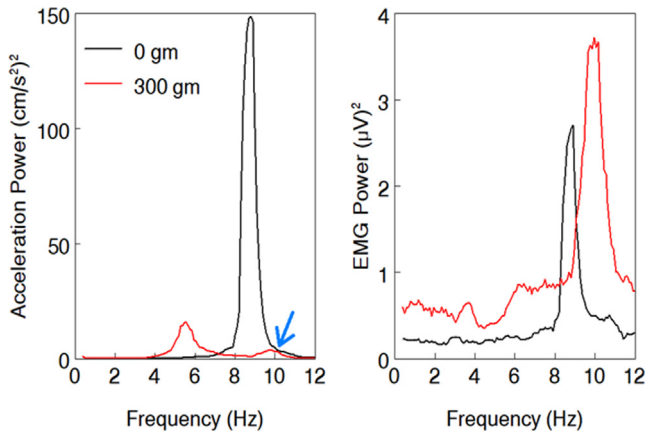

Fig. 6. Hand tremor and rectified-filtered extensor carpi radialis brevis EMG spectra were recorded from a healthy 34-year-old woman with (red lines) and without (black lines) a 300-gm load. With no load, there is an 8.8 Hz peak in acceleration power and a corresponding peak in the EMG spectrum. The inertial load reduced the mechanical resonant frequency to 5.5 Hz and disclosed a second oscillation at 10 Hz (blue arrow). The EMG spectral peak frequency increased from 8.8 Hz to 10 Hz with loading, and there was no EMG modulation at the 5.5 Hz mechanical resonant frequency. This is an example of how the 8–12 Hz central neurogenic oscillation and mechanical component can resonate together when their frequencies are similar. This resonance is not seen when the two tremor components have widely disparate frequencies, as in elbow tremor and finger tremor (Fox and Randall, 1970, Stiles and Randall, 1967). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to produce an EMG spectral peak during steady horizontal extension of the hand.

Observations in humans suggest that spinal and supraspinal transcortical pathways are involved in the 8–12 Hz oscillation (Koster et al., 1998, Raethjen et al., 2002, Raethjen et al., 2004b). Recordings from motor cortex, deep cerebellar nuclei, pontomedullary reticular formation and spinal cord in monkeys have demonstrated 8–12 Hz oscillation that is coherent with 8–12 Hz tremor, and the spinal oscillation appears to limit tremor by phase cancellation of oscillation from higher sources (Williams and Baker, 2009, Williams et al., 2010). In humans, 6–9 Hz rhythmic EMG activity during slow finger movements was found to be coherent with oscillatory activity in the cerebellothalamocortical motor loop, as measured with magnetoencephalography (MEG) (Gross et al., 2002). Furthermore, transcranial alternating current stimulation (TACS) over the cerebellum at physiologic tremor frequency (≈8.5 Hz) entrained the phase of the ongoing index finger tremor during horizontal extension of the supinated hand and during slow repetitive extension and flexion of the metacarpophalangeal joint (Mehta et al., 2014). A similar effect was seen when TACS was performed over the primary motor cortex, but here the effect was only seen during postural tremor (Mehta et al., 2014). Further evidence for participation of the cerebellothalamocortical circuit in physiologic tremor comes from stereotactic surgery studies. In patients with Parkinson disease, ventrolateral thalamotomy reduced not only amplitude of the 4–6 Hz Parkinson tremor, but it also selectively removed high-frequency (7.5–12.6 Hz) components in the power spectrum (Duval et al., 2005). Participation of the cerebellothalamocortical circuit in physiologic tremor is not surprising because this same circuit is involved in virtually all pathological tremors (Nieuwhof et al., 2018).

The physiologic purpose of the 8–12 Hz oscillation, if any, is unknown, but it has long been hypothesized that this oscillation serves to coordinate or amplify signals in various motor pathways (Gross et al., 2002, Ohara et al., 2001, Raethjen et al., 2004b). For example, this rhythm may reflect a mechanism for temporal sampling of movement-related activities within the cerebellothalamocortical circuit (Marsden et al., 2000), and intermittent or rhythmic motor control could reduce computational load within the nervous system (Gross et al., 2002).

The 15–30 Hz component of physiologic tremor appears to emerge from cortical rhythmicity (Baker et al., 1999, Baker et al., 1997, Conway et al., 1995, Halliday et al., 1998, Salenius et al., 1997). The physiologic purpose of this rhythmicity is unclear, but like the 8–12 Hz oscillation, the 15–30 Hz oscillation may facilitate the coordination of activities in distinct cortical regions (Baker et al., 1999).

2.3. Enhanced physiologic tremor

The mechanical oscillations of physiologic tremor are not associated with rhythmic modulation of motor-unit activity unless the sensitivity of the reflex arc is increased by drugs (e.g., adrenaline), thyroid hormone, fatigue, anxiety, or corticospinal lesions (Hagbarth and Young, 1979, Hashimoto et al., 2002, Logigian et al., 1988, Young et al., 1975). This modulation of motor-unit activity produces a peak in the rectified-filtered EMG Fourier spectrum at the mechanical resonant frequency (Fig. 7). Tremor frequency becomes less responsive to inertial loading with increasing involvement of the stretch reflex (Stiles, 1976). The frequency of enhanced mechanical-reflex oscillation decreases as the amplitude increases, possibly due to a reduction in joint stiffness with increasing amplitude of oscillation (Agarwal and Gottlieb, 1984, Gottlieb and Agarwal, 1977, Lakie et al., 1984, Milner and Cloutier, 1998, Zahalak and Pramod, 1985).

The characteristics of enhanced physiologic tremor beg the question of whether the stretch reflex normally serves to control mechanical oscillation. Limb ischemia sufficient to suppress the stretch reflex reduces physiologic tremor and associated motor unit entrainment (Christakos et al., 2006, Lakie et al., 1994). People with deafferented limbs exhibit broad-frequency arrhythmic fluctuations in limb position when their tremor is enhanced, but they do not exhibit the rhythmic tremor and motor unit entrainment at the mechanical resonant frequency (Sanes, 1985). Thus, sensory feedback seems to entrain or concentrate tremor at a particular frequency, resulting in rhythmic oscillation, but appears to be incapable of suppressing tremor completely.

In 60 s recordings of hand (wrist) tremor during steady horizontal posture, 62% of normal adults had no modulation of forearm EMG activity, and only 5–6% exhibited consistent EMG modulation at the mechanical resonant frequency (Elble, 2003). Therefore, the

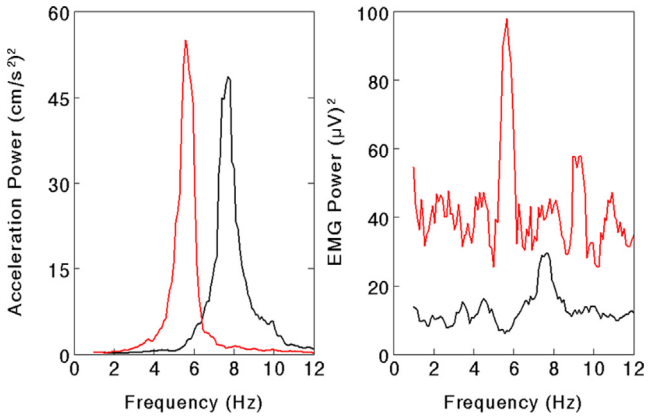

Fig. 7. Hand tremor was recorded from an adult patient with enhanced mechanical-reflex tremor due to thyrotoxicosis. Tremor frequency decreased from 7.7 Hz to 5.6 Hz with 500 gm loading (red lines), and EMG modulation occurred with and without (black lines) loading. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

presence of consistently enhanced mechanical-reflex tremor should prompt a search for pathologic reflex enhancement (e.g., thyrotoxicosis, medications, illicit drugs, and systemic disorders) and should not be assumed have physiologic causes (e.g., situational anxiety or fatigue).

2.4. Low-frequency error

Physiologic tremor accounts for only a small fraction of the total error in position or force when a person tries to maintain a steady posture (Carignan et al., 2010). Most of the error is aperiodic (arrhythmic), and the log spectral power (square error) is inversely proportional to frequency (Carignan et al., 2010, Sutton and Sykes, 1967a, 1967b, Yoshitake and Shinohara, 2013). The aperiodic error below 6 Hz is orders of magnitude greater than the mechanical-reflex and central neurogenic oscillations. This low-frequency error is less evident in velocity and acceleration spectra because velocity and acceleration transducers have the effect of taking the first and second derivatives of position, thus amplifying signals in proportion to frequency and squared frequency, respectively (Carignan et al., 2010).

The distribution of total error with respect to frequency is explained by the dynamics of each component of the stretch reflex loop, shown schematically in Fig. 8 and quantitatively elsewhere (Roberts et al., 1971). The second-order overdamped transfer function of skeletal muscle attenuates irregularities in motoneuron activity at frequencies above a cutoff frequency of approximately 3 Hz (Milner-Brown et al., 1973). The irregularities in muscle force will produce resonant oscillation at a frequency defined by joint stiffness and inertial mass (joint mechanics). Irregularities above this natural frequency will be further attenuated. Consequently, the 15–30 Hz central neurogenic component of physiologic tremor will be markedly attenuated except in the fingers, which have a natural frequency of oscillation in the same frequency band. Somatosensory receptors (i.e., muscle spindles and Golgi tendon organs) have a sensitivity that is proportional to frequency and squared frequency (velocity and acceleration), so all but the smallest error fluctuations will produce modulation of sensory feedback to the central nervous system (Roberts et al., 1971), and this feedback couples the periphery with central sources of oscillation.

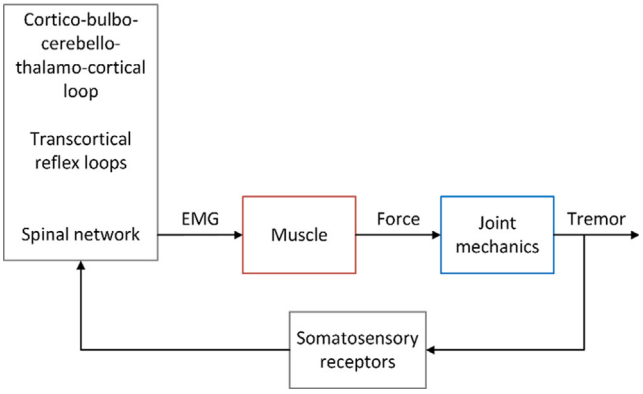

Fig. 8. During a postural task, the central nervous system attempts to drive muscles with motor unit activity that will produce a steady net force or torque acting on the joint(s). However, the motor unit drive to muscle is not perfectly smooth and contains random irregularities over a broad frequency range (0 to >40 Hz) and central neurogenic entrainment at 8–12 Hz and 15–30 Hz. The second-order lowpass filtering properties of skeletal muscle attenuate irregularities and rhythms logarithmically at frequencies above 3 Hz. The surviving force fluctuations drive joint oscillation at the resonant natural frequency of the joint and at the central neurogenic frequencies, and joint mechanics will further attenuate force irregularities logarithmically at frequencies above the natural frequency. The resulting error in joint position (angle) consists of low-frequency arrhythmic error, the mechanical resonant component of tremor, and the two central neurogenic components. These sources of error (tremor) induce somatosensory feedback in proportion to their amplitude, velocity (i.e., first derivative) and acceleration (second derivative).

3. Essential tremor and essential tremor plus

3.1. Clinical definition

Essential Tremor (ET) is one of the most prevalent movement disorders. The concept of ET as tremor syndrome was introduced by a task force of the International Parkinson and Movement Disorder Society (IPMDS) in 2018 (Bhatia et al., 2018). This task force defined ET as an isolated tremor syndrome of bilateral upper limb action tremor of at least 3 years duration, with or without tremor in other body locations (e.g., head, voice, or lower limbs), and with the absence of other neurological signs, such as dystonia, ataxia, or parkinsonism (Table 2).

People with ET often exhibit neurologic signs of uncertain abnormality or relevance (“soft neurological signs”), and the IPMDS task force introduced the classification essential tremor plus (ET plus) for people with soft signs. ET plus is used when a patient meets the criteria of ET but has additional “mild neurological signs of uncertain significance such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurological signs of unknown significance” that do not rise to the level of being classified as a different tremor syndrome or diagnosis (e.g., dystonic tremor syndrome, tremor with parkinsonism, etc.). ET and ET plus share the same exclusionary criteria, namely the presence of isolated focal tremors such as isolated head tremor or isolated voice tremor, the presence of orthostatic tremor with a frequency > 12 Hz, task- and position-specific tremors, and sudden onset and step-wise deterioration (Table 2).

ET and ET plus are defined solely in terms of clinical features, which may include electrophysiologic features. ET and ET plus are clinical (axis 1) classifications that explicitly avoid any implication of underlying etiologies, which are defined in axis 2. Importantly, it is anticipated that people with ET or ET plus may change into another axis 1 diagnosis over the course of their disease. For example, a patient with ET for many years may eventually develop unequivocal dystonia and is then reclassified as dystonia-tremor syndrome with antecedent ET.

Table 2
International Parkinson and Movement Disorder Society Consensus inclusion and exclusion criteria for essential tremor (ET) and ET plus (Bhatia et al., 2018).

Syndrome	Inclusion Criteria	Exclusion Criteria
Essential tremor	Isolated tremor syndrome of bilateral upper limb action tremor At least 3 years duration With or without tremor in other locations (e.g., head, voice, or lower limbs) Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism.	Isolated focal tremors (voice, head) Orthostatic tremor with a frequency > 12 Hz Task- and position-specific tremors
Essential tremor plus	Tremor with the characteristics of ET and additional neurological signs of uncertain significance such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurologic signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis. ET with tremor at rest should be classified here.	Sudden onset and step-wise deterioration

3.2. Clinical presentation

It is estimated that the prevalence in the general population across all ages is at 0.4%, with a steady increase in prevalence over the decades of life (Louis and Ferreira, 2010). In a population-based study using electrophysiology to further characterize tremor phenotypes in subjects aged 50–89, tremor was present in 14.5%. The most common form of tremor in this cohort was enhanced physiological tremor (9.5%), followed by ET (3.1%) and parkinsonian tremor (2.8%) (Wenning et al., 2005). Emerging data on the prevalence of ET plus suggests that ET plus may be more common than ET (Bellows and Jankovic, 2021, Prasad and Pal, 2019, Rajalingam et al., 2018).

The typical age of onset in ET shows a bimodal distribution with one peak in the second decade and another peak in the sixth decade of life. The phenotypic differences in early- and late-onset ET patients support the notion of two ET subgroups. Early-onset ET is significantly associated with higher proportions reporting a positive response to alcohol as well as a positive family history of tremor, compared to patients with late-onset ET. Furthermore, late-onset ET tends to progress faster than early-onset ET (Hopfner et al., 2016).

The estimates of proportion of patients with a positive family history of ET range from 20% to 90%. Twin studies reported a concordance for ET between 60% and 93% for monozygotic twins and 27–29% for dizygotic twins (Kuhlenbaumer et al., 2014, Lorenz et al., 2004). The heritability of ET was estimated between 75% and >90% (Diez-Fairen et al., 2019, Lorenz et al., 2004).

ET is usually a bilateral, upper limb action tremor. Other body parts may be affected as well, the head and neck most commonly, followed by the voice, lower extremities, trunk and chin (Whaley et al., 2007). Importantly, isolated tremor of the head, which had been included as part of the ET phenotype in the prior 1998 Movement Disorders Society (MDS) classification of tremor disorders (Deuschl et al., 1998a), has now been reclassified as an isolated focal tremor syndrome, together with isolated focal tremors of the voice, isolated task- and position tremors, and essential palatal tremor (Bhatia et al., 2018). The most common "soft" neurological signs that lead to the diagnosis of ET plus include rest tremor, tandem gait impairment, memory impairment, mild peripheral neuropathy, and questionable dystonic posturing (Huang et al., 2020, Rajalingam et al., 2018).

A minimum 3-year duration of tremor is required for the diagnosis of ET and ET plus to reduce the odds of subjects developing other neurological signs, such as parkinsonism, dystonia, or ataxia. Tremor of less than 3 years that otherwise fulfills the criteria for ET or ET plus is referred to as "indeterminate tremor" (Bhatia et al., 2018). It is critical to understand that ET and ET plus are axis 1 syndromes, not specific diseases. Therefore, it is expected that ET and ET plus may transition into other tremor syndromes.

3.3. Pathophysiology

Coherence analysis of peripherally recorded tremor with EEG or MEG has played a crucial role in identifying and elucidating tremorogenic oscillation in the corticobulbocerebellothalamocortical loop. This loop is involved in all forms of tremor, but it is likely that differences will be found that will aid in the classification and pathophysiologic understanding of ET and other tremor disorders (Muthuraman et al., 2012, Muthuraman et al., 2018, Schnitzler and Gross, 2005). The methodology is discussed in a companion review (Hallett et al., 2021). Structural imaging has revealed circumscribed areas of atrophy, but none of them survived rigid statistical testing (Luo et al., 2019). Despite the strong heritability of ET, genetic analyses have revealed only a few rare disease-causing mutations, but there are several promising gene loci (Diez-Fairen et al., 2019, Kuhlenbaumer et al., 2014, Magrinelli et al., 2020).

The pathology of ET is controversial. One group has reported cerebellar changes associated with Purkinje cell loss (Louis and Faust, 2020), but this has not been confirmed by others (Rajput et al., 2013, Shill et al., 2012). Furthermore, how this pathology might lead to tremorogenic oscillation is unclear. Nevertheless, hypotheses regarding the pathophysiology of ET have clearly shifted from the earlier idea that the rhythm of ET is generated within the inferior olive (Llinas, 1984, Louis and Lenka, 2017). The possibility of GABAergic loss in the cerebellum suggests that a deficit in inhibitory Purkinje neurons leads to pathologic oscillation (Schaefer et al., 2018). A related hypothesis is that diminished pruning of the dendritic arbor of Purkinje cells contributes to abnormal rhythmicity (Pan et al., 2020). The effects of normal aging and age-associated comorbidities must also be considered because ET frequently seems to accelerate late in life (Louis, 2019). The notion of aging-related (senile) tremor is based on the observation that late-onset ET patients have other biological signs of aging and that aging and age-associated comorbidities may lead to the development of tremor (Deuschl et al., 2015). These hypotheses are not mutually exclusive, and the ultimate answers will likely vary among patients, depending on axis 2 etiology. All hypotheses must ultimately be conceptualized and studied electrophysiologically.

3.4. Laboratory assessment

3.4.1. Electromyography and motion transducers

Recordings of ET typically reveal oscillatory motion and corresponding rhythmic bursts in the sEMG (Fig. 9). The timing of tremor bursts in antagonistic muscles can be co-contracting, alternating, or a mixture of both (Deuschl et al., 1987), and the phase appears to depend on the cortical drive to the spinal network (Gallego et al., 2015a, Gallego et al., 2015b). Therefore, it appears unlikely that antagonist muscle interaction will prove useful in the axis 1 classification of ET, and for any tremor, it is important to control for the effect of tremor amplitude.

Recordings like those of Fig. 9 are useful in quantifying tremor onset or suppression in relation to voluntary movements. ET begins with the initial burst of agonist muscle activity when a voluntary movement is performed. In other words, ET is activated immediately by voluntary movement. This is diagnostically different from Parkinson rest tremor and functional tremor, as discussed in Sections 4 and 13.

Intermuscular coherence analysis in ET shows significant coherence between ipsilateral muscle-pairs, but there is no coherence in side-to-side comparison of muscle-pairs, which is consistent with separate, lateralized central oscillating sources of ET (Lauk et al., 1999a, van der Stouwe et al., 2015).

As illustrated in Fig. 3, sEMG and accelerometry with and without mass loading are useful in distinguishing mild ET (a central neurogenic tremor) from physiological tremor. This protocol for distinguishing ET and physiologic tremor has been used since 1986, so there is considerable experience among tremor electrophysiologists. Only 8% of normal adults exhibit a central neurogenic tremor (Raethjen et al., 2000) that cannot be definitely distinguished from ET (Elble, 2003). Therefore, the estimated specificity of this protocol for ET versus controls is 92% (Elble, 2003), but this is not specific for ET versus other pathologic tremors such as Parkinson tremor and dystonic tremor.

Gironell and coworkers proposed neurophysiological criteria for the diagnosis of ET, comprising six individual criteria: (1) rhythmic bursts of postural tremor on sEMG, (2) tremor frequency greater than or equal to 4 Hz, (3) rest tremor absent, (4) absence of latency from rest to postural position, (5) changes

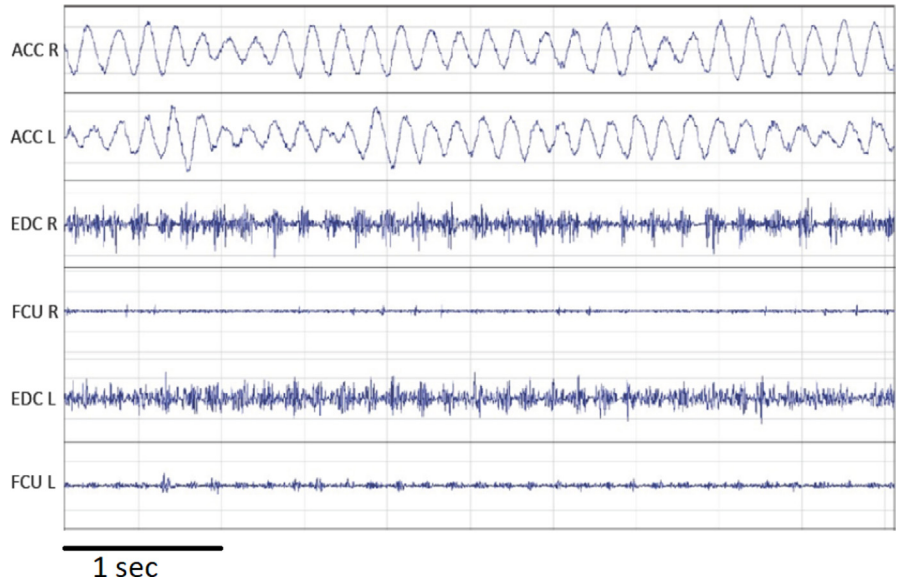

Fig. 9. Raw time-series data of a postural tremor recording of a patient with ET, using a 6-channel polygraphic setup with concurrent recording of both hands. Accelerometers (ACC) were located on the dorsum of the right (R) and left (L) hand, at the mid-point of the third metacarpal bone, with uniaxial alignment to capture the flexion/extension movement of the wrist. Surface EMG were placed over agonist- and antagonist pairs of each wrist (EDC: extensor digitorum communis, FCU: flexor carpi ulnaris). The x-axis is time in seconds. Visual inspection reveals a bilateral 6-Hz tremor, with corresponding sEMG bursts, predominantly in the extensor muscles.

in the dominant frequency peak less or equal to 1 Hz after weight loading, and (6) no changes in tremor amplitude after mental concentration. With the requirement of all six neurophysiological criteria being present, a sensitivity of 97.7%, specificity of 82.3%, a positive predictive value of 95.1% and negative predictive value of 91.1% for the diagnosis of ET could be achieved in a large population of clinic patients with ET (77%), postural parkinsonian tremor (10%), enhanced physiologic tremor (3%), drug-induced tremor (3%), functional tremor (3.3%), dystonic tremor (2%), cerebellar tremor (1%), cortical tremor (0.6%), and Holmes tremor (0.3%) (Gironell et al., 2004).

3.4.2. Computer tablet analysis

Log-transformed tremor amplitudes extracted from handwriting and spiral drawings correlate well with clinical ratings of tremor (Elble et al., 1996, Haubenberger et al., 2011, Legrand et al., 2017, Pullman, 1998), and tablet measures and clinical ratings have comparable ability to detect change that exceeds the natural within-subject variability of tremor amplitude (Elble and Ellenbogen, 2017).

The resolution and accuracy of digitizing tablets and tablet computers are not sufficient to record physiologic tremor. Therefore, a tremor spectral peak in writing or drawing is definitely a sign of abnormal tremor, not physiologic tremor. Tremor that is barely visible or even questionably visible can be detected with a modern tablet and spectral analysis (Elble et al., 1996).

The fluctuating distance between lines of an Archimedes spiral can be quantified in terms of a spiral width variability index. This index can be viewed as a measure of subtle ataxia and correlates well with intention tremor severity in patients with ET (Louis et al., 2012). This index also predicted the development of early tolerance in ET patients undergoing deep brain stimulation (Merchant et al., 2018b).

The axis or direction of tremor in a spiral is determined by proximal versus distal joint oscillation in the upper limb, and tremor direction is easily computed from tablet recordings (Wang et al., 2005). There is some evidence that ET and dystonic tremor can be distinguished on this basis, but the sensitivity and specificity are modest (Michalec et al., 2014).

4. Parkinson tremor and variants

4.1. Clinical definition

According to the 2018 IPMDS consensus statement (Bhatia et al., 2018), tremor with parkinsonism is a combined tremor syndrome that is defined within axis 1 as tremor accompanied by bradykinesia and/or rigidity. Multiple axis 2 etiologies have been identified, but most cases are still idiopathic.

4.2. Clinical features of parkinsonian tremors

4.2.1. Tremors in Parkinson's disease

Classical Parkinson tremor is a 4–7 Hz rest tremor of the hand ("pill-rolling" tremor), lower limb, jaw, tongue, or foot that subsides, at least transiently, with voluntary muscle activation. However, postural and kinetic tremors also occur in patients with and without rest tremor (Deuschl et al., 1996b). Isolated rest tremor is also seen but should not be referred to as a Parkinson syndrome when there is no bradykinesia or rigidity.

Approximately 75% of patients with Parkinson disease will develop rest tremor, and 40–65% will present with rest tremor (Gigante et al., 2017, Hughes et al., 1993, Uitti et al., 2005). Rest tremor usually starts distally in one upper limb (Jankovic, 2008) and spreads to the other side or to the lower limbs, tongue or jaw (Gigante et al., 2017), but tremor can start in any of these locations. In most patients, bradykinesia and rigidity are greatest in the limb with greatest tremor, but there are exceptions in which "wrong-sided tremor" occurs contralaterally to the limb with greatest rigidity and bradykinesia (Koh et al., 2010). Tremor may decrease or even disappear in the later stages of the disease (Toth et al., 2004).

Rest tremor typically increases in response to psychological stress or cognitive load, such as serial subtraction (Raethjen et al., 2008, van der Heide et al., 2021, Zach et al., 2017). Tremor may also increase during walking or during distracting motor tasks such as finger tapping with the contralateral hand.

The suppression of rest tremor with voluntary muscle activation is highly specific for Parkinson disease. Suppression is rarely

seen in dystonic rest tremor or in ET plus rest tremor (Erro et al., 2014, Papengut et al., 2013). In many Parkinson patients, the rest tremor re-emerges after a variable delay if stable voluntary posture or movement is maintained.

Re-emergent tremor occurs in roughly two thirds of Parkinson patients with tremor (Dirkx et al., 2018, Jankovic et al., 1999, Lance et al., 1963, Zimmermann et al., 1994). Re-emergent tremor greatly resembles rest tremor in terms of frequency, amplitude, and response to dopaminergic medication. It is therefore believed to be an extension of rest tremor that re-emerges in a stable posture (Dirkx et al., 2018). The latency of tremor re-emergence is seconds to a minute or more (Jankovic, 2016). Re-emergent tremor usually has a slightly higher frequency (+0.4 Hz) and tends to be less responsive to dopaminergic medication than rest tremor (Dirkx et al., 2018), but this has not been observed in all studies (Belvisi et al., 2017). Thus, differences may exist in pathophysiology of rest tremor and re-emergent tremor. This hypothesis is supported by the observation that single-pulse transcranial magnetic stimulation (TMS) over the cerebellum can reset re-emergent tremor but not rest tremor, which suggests that the cerebellum is more involved in re-emergent tremor (Helmich et al., 2021, Ni et al., 2010).

Postural tremor without rest tremor occurs in roughly 15% of patients with Parkinson disease (Dirkx et al., 2018). This type of tremor has a lower amplitude, higher frequency, and, unlike re-emergent tremor, starts immediately with voluntary muscle activation (Dirkx et al., 2018). Pure postural tremor does not respond to dopaminergic medication, suggesting that non-dopaminergic mechanisms are involved. It was previously suggested that this type of tremor was a co-occurring essential tremor (Louis and Frucht, 2007), and in some cases, there is a history compatible with longstanding antecedent essential tremor. However, in most cases, the postural tremor is probably a unique type of Parkinson tremor (Dirkx et al., 2018).

In addition to postural tremor of the upper limbs, patients may also complain of trembling or unsteadiness in the legs upon standing. This may be caused by co-occurring orthostatic tremor (OT), which is referred to as OT-plus (as it is accompanied by parkinsonism) (Mestre et al., 2012). Both classical OT (i.e., frequency range of 13–18 Hz and strong bilateral coherence) and slow OT (frequency < 13 Hz) have been reported in patients with PD (Leu-Semenescu et al., 2007). Although the exact prevalence is unclear, up to 11% of patients with OT have co-existent parkinsonism (Hassan and van Gerpen, 2016). Dopamine replacement therapy may sometimes reduce OT in these specific cases, but OT usually does not respond very well to any type of treatment. Unsteadiness upon standing may also be caused by orthostatic myoclonus, which is sometimes seen in patients with Parkinson disease and other forms of parkinsonism. Up to 33% of patients with orthostatic myoclonus have co-existing parkinsonism (Hassan and van Gerpen, 2016).

Kinetic tremor is defined as tremor produced by voluntary movement, such as reaching or drawing, and this type of tremor is often seen in Parkinson disease. In fact, it was suggested that all Parkinson patients exhibit at least a mild form of kinetic tremor (Bhatia et al., 2018), although this depends upon the exact definition of kinetic tremor (Bain et al., 1993, Wenzelburger et al., 2000). Kinetic tremor in Parkinson disease has a higher frequency than rest tremor (+1 Hz) and appears to be unresponsive to dopaminergic medication (Raethjen et al., 2005, Wenzelburger et al., 2000).

4.2.2. Phenomenology and subtypes of tremor in atypical parkinsonism

Tremor occurs in other forms of parkinsonism, albeit less frequently. The exact phenomenology depends on the specific hypokinetic-rigid disorder.

Postural tremor is the most common type of tremor in multiple system atrophy (MSA), but rest and intention tremors also occur. In a large sample of 160 pathologically confirmed MSA cases, postural tremor occurred most often in the parkinsonian subtype of MSA (MSA-P; 29.1% of 103 cases) compared to the cerebellar subtype (MSA-C; 14% of 57 cases) (Miki et al., 2019). Postural tremor in MSA is generally more jerky or irregular. In fact, it may be hard to differentiate it from polyminimyoclonus, which is also common in MSA (Salazar et al., 2000). Electrophysiologic testing is consistent with cortical myoclonus (Okuma et al., 2005), but detailed studies are rare. Nevertheless, this study suggests that the jerky repetitive movements seen in MSA are myoclonus, not tremor. Intention tremor is another subtype of tremor in MSA that can be present at onset but usually arises later in the disease (Kaindlstorfer et al., 2013). Intention tremor is usually a feature of cerebellar pathology and therefore mostly seen in MSA-C (33%) versus MSA-P (11%) (Wenning et al., 1994). Finally, rest tremor is present in 27.5% of cases, but this is rarely the classical pill-rolling tremor seen in Parkinson disease (Miki et al., 2019). Only 3.8% of pathologically confirmed MSA patients had a typical pill-rolling tremor (Miki et al., 2019).

As many as 42% of progressive nuclear palsy (PSP) patients exhibit tremor (Fujioka et al., 2016). Tremor is usually relatively mild in PSP and is therefore often overlooked or neglected. The location of tremor is usually restricted to the upper limbs but is sometimes seen in lower limbs and face. Postural tremor seems to be the most prevalent type of tremor in PSP and is reported in 31% of patients with tremor, followed by rest tremor (23%) and intention tremor (8%) (Fujioka et al., 2016). Interestingly, 12.4% of 89 patients in an ET brain bank had subclinical PSP pathology (Louis et al., 2013).

Corticobasal syndrome (CBS) is an atypical parkinsonian syndrome with a heterogeneous spectrum of pathologies. Although usually not the most prominent feature, tremor is frequently seen in CBS, occurring in 20% of cases at presentation and 39% at some point in the disease (Shimohata et al., 2015). Postural tremor is the most prominent type of tremor and is usually more jerky, irregular and faster (6–8 Hz) than tremor in Parkinson disease (Mahapatra et al., 2004). Similar to MSA, myoclonus is seen in up to 27% of cases (Shimohata et al., 2015) and is often stimulus-sensitive.

Drug-induced parkinsonism (DIP) is usually the result of antipsychotic medication. Asymmetrical parkinsonism with tremor may occur in up to 30–50% of DIP patients, and this can sometimes cause a diagnostic dilemma when considering Parkinson disease (Shin and Chung, 2012). Some patients with DIP have a preclinical stage of Parkinson disease that is unmasked by the offending drug (Shin and Chung, 2012). Electrophysiological differences between Parkinson tremor and DIP tremor have been found: a slightly higher frequency (5.9 versus 4.7 Hz), longer burst duration (103 vs 88 ms), much lower amplitude (0.16 vs. 0.41 mV), and synchronous agonist–antagonist EMG pattern in DIP (Nistico et al., 2016). As previously noted in Section 3.2, the significance of an agonist–antagonist EMG pattern must be interpreted in the context of tremor amplitude.

Vascular parkinsonism (VP) is generally characterized by lower-body parkinsonism and the absence of rest tremor (Kalra et al., 2010). Postural tremor is very common feature observed in roughly two thirds of patients (Demirkiran et al., 2001).

Finally, another clinical entity named ‘monosymptomatic tremor at rest’ or ‘benign tremulous parkinsonism’ has been described in patients with rest tremor that resembles Parkinson tremor but no other signs of parkinsonism, despite many years of disease (Ghaemi et al., 2002, Josephs et al., 2006). Most of these patients develop classical or tremor dominant PD, so this may be a subtype of Parkinson disease.

4.3. Pathophysiology of Parkinson tremor

Parkinson tremor is caused by central mechanisms (Deuschl et al., 2003, Deuschl et al., 2000, Elble, 1996), although peripheral mechanisms (e.g. somatosensory afferents) may also influence the appearance and continuation of tremor (Dirkx et al., 2019). The main electrophysiological techniques used to investigate tremor-related brain regions are surface EMG and accelerometry to record tremor that is mathematically correlated in the frequency domain (coherence analysis) with MEG, EEG, or intra-operative microelectrodes. Microelectrode recordings have revealed neurons firing at tremor frequency in the ventral intermediate nucleus of the thalamus (ventralis intermedius: Vim) (Lenz et al., 1994, Magnin et al., 2000), but also in the subthalamic nucleus (STN) (Hirschmann et al., 2013, Levy et al., 2000, Moran et al., 2008) and pallidum (Raz et al., 2000). Additionally, tremor is associated with increases in power in the low-gamma frequency band (35–55 Hz) of recorded local field potentials (LFPs) in the basal ganglia (Weinberger et al., 2009), but also in the alpha/low-beta range (Fig. 2C) (Hirschmann et al., 2019). Interestingly, the basal ganglia exhibit a spatial distribution of tremor-related LFPs that are coherent with the tremor-related EMG signal of different muscles (Reck et al., 2009). This may explain why tremors in different limbs are typically not coherent with each other (Hurtado et al., 2000).

Pallidal neurons are only transiently and inconsistently coherent with tremor (Hurtado et al., 1999, Raz et al., 2000), while Vim activity is highly synchronous with tremor (Lenz et al., 1994, Timmermann et al., 2003) (Fig. 10A/B). Combined EMG-MEG and EMG-EEG studies confirm this observation, showing highly synchronous tremor-related oscillatory activity in a network consisting of primary motor cortex, cerebellum, and a diencephalic region that is probably the thalamus (Muthuraman et al., 2018, Timmermann et al., 2003, Volkmann et al., 1996).

Imaging studies have confirmed the role of both basal ganglia and a cerebellothalamocortical circuit in Parkinson tremor. PET studies have shown tremor-related hypermetabolism of the cerebellothalamocortical circuit (Deiber et al., 1993, Fukuda et al., 2004) and putamen (Mure et al., 2011), and structural MRI studies have shown reduced grey matter in cerebellum (Benninger et al., 2009) and increased grey matter in the ventrolateral nucleus of the thalamus (VLp, which corresponds to Vim) (Kassubek et al., 2002). Clinical intervention studies targeting either basal ganglia or parts of the cerebellothalamocortical circuit have shown that both circuits are important targets for modulating and treating tremor. Stereotactic disruption of basal ganglia (GPi, STN) or thalamus (Vim) with deep brain stimulation (DBS) or neurosurgical lesioning is effective treatment of Parkinson tremor (Benabid et al., 1991, Krack et al., 1997, Lozano et al., 1995). Furthermore, transcranial magnetic stimulation (TMS) and alternating current stimulation (tACS) of the motor cortex are capable of resetting the rhythm of rest tremor and postural tremor (Britton et al., 1993, Ni et al., 2010, Pascual-Leone et al., 1994) and reduce tremor amplitude (Brittain et al., 2013, Helmich et al., 2021). Interestingly, transcranial stimulation of the cerebellum can reset re-emergent postural tremor but not rest tremor (Helmich et al., 2021, Ni et al., 2010). These findings suggest that the primary motor cortex controls both the amplitude and the rhythm of rest tremor, while the cerebellum may play a greater role in controlling the rhythm of postural tremor.

Although the involvement of both basal ganglia and cerebellothalamocortical circuit is clear, the exact role and interaction of these circuits have remained elusive. Combined EMG and functional MRI has been used to investigate the differential role of basal ganglia and cerebellothalamocortical circuit (Helmich, 2018). Based on these data, a dimmer-switch hypothesis was posed (Helmich et al., 2012), stating that the basal ganglia initiate a tremor episode (analogous to a light switch) whereas the cerebellothalamocortical circuit modulates tremor amplitude (analogous to a light dimmer) (Fig. 11). Evidence for this theory comes from the observation that fluctuations in tremor amplitude are related to activity in a cerebellothalamocortical circuit, whereas tremor occurrence is related to activity in the basal ganglia (Dirkx et al., 2016, Dirkx et al., 2017, Dirkx et al., 2019, Helmich et al., 2011). Subsequent studies replicated and extended these initial findings and showed that dopamine replacement therapy reduced tremor by selectively inhibiting the cerebellar thalamus (VLp/Vim) (Dirkx et al., 2017), while this effect was reduced in patients with a dopamine-resistant tremor. In contrast, patients with a dopamine-resistant tremor showed more tremor-related activity in non-dopaminergic areas, particularly the cerebellum (Dirkx et al., 2019). Furthermore, it was found that the increase of tremor during cognitive load was associated with increased interactions

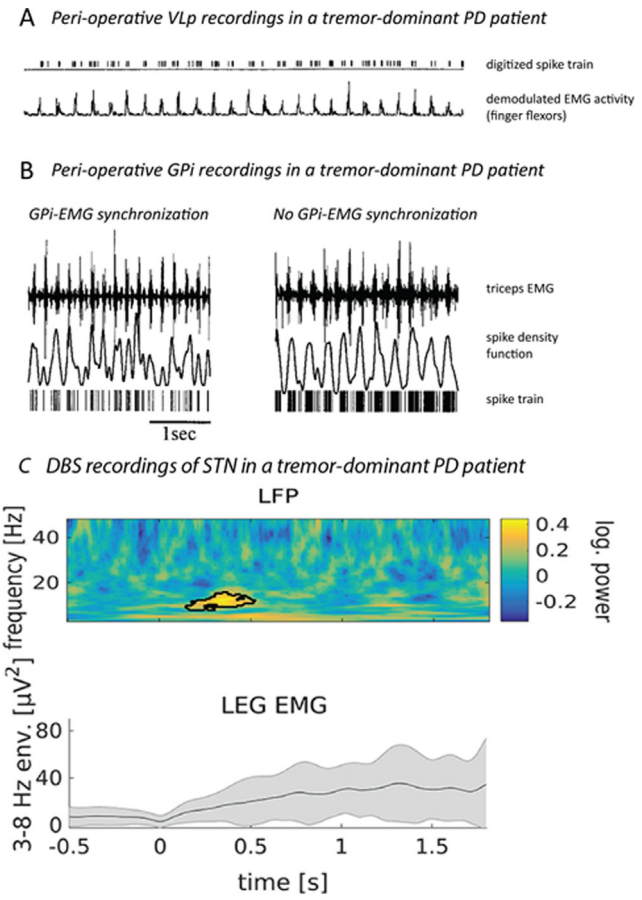

Fig. 10. Neuronal correlates of Parkinson disease tremor. (A) Simultaneous recording of thalamic posterior VL (VLp) single-unit activity and peripheral EMG during tremor in a parkinsonian patient. These data show continuous synchronization between internal globus pallidus activity and peripheral EMG. *Adapted from (Lenz et al., 1988), Copyright 1988 Society for Neuroscience.* (B) Simultaneous recording of internal globus pallidus (GPi) multi-unit activity and peripheral EMG during tremor in a patient with Parkinson disease (PD). The two plots illustrate the raw signals of two epochs of data sampled 5 min apart. Note that in the left trace the peaks in the spike density function coincide with the EMG bursts, whereas in the right trace the oscillations in the spike density function occur at a lower frequency than the EMG. These data show that synchronization between neuronal activity in internal globus pallidus and peripheral EMG is transient in nature. *Adapted from (Hurtado et al., 1999), Copyright 1999 National Academy of Sciences.* (C) Concurrent recording of local-field potentials of the STN and EMG of a trembling leg in PD, showing an increase in subthalamic power at alpha/low beta frequencies during tremor onset. *Adapted from (Hirschmann et al., 2019).* PD = Parkinson disease; VLp = posterior ventrolateral nucleus of thalamus; GPi = internal globus pallidus; EMG = electromyography.

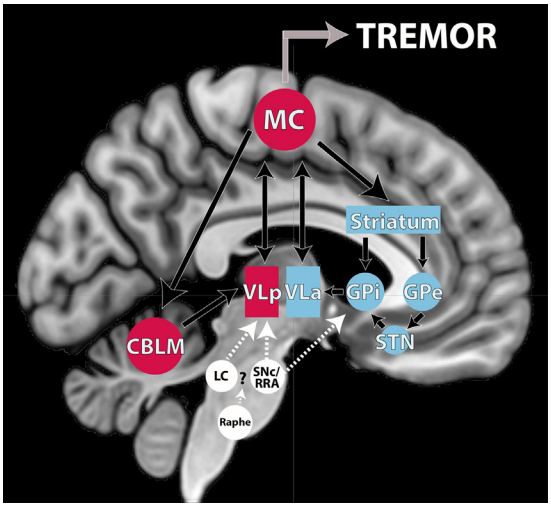

Fig. 11. Illustration of the cerebral network underlying Parkinson rest tremor involving both the basal ganglia (blue) and cerebellothalamocortical circuit (red). According to the dimmer-switch model the basal ganglia initiate a tremor episode (analogous to a light switch) whereas the cerebellothalamocortical circuit produces and modulates tremor amplitude (analogous to a light dimmer). Importantly, multiple neurotransmitter systems are involved, including the dopaminergic retrorubral area (which influences the cerebral tremor circuit through basal ganglia and VLp), noradrenergic locus coeruleus (which influences the cerebral tremor circuit through the VLp) and serotonergic raphe nuclei (unsure where this region targets the cerebral tremor circuit). MC = motor cortex, GPe = globus pallidus externa, GPi = globus pallidus interna, STN = subthalamic nucleus, VLa = anterior ventrolateral nucleus of the thalamus, VLp = posterior ventrolateral nucleus of the thalamus, CBLM = cerebellum, LC = locus coeruleus, RRA = retrorubral area, SNc = substantia nigra pars compacta. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

between a cognitive control network and the cerebellothalamocortical circuit, as well as excitatory effects onto the thalamus (VLp/Vim).

Many questions remain unanswered. Due to the limited temporal resolution of fMRI, it remains elusive which brain region(s) determine tremor frequency. Previous accounts have suggested that the tremor pacemaker may be either part of basal ganglia (Bergman et al., 1998, Plenz and Kital, 1999) or the cerebellothalamocortical circuit (Llinas, 1988) or both (Cagnan et al., 2014). It is also unclear how and under what circumstances the basal ganglia trigger tremor episodes. A recent case report showed a transient increase in subthalamic power at alpha/low beta frequencies at tremor onset (Hirschmann et al., 2019), suggesting that this may represent the tremor trigger (Fig. 10C). However, the temporal causality is not completely clear, as the signal appears to occur shortly after onset of tremor. Furthermore, it is unclear how this signal would be communicated to the cerebellothalamocortical circuit, given that there are typically no tremor oscillations in the pallidal receiving nucleus of the thalamus (Vop) (Magnin et al., 2000). A recent study indicated that GPi can modulate excitability and plasticity of the primary motor cortex via a direct connection (Ni et al., 2018), but confirmation of this anatomical pathway is lacking.

4.4. Laboratory assessment

4.4.1. Electrophysiological assessment of tremor characteristics

In clinical practice, it is rarely necessary to objectify tremor with electrophysiological tools. There are a few situations in which sEMG polymyography and motion transducers (preferably IMUs) are useful in clinical diagnosis. First, polymyography is useful in differentiating tremor from myoclonus. Features that can distinguish myoclonus from tremor include short electromyogram bursts (<50–100 ms), very irregular frequency, a wider range of frequencies (7–18 Hz), and EMG silent periods corresponding to negative myoclonus (Okuma et al., 2005). Single EMG bursts and silent periods will perturb the mechanical-reflex system, resulting in abnormal "enhanced" mechanical-reflex tremor (Elble, 1991, Shahani and Young, 1976). Furthermore, tremor recordings can be used to distinguish specific subtypes of parkinsonian tremor, such as re-emergent, pure postural and orthostatic tremor. The most important features of Parkinson tremor subtypes and their mimics are summarized in Table 3.

Tremor in Parkinson disease is highly variable, not only in amplitude but also in the involved muscles and joints. For instance, upper limb tremor may spontaneously change from wrist flexion/extension to hand pronation/supination to thumb flexion/extension. Multiple IMUs, one on each body segment of interest, are required to fully capture this complexity (Ben-Pazi et al., 2001). Distal limb muscles (e.g., flexor carpi radialis, extensor digitorum communis, abductor pollicis longus, first dorsal interosseus) are usually involved, but proximal muscles (e.g., biceps, triceps and deltoid) may also contribute. In the specific case of orthostatic tremor, recording may be extended to lower limb muscles (e.g., bilateral tibialis anterior and gastrocnemius) (Vial et al., 2019).

Rest tremor in the upper limb is best measured when patients are seated in a comfortable chair, with both forearms relaxed on

Table 3
Overview of the various tremor subtypes that are found in Parkinson disease.

Tremor type	Prevalence	Frequency	Amplitude	Response to dopaminergic medication	Response to non-dopaminergic medication	Clinical Characteristics
Rest tremor	75%	4–7 Hz	Medium - large	+[n]	+/–[m]	- Asymmetric, distal - Pill-rolling aspect - Suppressed by voluntary movement - Spontaneous waxing/waning - Increase with cognitive/motor activation
Re-emergent postural tremor	66%	4–7 Hz (±0.4 Hz higher than rest)	Medium - large	+[n]	?	- Onset seconds to minutes after posturing
Pure postural tremor	15%	7–12 Hz	Small	–	?	- Starts immediately upon posturing
Kinetic tremor	>80%	5–8 Hz (±1 Hz higher than rest)	Medium	–	?	- May resemble enhanced physiologic tremor
(Pseudo-) orthostatic tremor	Rare	4–18 Hz	Small	+/–	?	- Should be considered in patients with unsteadiness

[n] On average good response to dopaminergic medication, however large inter-subject variability.
[m] No reliable clinical trials, but beta-blockers, anticholinergics or clozapine are sometimes effective.

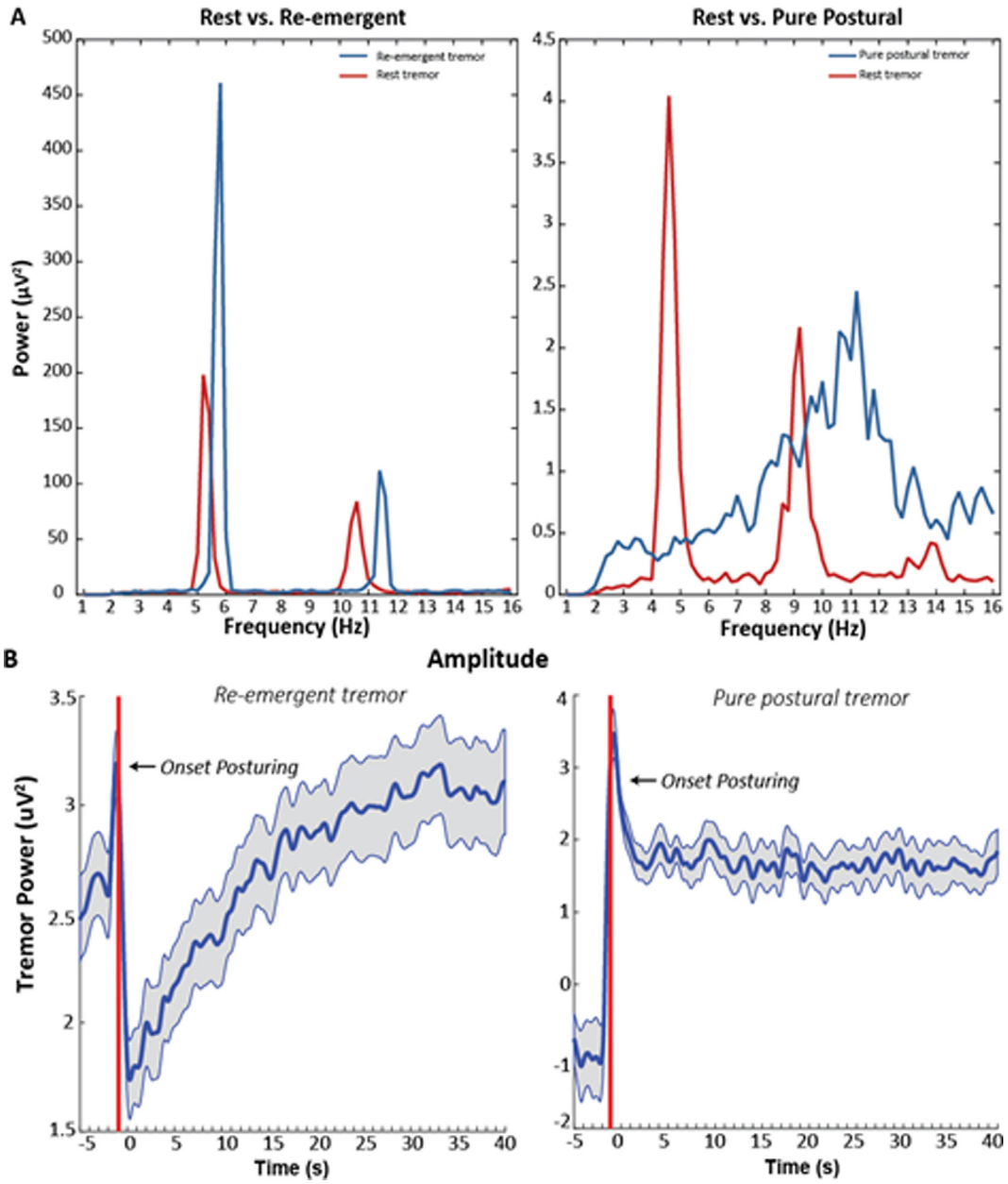

Fig. 12. Electrophysiological properties of Parkinson disease rest tremor, re-emergent tremor and pure postural tremor. (A) comparison of power spectra between rest- and postural tremor in Parkinson disease, showing that re-emergent tremor very much resembles rest tremor whereas pure postural tremor displays a higher frequency and broader peak in the power spectrum. (B) Course of tremor amplitude upon posturing showing that pure postural tremor starts immediately upon posturing, whereas re-emergent tremor may take seconds to minutes to increase in amplitude. *Adapted from (*Dirkx et al., 2018*) with permission of Wolters Kluwer Inc.*

arm rests and the hands dangling freely. As the classical parkinsonian rest tremor waxes and wanes spontaneously, a several minutes of recording may be necessary to capture mild rest tremor. Additionally, the effect of cognitive load (e.g., serial subtraction) is commonly used to elicit and amplify a subtle rest tremor (Dirkx et al., 2020, Raethjen et al., 2008, Zach et al., 2017) Rest tremor usually has a frequency of 4–7 Hz and produces a narrow peak in the power spectrum (half-power bandwidth $\leq$ 1 Hz). Furthermore, peaks at double and triple tremor frequency (first and second harmonic) are often observed in the power spectrum (Raethjen et al., 2009). Harmonic distortion is a characteristic of nonlinear oscillators, and all tremors emerge from nonlinear properties of neural networks. Nonlinear oscillation exhibits harmonic distortion that increases with amplitude (http://physics.bu.edu/py231/osc-nl-fourier.pdf). Therefore, it is necessary to control for tremor amplitude when interpreting harmonics. One study found greater harmonic distortion in Parkinson tremor than ET, but the amplitude of ET was much less (Muthuraman et al., 2011), illustrating once again the need to control for amplitude when interpreting electrophysiologic tests.

Once a rest tremor is present, patients may be instructed to extend their wrists as fast as possible in order to evaluate whether tremor is suppressed. The suppression of tremor by voluntary movements is highly specific for tremor in Parkinson disease (Papengut et al., 2013) and can best be detected during rapid movements (Fig. 12). If there is an immediate postural tremor without transient suppression, then pure postural tremor may be present and usually has a higher frequency (±8 Hz), lower amplitude, and wider half-power bandwidth (Dirkx et al., 2018). It should be noted that loading of the wrists does not change tremor

frequency of postural tremor in Parkinson disease, as mainly central mechanisms are involved (Deuschl et al., 2000). If clinically suspected, orthostatic tremor during standing can be evaluated with methods described in Section 7.

4.4.2. Wearables for parkinsonian tremor

Wearable sensors (IMUs) may be used to retrieve an objective longitudinal overview of tremor and other symptoms in patients with Parkinson disease (Cohen et al., 2016, Maetzler et al., 2013). Currently, a number of devices have been validated for the detection of tremor in Parkinson disease, including proprietary devices such as Kinesia™, Parkinson KinetiGraph (PKG™) (Giuffrida et al., 2009, Woodrow et al., 2020), and many smartwatches (Powers et al., 2021). Current consensus states that these devices may be superior to qualitative assessment in the evaluation of treatment effect (both under- and overtreatment) (Odin et al., 2018, Powers et al., 2021), especially when compared to inexperienced clinicians. However, more evidence is required before wearables will become common practice.

5. Dystonic tremor

5.1. Clinical definition

Dystonic tremor syndromes comprise tremor and dystonia as the main neurological signs. Two types of tremor in dystonia are specified in the current consensus classification scheme: dystonic tremor, which is defined as tremor in the same body part affected by dystonia, and tremor associated with dystonia, defined as tremor in a body part not affected by dystonia (Bhatia et al., 2018). An example of dystonic tremor is focal cervical dystonia with concomitant head tremor while an example of tremor associated with dystonia is hand tremor in a patient with focal cervical dystonia. Tremor can be focal, segmental, or generalized, and it may be task- or position-specific. The anatomical distributions of tremor and dystonia may differ in a patient.

5.2. Clinical features of dystonic tremor syndromes

Tremor has been observed in 14–87% of patients presenting with dystonia, particularly in segmental and multifocal dystonia (Pandey and Sarma, 2016). Tremor in dystonia mostly occurs during posture and movement, but rest tremor is also common (Erro et al., 2014, Gigante et al., 2016). The distribution of tremor and the relationship between tremor and dystonia onset are highly variable (Defazio et al., 2013). Tremor may begin before dystonic contractions are apparent (Defazio et al., 2015, Schiebler et al., 2011).

Dystonic tremor is often described as coarse, jerky, irregular, directional, and sometimes position-specific. None of these characteristics are operationally defined with quantitative electrophysiology, and dystonic tremor can be as rhythmic as most other tremors (Yanagisawa and Goto, 1971). The peak frequency of dystonic tremor usually ranges from 3 to 7 Hz, which is overlapping with essential tremor (ET) and Parkinson tremor. Irregularity of tremor amplitude and frequency, asymmetric involvement, and unusual posturing suggest a dystonic tremor syndrome rather than ET (Jedynak et al., 1991, Rudzinska et al., 2013, Shaikh et al., 2008). However, making a diagnosis of dystonic tremor syndrome is challenging in tremulous patients with subtle signs of dystonia (Elble et al., 1990). Overflow, mirror dystonia, sensory trick, and unusual posturing are helpful (Albanese et al., 2013), but the sensitivity and specificity of these signs are modest and probably vary with anatomic distribution of dystonia (Sitburana and Jankovic, 2008). Furthermore, inter-rater reliability in the diagnosis of dystonia and tremor in dystonia is poor (Becktepe et al., 2021, Logroscino et al., 2003, Shaikh et al., 2021).

Rest tremor in dystonia can mimic Parkinson rest tremor, but irregular tremor with thumb extension instead of thumb flexion with pill-rolling patterns is more suggestive of dystonia (Erro et al., 2016). Suppression of rest tremor with voluntary movement and re-emergence strongly supports the diagnosis of Parkinson rest tremor (Papengut et al., 2013).

Dystonia with tremor can be confused with a functional movement disorder. The aforementioned characteristics including jerky and irregular tremor are mostly described in dystonia. Distractibility and entrainment are common signs of functional tremor (Hallett, 2016a).

5.3. Pathophysiology of dystonic tremor syndromes

The pathophysiology of tremor in dystonia likely involves both the cerebellothalamocortical and basal ganglia-thalamocortical pathways (Madelein van der Stouwe et al., 2020, Nieuwhof et al., 2018, Tsuboi et al., 2021). Several lines of evidence indicate that dystonic tremor also shares similar neuroanatomy and physiology of dystonia without tremor, including loss of inhibition at spinal, brainstem, and cortical levels (Cerasa et al., 2014, Conte et al., 2015, Munchau et al., 2001, Nistico et al., 2012, Tinazzi et al., 2013).

Data from functional imaging studies suggest that networks involving both the cerebellum and basal ganglia are involved in dystonic tremor (DeSimone et al., 2019, Madelein van der Stouwe et al., 2020). The relative contributions of basal ganglia versus cerebellothalamortical pathways to the genesis of tremor versus dystonia are unclear. Deep brain stimulation in ventralis intermedius, the nucleus that receives afferents from the cerebellum, is often effective in the treatment of dystonic tremor (Tsuboi et al., 2020), but the optimum target for dystonic tremor is often located more anteriorly at the border of ventralis intermedius and ventralis oralis posterior (Tsuboi et al., 2021). Thus, cerebellothalamocortical and basal ganglia-thalamocortical pathways are both likely involved, and their relative contributions to tremorogenesis may vary among patients and etiologies (Fig. 13).

Pallidal single neuron recordings during DBS revealed similar firing patterns in patients with cervical dystonia without tremor and cervical dystonia with jerky tremor but different firing patterns in cervical dystonia with sinusoidal tremor (Sedov et al., 2020). The different firing patterns may reflect the relative influ-

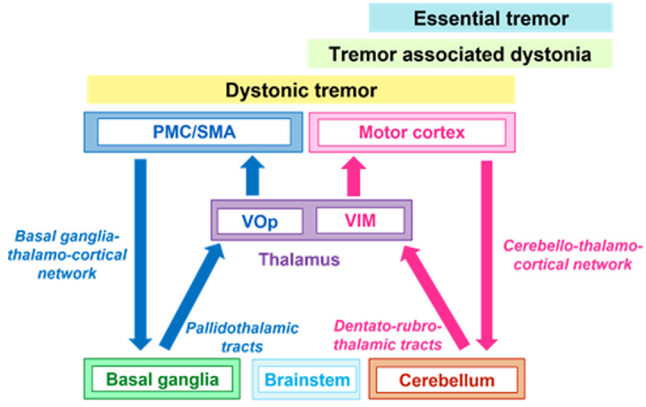

Fig. 13. The proposed tremor-related network in dystonic tremor syndromes. The pathophysiology of DT may likely involve both the basal ganglia-thalamocortical and cerebellothalamocortical pathways while TAWD primarily involves the cerebellar networks similar to ET. The basal ganglia connect to premotor cortex and supplementary motor area via ventralis oralis posterior (Vop) nucleus of thalamus. The cerebellum connects to the motor cortex via the ventrointermediate nucleus of thalamus (VIM).

ence of cerebellothalamocortical and basal ganglia-thalamocortical networks on tremor and dystonic contraction (Madelein van der Stouwe et al., 2020).

The functional influence of the cerebellothalamocortical pathway was studied with paired-pulse TMS of the cerebellum and contralateral motor cortex in patients with dystonic tremor, tremor associated with dystonia, and essential tremor. Patients with dystonic tremor had decreased cerebellothalamocortical inhibition compared to those with tremor associated with dystonia and essential tremor, suggesting a lesser role of the cerebellothalamocortical pathway in dystonic tremor (Panyakaew et al., 2020).

5.4. Laboratory assessment

Given difficulties that clinicians have in clinical diagnosis, diagnostic electrophysiologic tests for dystonic tremor would be very helpful. However, most tests have proven to have poor sensitivity and specificity. For example, Archimedes spirals with multidirectional tremor were more common in dystonic tremor than essential tremor in one small study, but the sensitivity and specificity of this method were only 68% and 60% (Michalec et al., 2014). Furthermore, the spiral axis score in this study correlated with tremor severity, which illustrates a recurring problem in diagnostic electrophysiology for tremor disorders: the kinematic features of tremor (e.g., rhythmicity, harmonic distortion) may be strongly influenced by tremor severity, largely obscuring any effect of diagnosis (Wang et al., 2005).

Currently, there are no validated electrophysiological criteria for diagnosis of dystonic tremor syndromes. EMG recordings of the agonist and the antagonist muscles are useful in demonstrating frequency variability and co-contraction (Fig. 14). Mirror tremor can be seen in the contralateral limb of focal/segmental dystonia (Fig. 15). The reduction of tremor amplitude with sensory trick can also be quantified with sEMG and motion transducer recordings (Masuhr et al., 2000).

A wide peak in the accelerometer or EMG spectrum (large half-power bandwidth) is a measure of tremor irregularity. Tremor stability index (TSI) is another measure of frequency variability that can be calculated from a motion transducer tracing to measure the range of frequency variation over time (di Biase et al., 2017). Higher TSI means greater cycle-to-cycle variation in tremor frequency. Higher TSI has been found in dystonic tremor compared to essential tremor, but the amplitude of dystonic tremor was significantly lower (Panyakaew et al., 2020).

Frequency variability and co-contraction may mimic functional tremor, but the electrophysiological signs of distraction and entrainment are more in favor of functional tremor (Schwingenschuh et al., 2011) (Fig. 16).

Several electrophysiological tests have been used to decipher the pathophysiology of dystonia versus other conditions. Somatosensory temporal discrimination threshold is the shortest interval to discriminate two tactile stimuli. Temporal discrimination threshold was increased in patients with tremor associated with dystonia but was normal in essential tremor (sensitivity = 90%, specificity = 85%) (Tinazzi et al., 2013). This test had a sensitivity = 60% and specificity = 71% in a study comparing patients with questionable dystonic upper limb tremor (i.e., asymmetric, jerky tremor) with essential tremor (Govert et al., 2020). Loss of inhibition in the blink reflex recovery curve was observed in dystonic tremor but not in essential tremor (sensitivity = 100%, specificity = 100%) (Nistico et al., 2012). Loss of presynaptic reciprocal inhibition was reported in a subgroup of patients with cervical

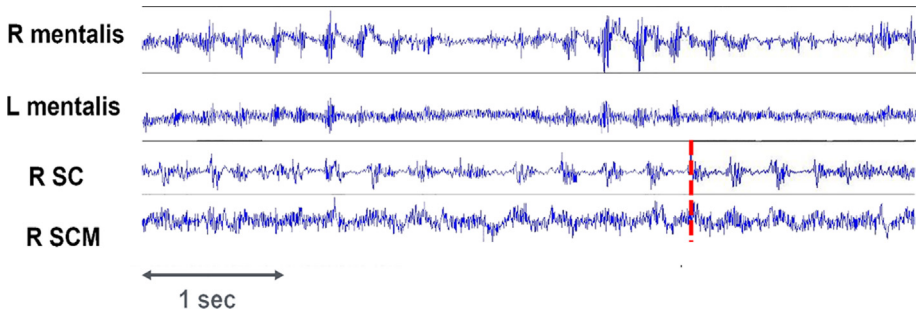

Fig. 14. Surface EMG recordings in a patient with craniocervical dystonia with head and jaw tremor. The tracing showed intermittent tremor with co-contraction of the antagonist pairs of neck muscle. SC: splenius capitis, SCM: sternocleidomastoid.

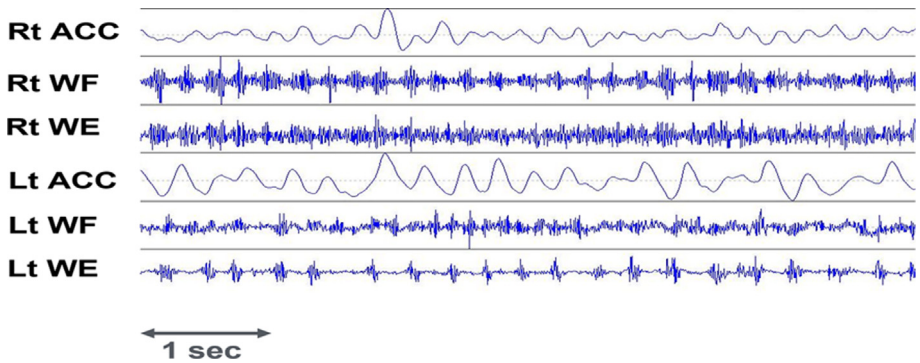

Fig. 15. The accelerometry (ACC) and surface EMG recordings during writing in a patient with writer's cramp with tremor of the right hand (DT) accompanied with mirror dystonia and tremor of the left hand. The top tracing (right ACC) showed irregular tremor with co-contraction of the antagonist pairs of the right wrist muscles, and mirror tremor and dystonia on the contralateral hand. WF; wrist flexor, WE: wrist extensor.

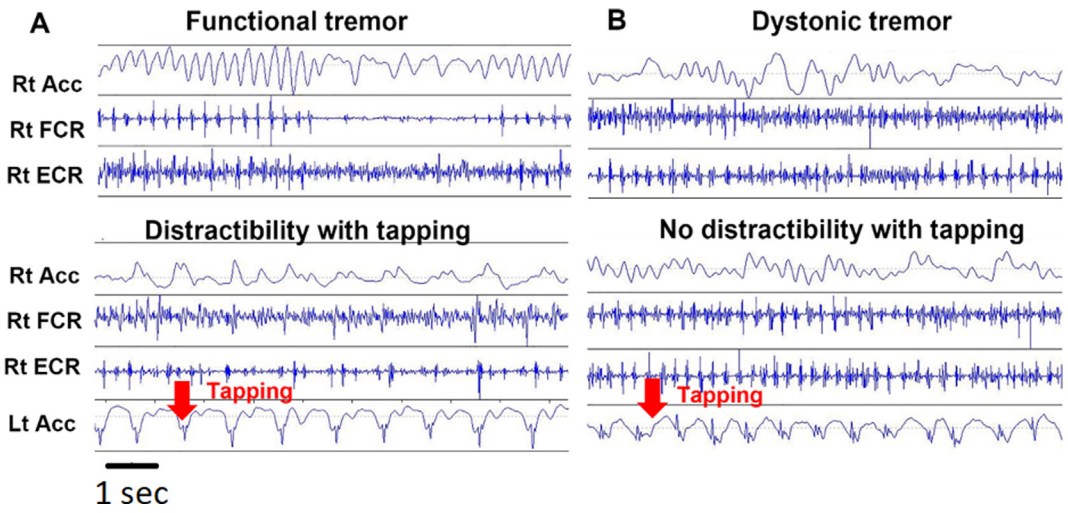

Fig. 16. The accelerometry (ACC) and surface EMG recordings in patients with right (Rt) upper limb functional tremor (A) and dystonic tremor (B). Both patients exhibited variability of tremor frequency, but only functional tremor was disrupted and suppressed during left (Lt) finger tapping. FCR; flexor carpi radialis, ECR; extensor carpi radialis.

dystonia and hand tremor but not in essential tremor, and dystonic patients are more likely to exhibit co-contraction of the antagonist muscles during the initiation of ballistic wrist movements (sensitivity and specificity unknown) (Munchau et al., 2001).

6. Task-specific tremors

6.1. Clinical definition

Task-specific tremors (TST) are defined as action tremors occurring only during the exertion of a specific and usually skilled task (Bhatia et al., 2018). Different parts of the body (e.g., hand, head, lips) may be affected, and TST has been described for several activating conditions including writing, sports, or certain professions.

TST should be distinguished from position-specific tremor, in which no specific task is needed to induce the tremor, but the position itself triggers the occurrence of the shaking.

6.2. Specific clinical features of task-specific tremors

No epidemiologic data exist on primary writing tremor (PWT) as originally described (Rothwell et al., 1979), but PWT is regarded as the most common form of TST and has been studied most extensively (Bain et al., 1995b, Elble et al., 1990, Latorre et al., 2021, Modugno et al., 2002).

PWT is characterized by a tremor of the hand occurring only during writing (type A) or also on adopting the hand posture that is normally used for writing (type B) (Bain et al., 1995a). While type A writing tremor represents a task-specific tremor in the narrow sense, type B writing tremor is rather position-specific. It is not clear whether these conditions truly represent distinct clinical entities (Bain et al., 1995a).

Large epidemiologic trials on PWT are lacking, but within the published studies, a strong male prevalence was evident, and the mean onset age in one of the largest studies of PWT was 50.1 years (Bain et al., 1995b, Elble et al., 1990, Latorre et al., 2021, Modugno et al., 2002). PWT usually remains focal but bilateral PWT has been described (Jimenez-Jimenez et al., 1998) as well as subsequent development of a postural or kinetic tremor component (Bain et al., 1995a, Elble et al., 1990). In about one third of the patients, tremor markedly improves or abolishes after alcohol consumption (Bain et al., 1995a).

Apart from PWT, tremor in several other tasks has been described, including tremors restricted to the mandible only while drinking from a cup or glass (Miles et al., 1997), speech-related tremor of the lips (Morita et al., 2002), hand- or arm tremor in skilled craftsmen, dentists, golfers, dart players, rifle shooters, and musicians (Frucht et al., 2001, Soland et al., 1996).

According to the current tremor classification, the axis 1 category of TST can be combined with different etiologies on axis 2 (Bhatia et al., 2018). The etiology is unknown in most patients with TST, including PWT. About one third of the PWT patients have a positive family history for this condition and about one fifth of the patients report a preceding, usually mild, trauma to the dominant arm and occurrence of tremor after a variable delay between several months to years (Bain et al., 1995a).

Since the first descriptions of PWT, there has been an ongoing debate whether this type of tremor is a form of task-specific dystonia, a variant of ET (Kachi et al., 1985, Koller and Martyn, 1986), or a separate disease entity (Bain et al., 1995a, Berg et al., 2000). Task- and position-specific tremors are no longer considered variants of ET (Bhatia et al., 2018).

Case descriptions of PWT in both hands with a positive family history of ET, alcohol sensitivity and therapeutic response to propranolol or primidone treatment as well as the lack of a sensory trick in the majority of patients have been regarded as arguments for PWT being a variant of ET (Jimenez-Jimenez et al., 1998, Kachi et al., 1985, Koller and Martyn, 1986). However, reports of PWT and writer's cramp within the same patient, a positive family history of dystonia, mirror tremor provoked by writing with the contralateral hand in analogy to mirror dystonia, and single cases of TST with successful tremor improvement by a sensory trick argue for a dystonic nature of PWT (Bagella et al., 2017, Cohen et al., 1987, Elble et al., 1990, Erro et al., 2015, Hayashi and Koide, 1997, Pita Lobo et al., 2013, Schreglmann et al., 2015).

Some patients with TST develop Parkinson disease. In a recent case series of 12 Parkinson patients with TST, the first sign of Parkinson disease was rest tremor in 10 and bradykinesia in two. The mean duration between onset of TST and the onset of PD was 13.66 ± 14.36 years. In all patients with upper limb TST, PD rest tremor appeared ipsilateral to the TST arm, suggesting that TST was a precursor to PD in this population (Koneru and Ondo, 2021).

6.3. Pathophysiology

Patients with PWT do not exhibit unequivocal dystonic posturing of the hand during writing, but posturing suggestive of dystonia may be seen (Elble et al., 1990). The usual concern is whether this posturing is a compensatory measure to control tremor or true dystonia. In one study, EMG revealed abnormal coactivation of antagonistic muscles with spread to proximal muscles, in addition to suspicious hand/wrist posturing, suggestive of dystonia (Elble et al., 1990).

Normal reciprocal inhibition of forearm antagonist muscles, which is typically reduced in writeŕs cramp, has been found in type A and B PWT patients (Bain et al., 1995a, Modugno et al., 2002), and intracortical excitability studied with paired transcranial magnetic stimulation at short and long interstimulus intervals was abnormal in writeŕs cramp but normal in PWT (Modugno et al., 2002). In another study, patients with PWT and dystonic tremor had reduced blink recovery cycle inhibition and no effect of paired associative stimulation on long-interval intracortical inhibition, compared with ET patients and controls. These electrophysiologic results suggest that PWT is more like dystonic tremor than ET. However, these electrophysiologic tests exhibit considerable within-subject variability, and studies with small sample size (Sadnicka et al., 2021) and different etiologies of dystonia (Sadnicka et al., 2015) have produced conflicting results.

In professional violinists with bowing tremor, electromyographic tremor-specific muscular coactivation in the frequency range of 3 to 8 Hz was found, but not in the healthy controls. Additionally, no muscular activity was found at the resonance frequency range of the wrist, indicating an association between coactivation and bowing tremor at a specific frequency range and suggesting that central mechanisms play a dominant role, rather than mechanical-reflex mechanisms (Lee et al., 2013).

In summary, pathophysiologic knowledge about TST is still controversial, and knowledge is mainly based on small studies of PWT. Additional research is needed to fully understand the pathophysiology of PWT and TST in general.

6.4. Laboratory assessment

In most clinical encounters, the diagnosis of TST can be made without electrophysiological assessment. In PWT patients, electromyographic frequencies of 4–7 Hz can be found during writing, and patients can be assessed for overflow contraction, abnormal muscle co-contraction, and task specificity (Elble et al., 1990). When the arms are at rest, held outstretched, or placed in a typical posture for writing, type A PWT patients exhibit no rhythmic EMG activity, but type B PWT patients exhibit rhythmic EMG activity when the affected hand is placed in a writing posture or pronated to a critical angle.

7. Orthostatic tremor

7.1. Clinical definition

The key feature of OT is the occurrence of tremor during standing (Heilman, 1984, Pazzaglia et al., 1970, Thompson et al., 1986). The current consensus statement subdivides OT into the axis 1 syndromes of *primary OT, primary OT plus, and pseudo-orthostatic tremor* (Bhatia et al., 2018). Primary OT is a generalized high-frequency (13–18 Hz) isolated tremor syndrome that occurs when standing. Electrophysiologic confirmation of the tremor frequency is required to establish the diagnosis. When OT with a frequency of 13–18 Hz occurs in combination with other neurologic signs (e.g. parkinsonism, cerebellar ataxia, cognitive disturbances, peripheral neuropathy), it should be labeled primary OT plus (Gerschlager et al., 2004). OT with a tremor frequency below 13 Hz has been labeled as slow orthostatic tremor or tremor in orthostatism. This type of OT is frequently associated with additional neurological signs. According to the current tremor classification, orthostatic tremors below 13 Hz are classified as pseudo-orthostatic tremor (Bhatia et al., 2018).

The axis 1 categories of primary OT, primary OT plus, and pseudo-orthostatic tremor can be combined with different etiologies on axis 2 (Bhatia et al., 2018). The etiology of primary OT is unknown. Primary OT plus occurs with other neurologic disorders, most commonly parkinsonism, in about 9%. However, when excluding co-existent neurodegenerative conditions, OT cases (85%) do not evolve into a more pervasive neurologic disorder (Hassan et al., 2016). Approximately two-thirds of pseudo-orthostatic tremor cases occur in association with other neurologic conditions, such as parkinsonism, ataxia and dystonia (Hassan and Caviness, 2019).

7.2. Specific clinical features

Primary OT is considered uncommon, but its precise incidence and prevalence are unknown. The typical onset is the 6th decade, ranging widely between teenage and elderly years, and females are more commonly affected (Hassan et al., 2016). All patients report symptoms only when standing and not while seated. Symptoms may be confined to the legs or can spread to the trunk and arms while standing. Patients frequently report difficulty standing still. Patients often employ compensatory strategies, such as clawing the ground with their toes or shifting their weight from leg to leg, to assist balance or diminish tremor. Symptoms can be diminished by leaning against an object or with walking. For example, difficulty standing in a shopping line may be alleviated by leaning on a shopping trolley. With leaning, tremor can transmit to the upper limbs; patients may report shaky handwriting when standing and leaning to write. Additionally, OT may occur without an upright posture, e.g., when a patient is on all fours or when contracting leg muscles against resistance while sitting or lying supine. About half of patients report benefit from alcohol (Hassan et al., 2016, Hassan and van Gerpen, 2016).

Early on, symptoms are usually mild or have delayed latency to onset after standing. The tremor progressively worsens over time, with earlier onset after standing and greater unsteadiness. One-quarter of patients report falls. Coexistent essential-type tremor is reported in about a quarter of patients (Ganos et al., 2016, Hassan et al., 2016).

OT is difficult to see and can be reliably diagnosed only by surface electromyography (sEMG); leg muscle palpation and auscultation are not sufficiently sensitive or specific. sEMG also distinguishes primary OT from clinical mimickers (Hassan and van Gerpen, 2016). These include orthostatic myoclonus, nonspecific leg tremulousness due to disorders of stance and balance (e.g., ataxia, peripheral neuropathy), other orthostatic-generated disorders (e.g., orthostatic hypotension, pseudoclaudication with lumbar spinal stenosis), and functional tremor.

Patients with slow forms of OT have similar demographic and clinical features to *primary OT*. It is also more common in older females. Patients report leg shakiness and imbalance upon standing. However, gait unsteadiness, falls, and abnormal gait are more common than in *primary OT*. It may occasionally transmit to the limbs with leaning but not as reliably as primary OT (Rigby et al., 2015). It may persist walking backwards. In contrast with primary OT, one-third of cases are isolated, and two-thirds are associated with other neurologic disorders (Hassan and Caviness, 2019). Essential tremor is also present in about one-third. Clinical mimickers are similar to those of *primary OT*. Orthostatic myoclonus

is an important clinical mimicker of slow OT, with leg shaking on standing that does not abate with walking and does not transmit to the upper limbs with leaning. Parkinsonian re-emergent leg tremor may also resemble slow OT, but it is typically distinguished by the presence of unilateral or asymmetric leg tremor with standing.

7.3. Pathophysiology

7.3.1. Electrophysiology

The pathophysiology of pseudo-orthostatic tremors is mainly based on single case reports and series, and larger original research trials are lacking. Therefore, the following summary of electrophysiology and imaging findings will focus mainly on primary OT.

Spectral analysis of EMG recordings in primary OT patients reveals 13–18 Hz tremor in the muscles of the limbs, trunk, and even cranial muscles, and there is a uniformly very high (near one) coherence among ipsilateral and contralateral body parts (Koster et al., 1999). The tremor bursts are typically uniformly narrow and high amplitude, with typical burst duration of 25–40 ms. Frequency domain analysis of postural muscle EMG signals in primary OT patients demonstrates that the timing of OT bursts varies among patients and among motor tasks (McAuley et al., 2000).

Slower forms of OT are mostly reported to have low coherence (0.2–0.8) with a broader spectral peak (Rigby et al., 2015), although several cases with high coherence have been reported (Hassan and Caviness, 2019). The tremor bursts can be either synchronous or alternating, in either analogous muscles or in agonist/antagonist muscle pairs. Muscle burst duration can range from 50 to 150 ms and is variable.

Coherent source analysis in primary OT patients during standing showed cerebellothalamocortical EEG coherent with the peripheral tremor signal (Muthuraman et al., 2013). While this activation was bilateral for the first ~15 s, it subsequently became unilateral, providing a possible pathophysiologic clue to the subjective feeling of unsteadiness.

OT patients have a suppressed acoustic startle response in comparison with healthy controls, suggesting altered brainstem functions (Kiziltan et al., 2012). Additionally, OT can be reset by electrical stimulation over the posterior fossa at intensities that are below the threshold for motor evoked potentials, which supports involvement of the cerebellum (Wu et al., 2001).

7.3.2. Neuroimaging

The neuroanatomical and pathophysiological characteristics of primary OT have been studied with several different neuroimaging modalities including functional and structural MRI, magnetic resonance spectroscopy (MRS), single photon emission computerized tomography (SPECT), and positron emission tomography (PET).

In an $H_2^{15}O$ PET study, significantly greater cerebellar activation was demonstrated in primary OT patients during postural position of the right arm and during rest compared with age- and gender-matched controls (Wills et al., 1996). More recently, cerebral glucose metabolism was quantified with ^{18}F-fluorodeoxyglucose PET (^{18}F-FDG-PET) was increased in the pontine tegmentum, the posterior cerebellum (including the dentate nuclei), the ventral intermediate and ventral posterolateral nuclei of the thalamus, and the primary motor cortex bilaterally in the supine position and while standing. These results confirmed an abnormally activated ponto-cerebello-thalamo-primary motor cortical circuitry in primary OT which is present at rest already and further activated during standing. In comparison to other tremor disorders, the involvement of the pontine tegmentum in the pathophysiology of tremor generation may be a unique feature in OT (Schoberl et al., 2017).

In a multimodal neuroimaging study using resting state functional MRI (rs-fMRI) and voxel-based morphometry (VBM), increases of grey matter volume in the cerebellar vermis and supplementary motor area were found in patients with primary OT, and decreased grey matter in the lateral cerebellum was found. Additionally, functional connectivity between the lateral cerebellum and the supplementary motor area was abnormally increased in patients with OT. By applying repetitive transcranial stimulation, tremor severity and functional connectivity between the lateral cerebellum and the supplementary motor area were reduced (Gallea et al., 2016). In another rs-fMRI study, decreased connectivity between cerebellum and sensorimotor networks and increased connectivity in resting-state networks involved in cognitive processes (default mode network and frontoparietal networks) were found (Benito-Leon et al., 2016). In a diffusion tensor imaging (DTI) study applying whole-brain tract-based spatial statistics (TBSS), altered diffusion metrics preferentially located in the cerebellum and its efferent pathways, as well as in the pontine tegmentum and key components of the frontal–thalamic–cerebellar circuit (Benito-Leon et al., 2019b). Using a data mining approach applied to MRI-derived brain volume and cortical thickness data, OT patients could be distinguished from patients with essential tremor by four MRI features with 100% diagnostic accuracy. Key regions for the characterization were left thalamus volume, right superior parietal volume, right superior parietal thickness, and right inferior parietal roughness, underlining that OT and ET show distinct brain structural alterations (Benito-Leon et al., 2019a).

A SPECT study using 123I-FP-CIT ([123I]-2 β -carbomethoxy-3β-(-4-iodophenyl)-N-(3-fluoropropyl)-nortropane) dopamine transporter tracer showed a reduction of striatal tracer binding in OT patients compared to normal controls. In comparison to PD patients, tracer uptake was significantly less affected, more symmetrical and caudate and putamen were equally affected. Levodopa challenge in these OT patients did not significantly improve tremor (Katzenschlager et al., 2003), and subsequent SPECT studies did not find altered striatal dopamine transporters with 123I-FP-CIT SPECT imaging in primary OT patients (Trocello et al., 2008, Vaamonde et al., 2006). Therefore, a dopaminergic deficit not found in most OT patients.

In pseudo-orthostatic tremor, focal structural and/or functional imaging abnormalities are reported in about a fifth of cases, involving brain or spinal cord, and most commonly the cerebellum, pons, medulla, and upper spinal cord. In several cases with coexisting parkinsonism, SPECT imaging was abnormal reflecting dopaminergic deficit (Hassan and Caviness, 2019).

In summary, several lines of evidence from electrophysiological and neuroimaging studies indicate a central oscillating network that involves cerebellum, brainstem, thalamus, premotor- and primary motor areas as a key pathophysiologic feature in OT. This tremor network in primary OT seems to differ from networks in other tremor disorders (like ET) by its anatomical distribution and certain neurophysiological aspects. A dopaminergic deficit is present in some patients but is not a characteristic feature of primary OT.

7.4. Laboratory assessment

Electrophysiology is the gold standard for diagnosis of primary OT and is pathognomonic. It distinguishes primary orthostatic tremor from orthostatic myoclonus, functional leg shakiness, and other mimickers. It also subclassifies high frequency and low frequency OT.

Surface electromyography recording from at least one leg muscle (e.g., tibialis anterior) during standing is required for diagnosis of OT. In primary OT, the rapid tremor bursts sound like whirring helicopter blades when one listens to sEMG on a speaker. Simultaneous recording from multiple muscles (e.g., bilateral leg muscles, paraspinals, or upper limb muscles) is needed for coherence and phase analyses (Fig. 17). In primary OT, tremor is 13–18 Hz, and tremor bursts are uniformly short duration. Tremor up to 23 Hz

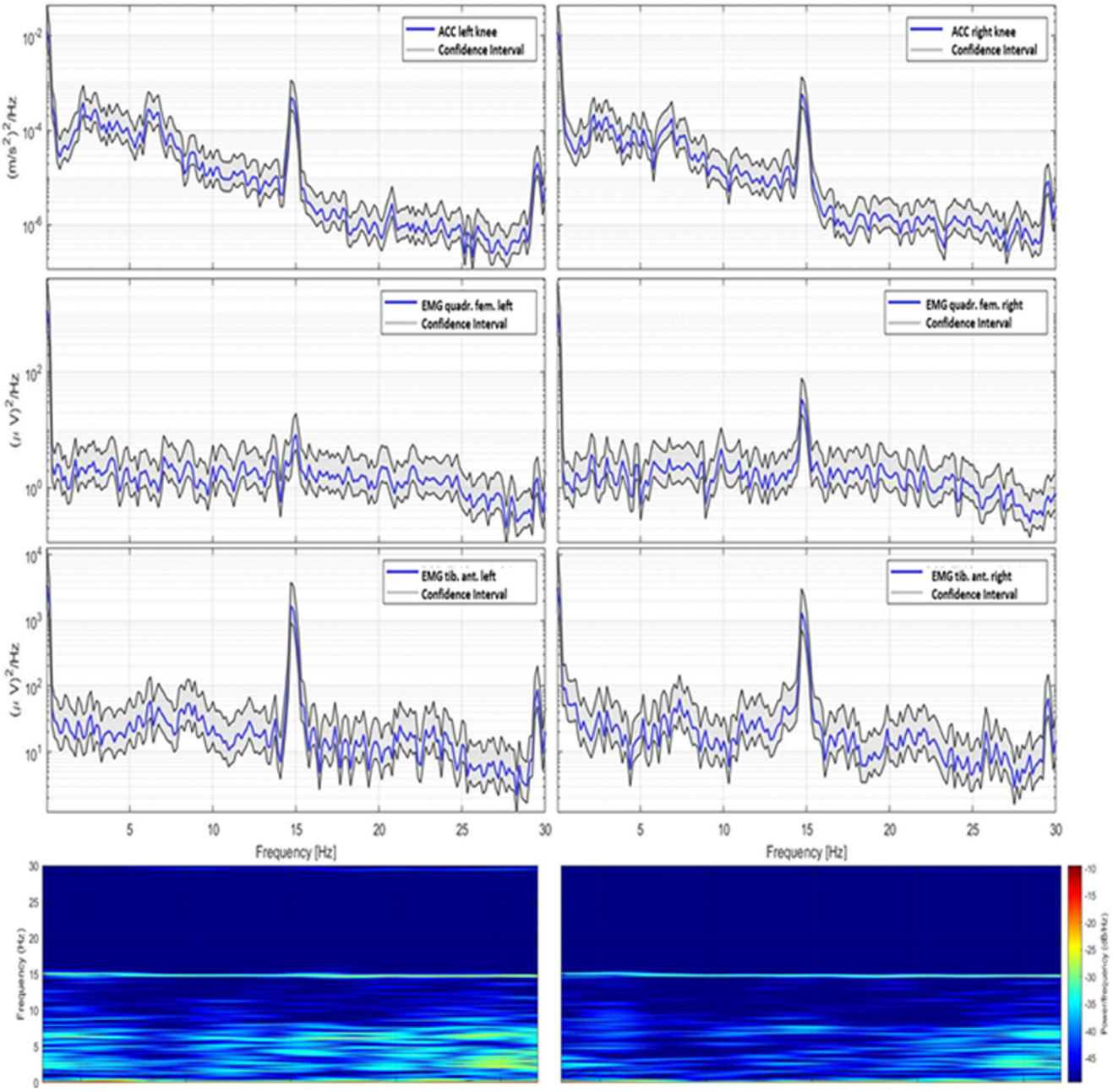

Fig. 17. Accelerometry (ACC) and surface electromyography (EMG) frequency spectrum of a patient with a highly coherent ~15 Hz primary OT. The accelerometers are placed on both knees, EMG electrodes are placed above the quadriceps femoris (quadr. fem.) and tibialis anterior (tib. ant.) muscles bilaterally. The time frequency spectrum in the lower part covers ~30 sec and shows the constancy of this tremor peak.

have been reported. Tremor frequency can also be determined with accelerometry.

Primary OT is highly synchronous in lower limb and paraspinal muscles (i.e., high intermuscular coherence). There may be a short latency to tremor onset, or tremor bursts may emerge almost immediately upon standing. With prolonged standing the amplitude of tremor bursts can increase (Fig. 18). The EMG tremor recordings are mostly of a single frequency, but occasionally vary slightly over a narrow range (e.g., 15–16 Hz). Other conditions can be assessed. With marching in place or walking, tremor may disappear in the swing phase of the leg and reappear in the stance phase. With leaning, tremor transmits into the arms at the same frequency, and simultaneously dissipates in the lower limbs. After leaning is ceased, tremor recurs again in the legs and disappears in the arms. Another tremor is detected electrophysiologically in approximately 30% of patients with OT. A postural upper limb tremor resembling essential tremor is recorded in about a quarter of patients, with substantially slower frequency and not a harmonic of OT (Torres-Russotto and Elble, 2019). Coexistent rest tremor, handwriting tremor, head tremor, jaw tremor, functional tremor, and myoclonus have been identified electrophysiologically in a few patients with primary OT.

The neurophysiology of slower orthostatic tremors seems to be more disparate when compared with primary OT. While the tremor frequency is defined as below 13 Hz, the median tremor frequency is 6–7 Hz (range 3–12 Hz) (Rigby et al., 2015). Lower intermuscular coherence, variable discharge duration, and less rhythmicity have been described, consistent with impaired muscle

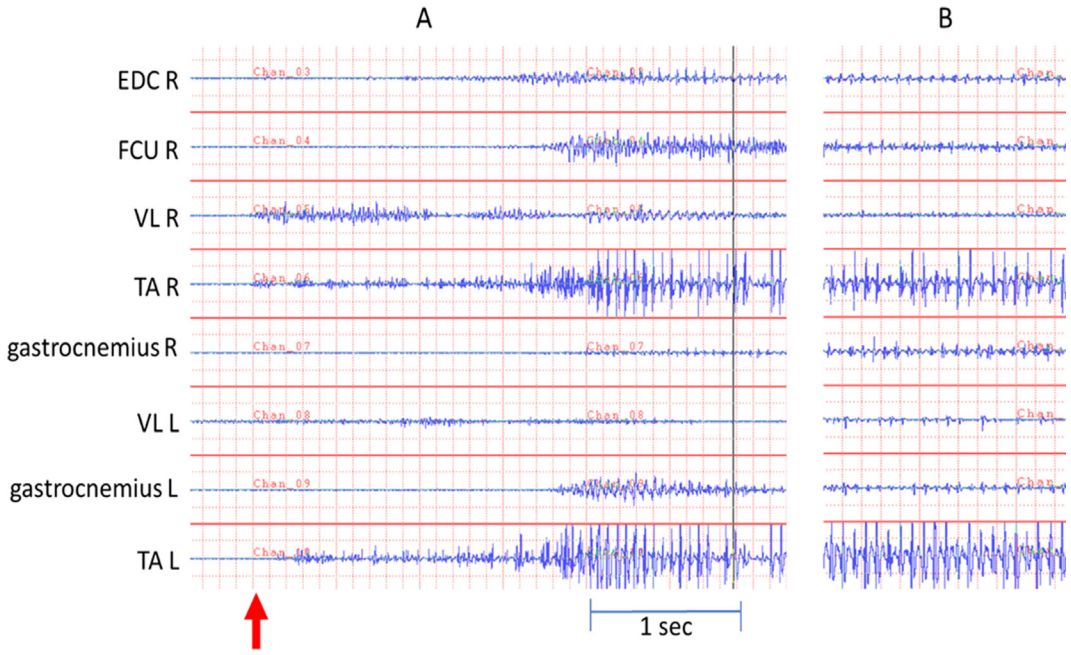

Fig. 18. Polygraphic EMG-recording from a patient with primary OT. (A) During transition from sitting to standing (red arrow). No rhythmic EMG activity is present in the sitting position, but rhythmic 16 Hz bursts appear approximately 2 seconds after the patient stands up. (B) During prolonged standing, there is rhythmic 16-Hz activity in almost all recorded muscles. Abbreviations: EDC: Extensor digitorum communis; FCU: Flexor carpi ulnaris; TA: Tibialis anterior, VL: Vastus lateralis, R: right, L: left.

coordination during standing (Hassan and Caviness, 2019). Slower tremors are also not task specific for standing (Hassan and Caviness, 2019).

Needle electromyography (EMG) can also be used to detect orthostatic tremor, and sometimes this occurs incidentally when the patient is undergoing EMG studies to assess for a neuromuscular cause of their leg symptoms.

Primary OT produces a tremor spectral peak in posturography recordings (Karlberg et al., 2005). This sway pattern in primary OT is unique from sway patterns in cerebellar, vestibular and phobic postural disturbances (Krafczyk et al., 2006).

Electroencephalography (EEG) has been studied in *primary OT* patients with both seated and standing recordings (McManis and Sharbrough, 1993). EEG studies are normal in most OT patients, but some may have midline electrographic discharge associated with the tremor (McManis and Sharbrough, 1993). The EEG frequency may be identical to OT frequency, a harmonic of the OT frequency, or non-harmonic, although OT artifact may not be unequivocally excluded in some cases (Hassan et al., 2016).

Smartphone applications with accelerometry can reliably record orthostatic tremor for frequency analysis and may present an easy, cheap, and sensitive screening tool (Bhatti et al., 2017).

8. Holmes tremor

8.1. Clinical definition

In 1904, Gordon Holmes first described a syndrome of rest, postural and intention tremor in a series of patients with lesions in the cerebello-rubral system (Holmes, 1904). Since then, this type of tremor was frequently labelled according to its presumed lesion locations (e.g., mesencephalic or midbrain tremor, rubral tremor, thalamic tremor). These anatomical assignments were often misleading, and the term Holmes tremor was introduced in 1998 (Deuschl et al., 1998a). Holmes tremor is defined as a syndrome of rest, postural, and intention tremor that typically emerges from proximal and distal rhythmic muscle contractions at low frequency (<5 Hz) and usually occurs in combination with prominent additional signs (Bhatia et al., 2018).

8.2. Specific clinical features

Holmes tremor is characterized by a large and disabling tremor amplitude and a slow tremor frequency between 2.5 and 5 Hz that may appear irregular. The tremor appears at rest and during posture against gravity and goal directed movements. In most cases, one upper extremity is affected predominantly, but cases with hemitremor and marked involvement of the lower extremity have been reported (Baysal et al., 2009, Walker et al., 2007), as well as cases with bilateral tremor (Raina et al., 2016). The median time from lesion to tremor onset is highly variable, with a median latency of 2 months and a range between 7 days and 228 months (Joutsa et al., 2019, Raina et al., 2016).

Holmes tremor is frequently accompanied by additional neurological signs consistent with pathology in the vicinity of the red nucleus. In a large series (n = 29) of patients with Holmes tremor, the most common associated symptoms were hemiparesis (62%), ataxia (52%), hypoesthesia (28%), dystonia (24%), and cranial nerve involvement (24%) (Raina et al., 2016). These additional signs help to localize the underlying lesion (Nsengiyumva et al., 2021). The two main lesions are in the brainstem close to the red nucleus and in the ventrolateral thalamic region. In Benedikt syndrome, oculomotor palsy occurs in combination with contralateral hemiparesis and, in some cases, Holmes tremor (Benedikt, 1889, Liu et al., 1992). In contrast, patients with thalamic lesions typically exhibit marked dystonia, choreoathetosis, or pseudoathetosis from proprioceptive sensory loss in the affected limb (Kim, 2001, Lehericy et al., 2001, Vidailhet et al., 1998), which signs that are not seen in patients with underlying brainstem lesions (Nsengiyumva et al., 2021).

The most common etiologies of Holmes tremor are cerebrovascular events (ischemic stroke, hemorrhagic lesions, vascular

malformations), head trauma, neuroinflammatory diseases and neoplasia (Nsengiyumva et al., 2021, Raina et al., 2016). Therefore, Holmes tremor is usually regarded as an irreversible condition. However, rare cases of Holmes tremor have resolved after successful treatment of the underlying nonketotic hyperglycemia (Tan et al., 2006), spontaneous intracranial hypotension (Iyer et al., 2017), and giant aneurysm of the middle cerebral artery (Poloni et al., 2019).

8.3. Pathophysiology

Holmes tremor was previously called rubral tremor because the responsible lesions commonly occurred in the vicinity of the red nucleus (Deuschl and Bergman, 2002). However, monkeys did not exhibit tremor when only the red nucleus was lesioned, and damage to neighboring cerebellothalamic and nigrostriatal pathways was required. This observation is seemingly supported by many imaging studies in humans (Deuschl et al., 1999, Masucci et al., 1984, Remy et al., 1995, Seidel et al., 2009), but many patients have no evidence of nigrostriatal deficiency (Gajos et al., 2010, Gajos et al., 2017, Miwa et al., 1996). Furthermore, the focal lesions that have caused Holmes tremor are not limited to the region surrounding the red nucleus. "Lesion network mapping" (Fox, 2018) of 36 patients revealed a network of eight brain regions associated with Holmes tremor: red nucleus, globus pallidus interna, thalamus (ventralis oralis posterior), pulvinar nuclei, pontomedullary junction, and cerebellum (cerebellar cortex and vermis in lobule VI and cerebellar cortex in lobule X) (Joutsa et al., 2019). Interestingly, the nigrostriatal tract was not a key part of this connectome circuit, and neither was the ventral intermediate thalamic nucleus.

Lesion location does not provide a complete explanation of Holmes tremor. The delayed onset of Holmes tremor must also be explained, and the delayed occurrence of other movement disorders after monophasic brain lesions is still poorly understood. Several hypotheses including neuroplasticity, transsynaptic neuronal degeneration, remyelination, ephaptic transmission, and central synaptic reorganization have been suggested (Mehanna and Jankovic, 2013a, Okuda and Tachibana, 1996, Scott and Jankovic, 1996). How the Holmes tremor lesion connectome ultimately produces a tremor generating circuit is unclear. Tremor amplitude-related brain activity was found in the contralateral sensorimotor cortex and cerebellar vermis in a patient with Holmes tremor (Nieuwhof et al., 2020). Although these regions only share little anatomical overlap with the previously described HT lesion connectome, connectivity analyses revealed that both activity clusters were functionally connected to several regions of the HT lesion connectome. This suggests that the lesion connectome triggers the development of oscillation in a "tremor" network that may differ from the lesion connectome (Nieuwhof et al., 2020). This general theme is also relevant to palatal tremor and myorhythmia, which commonly develop after a significant delay.

8.4. Laboratory assessment

In clinical routine, the diagnosis of Holmes tremor can usually be made without electrophysiological assessment. However, accelerometric or electromyographic measures provide the most accurate information about the tremor frequency, which lies below 5 Hz (Bhatia et al., 2018). Electromyographic burst durations of 150–170 ms with an alternating activation pattern of agonist and antagonist muscles have been described (Milanov, 2002, Miwa et al., 1996). None of these features is specific for Holmes tremor.

9. Palatal tremor

9.1. Clinical characteristics

Palatal tremor is defined as an involuntary, continuous, brief, rhythmic contraction of the palate at 0.5–5 Hz. The initial term was palatal myoclonus but was redefined as palatal tremor in 1990 at the first International Congress of Movement Disorders (Zadikoff et al., 2006).

Two different forms are distinguished: essential palatal tremor and symptomatic palatal tremor. Symptomatic palatal tremor is caused by a movement of the levator veli palatini innervated by the facial/glossopharyngeal nerve, and essential palatal tremor is caused by contraction of the tensor veli palatini innervated by the trigeminal nerve (Bhatia et al., 2018, Zadikoff et al., 2006). The movements of the soft palate can be distinguished by clinical inspection: the levator lifts the free edge of the palate, and the tensor lifts the roof of the palate as it uses the hamulus as a fulcrum (Deuschl et al., 1994a).

Essential palatal tremor is mostly accompanied by a troublesome ear click due to the contraction of the tensor veli palatini inserting at the opening of the Eustachian tube (Deuschl et al., 1994a). Symptomatic palatal tremor can have additional involvement of cranial nerves resulting in oculopalatal tremor with a pendular nystagmus or extension to spinal nuclei with a time-locked inhibition of EMG (Elble, 1991). Patients with oculopalatal tremor exhibit synchronous eye oscillations (pendular nystagmus) (Tilikete and Desestret, 2017). Other forms of palatal dyskinesia and middle ear hyperkinesia must be distinguished from essential and symptomatic palatal tremor (Ellenstein et al., 2013).

Essential palatal tremor has no known structural pathology and in particular no olivary abnormality. Symptomatic palatal tremor is mostly associated with lesions in the dentato-olivary pathway and olivary (pseudo-)hypertrophy (Deuschl et al., 1994b, Deuschl and Wilms, 2002, Guillain and Mollaret, 1931). The responsible lesion typically occurs weeks or months before the tremor (Deuschl et al., 1990, Deuschl et al., 1994b, Tilikete and Desestret, 2017). For degenerative causes of symptomatic palatal tremor, the lesion may not be obvious on MRI.

9.2. Specific clinical features

Clinically, essential palatal tremor presents with an ear click in up to 90% of patients, but patients have no other neurological abnormalities (Deuschl et al., 1990). The ear click is distressing for the patients and often audible to bystanders (Zadikoff et al., 2006). The tremor frequency varies between 0.5 and 5 Hz (Bhatia et al., 2018). Some patients are capable in suppressing the tremor with muscle contractions that produce pressure changes in the ear canal. The neurological examination is unremarkable except for the palatal tremor and a possible involvement of other neighboring muscle groups of the throat including the larynx.

Ear clicks occur in only 8% of patients with symptomatic palatal tremor. However, patients may have oscillopsia (7%), other tremor (10%), and other signs and symptoms of the underlying disease (Deuschl et al., 1990, Deuschl et al., 1994b). Additional clinical findings may include ataxia, ophthalmoplegia, other tremor forms such as Holmes tremor and myorhythmia, dysarthria, and dysphagia. Patients with ischemic or hemorrhagic strokes may have pyramidal tract signs. Some authors observed synchronous contractions of diaphragmatic muscles (Nagappa et al., 2018).

9.3. Pathophysiology of palatal tremor and related syndromes

Symptomatic palatal tremor is nearly always associated with pathology in the Guillain Mollaret triangle. The pathology may

be stroke, trauma, encephalitis, or demyelination. In a literature survey, cerebrovascular diseases were reported in 55% of 210 patients, cavernomas being most common (Deuschl et al., 1990).

Symptomatic palatal tremor also occurs in patients with neurodegenerative diseases as amyotrophic lateral sclerosis (ALS) (Maghzi et al., 2018, Rebello et al., 2020) or Wilson disease (Seliverstov et al., 2020). Genetic causes leading to degeneration have been found including variations in POLG and in WDR81, TENM4, EEF2, and NDUFS8 (Nagappa et al., 2018). Mutations in the glial fibrillary acidic protein (GFAP) gene on chromosome 17q21 (Li et al., 2005) cause a progressive form of leukodystrophy in adults: type II (late-onset) Alexander disease. Pathological characteristics of this disease are the presence of protein aggregates, so called Rosenthal fibers that accumulate in subpial, periventricular, and perivascular astrocytes of the cerebral hemispheres, cerebellum and brainstem (Baysal et al., 2009, Graff-Radford et al., 2014, Howard et al., 2008, Pareyson et al., 2008). The adult form (later than age 12) of Alexander Disease must be distinguished from the more typical, lethal early-onset form (neonatal, infantile, juvenile) (Kuhn and Cascella, 2021, Pareyson et al., 2008).

The syndrome of progressive ataxia and palatal tremor is usually a 4-repeat tauopathy consisting of hypertrophic olivary and tau-positive inclusions in olivary and infratentorial neurons (Cilia et al., 2007, Gao et al., 2017, Hainline et al., 2017, Mari et al., 2014), but this syndrome may have other causes, such as a dural arteriovenous fistula with brainstem ischemia (Peikert et al., 2019). There are also case reports of families with SCA20 presenting with dominantly inherited palatal tremor, ataxia, hypermetric saccades, dysphonia and dentate nucleus calcification (Knight et al., 2004, Storey and Gardner, 2012, Storey et al., 2005), which differs from the typical phenotype of sporadic progressive ataxia with palatal tremor (Samuel et al., 2004).

The etiology of essential palatal tremor is unknown, but there is considerable evidence that this is a functional movement disorder in most cases (Klein et al., 1998, Stamelou et al., 2012, Vial et al., 2020). Electrophysiological studies of essential palatal tremor demonstrated either a Bereitschaftspotential by back-averaging to the palatal tremor with EEG recordings or distractibility and entrainment during voluntary 1 Hz tapping with the left thumb during EMG (Pirio Richardson et al., 2006, Vial et al., 2020). In one case series, 70% of ETP patients were clinically re-classified as functional palatal tremor. Their tremor was incongruous, variable, entrainable, and distractible, and these findings were confirmed with EMG recordings in three of ten cases (Stamelou et al., 2012). Continuous finger tapping at a predefined frequency while using a mirror served as a therapeutic approach to successfully improve functional palatal tremor (Kern and Lang, 2015). However, many investigators have found no evidence for a psychogenic origin. Due to the rarity of the condition, larger cohorts of patients need to be assessed. An important differential diagnosis is a palatal tic in patients with Tourette syndrome (Schwingenschuh et al., 2007).

Guillain and Mollaret (Guillain and Mollaret, 1931) first reported that lesions in the dentato-rubro-olivary pathway cause olivary pseudohypertrophy and symptomatic palatal tremor. The critical lesion is hypothesized to be interruption of the inhibitory dentato-olivary fibers, not the excitatory rubro-olivary tract (Barmack, 2003, Shaikh et al., 2010). Hypertrophic degeneration of the inferior olive begins 3–4 weeks after the ictus (Nishie et al., 2002) and consists of neuronal vacuolation and enlargement (Konno et al., 2016). Ataxia occurs on the side contralateral to the degenerating inferior olive, and patients perform abnormally in motor learning tasks (Deuschl et al., 1996a, Deuschl et al., 1994a, Shaikh et al., 2010). Therefore, hypertrophic olivary degeneration probably induces impairment in cerebellar function, which is in contrast to normal olivary and cerebellar function in essential palatal tremor (Deuschl et al., 1996a).

The inferior olive is hypothesized to be the pacemaker of symptomatic palatal tremor (Deuschl et al., 1996a, Elble, 1991, Guillain and Mollaret, 1931). Normally, the gap junctions between olivary neurons are regulated by dentato-olivary GABAergic terminals, and loss of these terminals produces increased electrotonic coupling of olivary cells and putative synchronous oscillation of olivary neurons. More recently this olivary hypothesis was incorporated into a dual-mechanism model of oculopalatal tremor, in which oscillation is caused by abnormal olivary rhythmicity and is sustained by secondary neuroplastic change in cerebellar function (Shaikh et al., 2010). This model could also explain why patients continue to have palatal tremor when the initially hypertrophied inferior completely degenerates after some years (Goyal et al., 2000). The main problem with this olivary hypothesis and dual-mechanism model is that oculopalatal tremor also occurs in adult-onset Alexander disease in which there is severe olivary degeneration without hypertrophy and in rare patients with brainstem strokes that produce no olivary hypertrophy (Kattah et al., 2020, Pareyson et al., 2008). Therefore, it is possible that the inferior olive is not the source of rhythmicity and that olivary destruction leads to other tremorogenic maladaptive changes in the Guillain Mollaret triangle or its brainstem connections.

9.4. Laboratory assessment

Palatal tremor can be confirmed with EMG from the involved muscles. Assessment with needle EMG of the corresponding palatal muscles is possible but uncomfortable (Deuschl et al., 1991). Recording from the levator is easy, but recording from the tensor needs special training. Nasopharyngeal EEG electrodes have been used to record symptomatic palatal tremor (Elble, 1991). As for essential palatal tremor, co-activated muscle activity can sometimes be recorded from the anterior neck with sEMG. For symptomatic palatal tremor, the mentalis muscle (innervated through the mandibular branch of the facial nerve) is often involved in the palatal rhythm. This muscle twitch can be recorded with surface electrodes below the corner of the mouth (Deuschl et al., 1994b).

10. Myorhythmia

10.1. Clinical definition

Myorhythmia is defined as repetitive, rhythmic, slow (1–4 Hz) movements mainly affecting cranial and limb muscles. There is phenomenological overlap with myoclonus and other tremor syndromes. Due to its repetitive rhythmic properties, myorhythmia is classified as a tremor syndrome (Bhatia et al., 2018).

10.2. Specific clinical features

Myorhythmia is a unique but extremely rare tremor predominantly affecting limb and cranial muscles (tongue, face, jaw). The contractions occur at rest but often persist in posture and voluntary movement. Myorhythmia characteristically ceases during sleep. The frequency of myorhythmia is slower (1–4 Hz) than Parkinson rest tremor, lacks the other features of Parkinson rest tremor (Section 4), and is often jerkier and more irregular. There is some phenomenological (e.g., frequency) overlap between myorhythmia and Holmes tremor, but Holmes tremor typically persists or increases during action while myorhythmia is greatest at rest and does not increase during action. Other differential diagnoses are cortical tremor/myoclonus and epilepsia partialis continua; electrophysiologic assessment can help to differentiate (see below).

Cranial myorhythmia frequently occurs with symptomatic palatal tremor at a frequency of 2–3 Hz. Therefore, palatal tremor is considered within the spectrum of myorhythmia (Baizabal-Carvallo et al., 2015). Apart from pharyngeal and laryngeal muscles, the neck, diaphragm, and other branchial muscles can be affected. Oculomasticatory myorhythmia consists of 1–3 Hz rhythmic contractions of facial and masticatory muscles, combined with pendular vergence oscillations of the eyes (Schwartz et al., 1986), and this is virtually diagnostic of Whipple disease (Bally et al., 2018, Louis et al., 1996, Revilla et al., 2008, Schwartz et al., 1986).

10.3. Pathophysiology of myorhythmia

Cerebrovascular events are considered the most common cause of myorhythmia (Masucci et al., 1984, Mehanna and Jankovic, 2013a). Limb myorhythmia has been described following infarctions of the brainstem, thalamus and basal ganglia (Alarcon et al., 2004, Masucci et al., 1984), and limb myorhythmia combined with palatal tremor was reported secondary to pontine ischemic and hemorrhagic infarctions, associated with inferior olive hypertrophy (Hirono et al., 1990).

Oculomasticatory myorhythmia and oculo-facial-skeletal myorhythmia are an insensitive but quite specific finding for Whipple disease, occurring in about 10% of these patients (Bally et al., 2018, Louis et al., 1996, Revilla et al., 2008, Schwartz et al., 1986). Many patients with Whipple disease exhibit supranuclear ophthalmoplegia, cerebellar ataxia, seizures and dementia as well (Bally et al., 2018, Louis et al., 1996). Apart from Whipple disease, myorhythmia occurs in the context of Listeria encephalitis (Park et al., 2010), autoimmune and paraneoplastic diseases including anti-N-methyl-D-aspartate (NMDA) receptor encephalitis (Dalmau et al., 2011), multiple sclerosis (Mehanna and Jankovic, 2013b), steroid-responsive encephalopathy associated with autoimmune thyroiditis (Erickson et al., 2002), celiac disease associated encephalitis (Dimberg et al., 2007), and Hodgkin lymphoma (Wiener et al., 2003).

The pathophysiology of myorhythmia is not understood, and there is a lack of neurophysiological and functional imaging studies. Causative lesions are predominantly localized to the brainstem and components of the Guillain-Mollaret triangle but also occur beyond these structures in (sub-)thalamic areas and basal ganglia (Lera et al., 2000, Masucci et al., 1984). Pathological studies in patients with myorhythmia have shown lesions in components of the Guillain-Mollaret triangle are the most consistent finding. Additionally, affection of the substantia nigra has been reported in many cases, suggesting that a dopaminergic deficit is sometimes involved (Masucci et al., 1984). However, patients with myorhythmia usually have no parkinsonism, and dopaminergic drugs are usually not helpful (Baizabal-Carvallo et al., 2015).

10.4. Laboratory assessment

Electromyography reveals 1–4 Hz bursts of long (150–270 ms) duration. In a single case examination of a patient with myorhythmia of the right shoulder of presumably paraneoplastic etiology, no jerk-locked activity in the EEG was found. Additionally, SSEPs were normal, no pathological long latency reflexes were present, and there was no tremor reset following cortical transcranial magnetic stimulation (TMS), arguing against a cortical origin of myorhythmia. In this same patient, alteration of certain brainstem reflexes (masseter inhibitory reflex, acoustic blink reflex prepulse inhibition and blink reflex excitability) suggested a selective brainstem circuit dysfunction on a lateral olivopontomedullary level. Additionally, the inhibitory effect of cerebellar stimulation on motor cortex output ipsilateral to the myorhythmia (cerebellothalamocortical inhibition) was absent, suggesting altered inhibitory cerebellar efference in this patient (van Meerbeeck et al., 2010).

11. Cerebellar outflow tremor

Lesions in the cerebellothalamic pathway produce intention tremor in laboratory primates and in humans (Elble, 1998, Kuo et al., 2019). This pathway is necessary for feedforward motor control (Kuo et al., 2019), and a deficit in feedforward control was observed by Gordon Holmes in his description of intention tremor in people with cerebellar injury (Holmes, 1939). With loss of feedforward motor control, patients become more reliant on feedback control, which is not sufficient for smooth accurate movement (Elble, 1998, Kuo et al., 2019).

Laboratory primates exhibit kinetic (intention) tremor when the deep cerebellar nuclei are lesioned. This model of cerebellar outflow tremor has been reviewed extensively (Kuo et al., 2019). This tremor is clearly an abnormal mechanical-reflex oscillation in which rhythmic activity has been recorded from motor cortex, EMG, spindle afferents, and the cerebellar interpositus nucleus and in which mass loading predictably reduced tremor frequency (Elble et al., 1984).

Abnormal mechanical-reflex oscillation appears immediately after the cerebellar dentate nucleus, with or without interpositus, is inactivated or lesioned, but stable tremor evolves over a period of weeks (Elble et al., 1984, Vilis and Hore, 1980). This delay in tremor development is reminiscent of the typical delays in onset of Holmes tremor, palatal tremor, and myorhythmia following acute focal lesions. Gordon Holmes observed that "Voluntary movement is also often complicated and disturbed by the occurrence of tremor in the moving limb, but this is not such a prominent factor in the early as it is in the later stages of a cerebellar lesion". Clearly, tremorogenic changes occur in motor pathways in response to the initial ictus. This is probably also true when the underlying pathology evolves more slowly, as in neurodegenerative diseases, making pathophysiologic clinicopathologic correlation very difficult. Indeed, tremor evolved in monkeys after weeks of repeated reversible cooling of dentate and interpositus (Vilis and Hore, 1980).

Prospective systematic electrophysiologic studies of delayed tremorogenesis in humans are needed. An 8-year-old girl developed right upper extremity intention tremor following a left ventrolateral thalamic infarct (Qureshi et al., 1996). Tremor started about 2 months after the stroke and then increased dramatically over a period of 6 months. Her 4–5 Hz wrist tremor had the properties of mechanical-reflex oscillation.

It is unclear whether cerebellar outflow tremor is always a mechanical-reflex oscillation. There are simply too few electrophysiologic studies to draw any conclusions. It is conceivable that cerebellar outflow lesions could initially produce abnormal mechanical-reflex oscillation that ultimately evolves into central neurogenic oscillation.

12. Tremor associated with peripheral neuropathy

Tremor associated with peripheral neuropathy is often referred to as neuropathic tremor and neuropathy-related tremor. The latter two terms are somewhat presumptive because they suggest a pathophysiologic relationship that may not exist, and in many cases, the pathophysiologic relationship between neuropathy and tremor is unclear.

Tremors associated with peripheral neuropathy have heterogeneous pathophysiology and electrophysiology. One might predict that tremor associated with neuropathy would have a tremor frequency that is a function of segmental reflex loop time (i.e., nerve conduction velocities) and perhaps limb mechanics. However,

there is no relationship between tremor frequency and nerve conduction velocity in hereditary or acquired demyelinating neuropathies. One study of 43 patients with inflammatory neuropathy revealed no change in tremor frequency with 500 gm loading of the hand, but motion was not restricted to a single joint (wrist) in this study, making the results inconclusive (Saifee et al., 2013). Tremor with similar characteristics and response to mass loading was found in 13 of 23 patients with Charcot Marie Tooth hereditary neuropathy (Saifee et al., 2015). The frequency range of neuropathic tremor usually does not differ significantly from that of essential tremor (Saifee et al., 2013). However, some patients exhibit unusually low tremor frequency, jerky movements, and pseudoathetoid finger movements resembling dystonia (Breit et al., 2009, Morini et al., 2016, Pyatka et al., 2019). Other patients exhibit very mild tremor with features of enhanced physiologic tremor (Shahani and Young, 1976).

Tremor associated with neuropathy appears to be a central neurogenic tremor in most cases. Occasional patients undergo deep brain stimulation surgery, providing an opportunity for thalamic microelectrode recording. A 76-year-old woman with a disabling 4-Hz tremor due to IgM-paraproteinemia exhibited significant 4-Hz coherence between motor cortex EEG and contralateral EMG, and 4-Hz activity in ventralis intermedius was coherent with ipsilateral motor cortex and contralateral EMG (Weiss et al., 2011). Impaired eyeblink classical conditioning has been found in tremulous patients and inflammatory neuropathy but not in patients with no tremor (Schwingenschuh et al., 2013), suggesting cerebellar impairment in patients with tremor. However, these findings were not found in tremulous patients with Charcot Marie Tooth (Saifee et al., 2015). Eyeblink classical conditioning studies are frequently underpowered, and the results are influence by aging (Sadnicka et al., 2021).

It is not clear why some people with certain neuropathies develop tremor and others do not. It is possible that those with tremor have an additional tremor diathesis unrelated to the neuropathy per se. According to this hypothesis, the neuropathy triggers secondary tremorogenic changes in central motor pathways.

13. Functional tremor

13.1. Clinical definition

Functional tremor is the most common functional movement disorder (Carson et al., 2016). Quality of life is markedly impaired, comparable to that caused by Parkinson disease (Anderson et al., 2007). Functional tremor is characterized by involuntary tremulous movement of any body part that is inconsistent with any of the known other tremor disorders. The term "psychogenic" tremor was replaced by the more neutral term "functional", after it became clear that psychiatric or psychological causes are not necessarily linked with functional tremor (Edwards and Bhatia, 2012, Espay et al., 2018a).

13.2 Specific clinical features

Tremor may have an acute onset, sometimes even within seconds, minutes or hours, and patients with acute onset usually remember the situation or events surrounding tremor onset (Parees et al., 2014). Another characteristic is a rapid progression to maximum tremor severity (Thenganatt and Jankovic, 2014), but tremor often varies during the course of the disease. For example, patients might be severely affected over months, and experience a sudden, complete temporary remission. Patients often see multiple physicians. Tremor characteristics may change in distinct situations, for example in certain positions or at specific occasions (Carson et al., 2016). Tremor varies throughout different body parts. The arm is most frequently affected, followed by the legs or entire body.

13.3 Neurological examination

The neurological examination reveals one or more signs that support the diagnosis of functional tremor:

(1) Tremor presents with the same frequency and amplitude in rest, posture, and movement.
(2) Tremor amplitude often increases while obtaining history with a focus on the tremor, and tremor subsides when other topics are discussed (van Poppelen et al., 2011).
(3) Tremor amplitude, frequency, and direction change with distraction. Amplitude and frequency may increase or decrease, the direction might change between extension/flexion, abduction/adduction, or between pronation/supination (Schwingenschuh and Deuschl, 2016, Thenganatt and Jankovic, 2015).

The examiner may use different techniques:

(A) Distraction with voluntary motor tasks that result in frequency entrainment or suppression of tremor (see Section 1.2.2)
(B) Distraction with cognitive tasks, resulting in tremor suppression.
(C) Distraction with suggestion. For example, a vibrating tuning fork can be placed on the tremulous body part with the suggestion that "sometimes vibration decreases or increases tremor" (Thenganatt and Jankovic, 2014).
(1) The "coactivation sign" is suggestive for functional tremor: tremor is present when the agonist and antagonist muscles are activated. During slow passive movements, the tremor subsides when coactivation decreases (Deuschl et al., 1998b).
(2) If multiple body parts are affected, these body parts have the same frequency with strong coherence. This is in contrast to other tremors that exhibit slightly different frequencies and low coherence (Raethjen et al., 2004a, Thenganatt and Jankovic, 2015). With the exception of orthostatic tremor, most patients with bilateral tremors have independent tremor rhythms in different extremities. In contrast, approximately half of patients with functional tremor exhibit significant tremor coherence between the two hands (Raethjen et al., 2004a, Schwingenschuh et al., 2011).

13.4. Neuropsychiatric background

For many years, the etiology of functional tremor was considered neuropsychiatric. Psychological stressors or factors have been part of the diagnostic criteria, but the data from different studies have been contradictory (Roelofs and Pasman, 2016). Therefore, psychological factors or stressors are no longer required for the diagnosis of functional movement disorder. Nevertheless, childhood traumas (Epstein et al., 2016, Roelofs and Pasman, 2016) appear to play a major role and predominantly include emotional abuse and physical neglect (Baizabal-Carvallo et al., 2019). Traumatic events are often linked to greater fear. Patients with functional movement disorders might have an increased number of traumatic episodes, emotional stress, or recent life events (Kranick et al., 2011, Parees et al., 2014). Early life stressors also contribute to anxiety and depression (Heim et al., 2008). In a meta-analysis, patients with functional neurological disorders reported physical abuse in 5–79%, sexual abuse in 0–74%, emo-

tional abuse or neglect in 30–74%, and a traumatic life event in 14–100% (Roelofs and Pasman, 2016). In a study that included 64 patients with functional movement disorders, major lifetime depression occurred in 37%, generalized anxiety disorder in 20%, phobia in 14% and panic disorder in 3% (Kranick et al., 2011). In a study of 50 patients with functional movement disorders, 40 (80%) reported a physical event prior to the beginning of abnormal movements. The most common preceding events were injuries and infection (Parees et al., 2014).

13.5. Pathophysiology

Functional movement disorders appear to reflect a specific problem with voluntary control of movement, despite normal intent to move and an intact neural capacity for movement. Several neurobiological abnormalities have been identified in patients with functional tremor including abnormal patterns of cerebral activation and abnormal connectivity between the limbic and motor networks (Baizabal-Carvallo et al., 2019).

Functional tremor has been compared to voluntarily mimicked tremor using functional magnetic resonance imaging (fMRI). The most prominent difference was in the activation of the temporoparietal junction region, including connectivity of this area to parts of the motor system (Voon et al., 2010). The decreased functional connectivity between the right temporoparietal junction and bilateral sensorimotor regions led to a model whereby impaired motor feed-forward control and impaired sensorimotor integration produces an impaired sense of self-agency (Maurer et al., 2016).

The cingulate cortex is another region implicated in self-awareness, self-monitoring, and active motor inhibition (Roelofs et al., 2019). Increased activity of the cingulate cortex has been observed in patients with functional tremor and functional dystonia at rest or when individuals are exposed to emotional stimuli (Blakemore et al., 2016, Hedera, 2012). Increased activation of the paracingulate gyrus and left Heschl's gyrus was recorded in patients with functional tremor compared with healthy controls (Espay et al., 2018b). Altered emotional processing may represent a key link between psychosocial risk factors and core features of functional movement disorders (Pick et al., 2019). Dysfunctional emotion processing appears to play a major role in the perpetuation of symptoms for some patients (Epstein et al., 2016).

Abnormalities in higher order cognitive processing are also observed in patients with functional movement disorders (Baizabal-Carvallo et al., 2019). Patients with functional tremor exhibited increased visual attention toward the trembling limb when performing a motor task compared to patients with other tremor disorders (van Poppelen et al., 2011). Abnormalities in probabilistic reasoning and motor response inhibition have been observed in patients with functional tremor and other functional movement disorders, suggesting a disturbed capability to process novel sensory and cognitive data (Parees et al., 2012a). Abnormal beliefs and emotions may also influence the sense of agency and intentional binding (Edwards and Bhatia, 2012). In a study assessing the time the patients perceived tremor during the waking day, wrist-worn accelerometer recordings were compared with self-reported diaries in patients with functional tremor and other tremor disorders (Parees et al., 2012b). Functional patients reported 65% more tremor than registered by accelerometry, compared to 28% excess for patients with other tremor disorders (Parees et al., 2012b).

13.6. Laboratory assessment

The clinical suspicion of functional tremor can be strongly supported with electrophysiological testing particular for clinically difficult cases (Hallett, 2016b, Schwingenschuh et al., 2016, Vial et al., 2019). A recent survey-based study found that 60% of practitioners performed electrophysiological testing on a regular basis for diagnostic confirmation of functional tremor, with considerable differences among countries in practice patterns and access to testing (LaFaver et al., 2020). The recommended standard equipment (see 1.2.2.3.) includes two accelerometers, a four-channel electromyography, a metronome, and a 500 (-1000)-gram weight. Hand tremor is recorded at rest, at posture (with and without weight loading), and during movement. Recorded signals are analyzed in the time and frequency domains (Schwingenschuh et al., 2016, Vial et al., 2019). In patients with presumed functional tremor, tremor recordings aim to identify electrophysiological correlates of distractibility and entrainment, co-contraction, and synchronicity.

When looking for entrainment, the patient is asked to tap voluntarily at various frequencies with a body part unaffected or less affected by the tremor. The functional tremor is entrained if it assumes the frequency of the voluntary tapping and there is significant coherence between the EMG spectra of the tremulous and the tapping extremities at the tapping frequency (Hallett, 2016b, McAuley and Rothwell, 2004, Schwingenschuh et al., 2011, Schwingenschuh et al., 2016). While pure entrainment is seen in only about one third of patients with functional tremor (Schwingenschuh et al., 2011), significant changes in tremor frequency and marked frequency variability during tapping are by far more common (Schwingenschuh et al., 2011, Zeuner et al., 2003). Another indication of functional tremor is that the patient might have inexplicable difficulty doing the voluntary tapping at the requested rate. A less accurate tapping performance is only revealed if recordings from both arms are analyzed (Schwingenschuh et al., 2011, Schwingenschuh et al., 2016, Zeuner et al., 2003). If the original tremor frequency peak persists and is accompanied by a new spectral peak at the frequency of tapping, a mirror movement should be considered and should not be confused with entrainment (Merchant et al., 2018a).

In the ballistic movement test, the patient is asked to perform a quick movement with one hand while observing for a pause in the functional tremor during the quick movement (Kumru et al., 2004, Schwingenschuh et al., 2011). Other signs that may be observed in functional tremor include marked irregularities in the tremor frequency and amplitude, and an increase in tremor amplitude when weights are added to the limb (O'Suilleabhain and Matsumoto, 1998, Schwingenschuh et al., 2011, Zeuner et al., 2003).

The electrophysiological equivalent of the clinical "coactivation sign" is a short, approximately 300 msec, tonic coactivation phase on EMG before the onset of tremor bursts (Deuschl et al., 1998b, Schwingenschuh et al., 2011). This arises because coactivation of antagonistic muscles can lead to a clonus state that contributes to the subsequent functional limb tremor. There are no tonic-coactivation signs before tremor onset in other tremor disorders (Chen and Chen, 2020).

It is often the case that only some of the features described above are observed in individuals with functional tremor. Therefore, a battery of tests is usually needed for the diagnosis (Chen and Chen, 2020). A simple test battery consisting of tremor recordings at rest, posture (with and without weight loading), action, while performing tapping tasks (1, 3, and 5 Hz), and while performing ballistic movements with the less-affected hand was able to distinguish functional tremor from other types of tremor with excellent sensitivity and specificity. Tonic muscular co-activation, tremor coherence, pause in tremor with contralateral ballistic movement, increased tremor frequency with weight loading, and incorrect tapping performance to a given frequency were regarded as positive functional signs (Schwingenschuh et al., 2016). A score of at least 3 out of 10 points indicates a functional tremor. The test

battery was validated in a prospective study including 40 patients with functional upper limb tremor and 72 patients with tremors of other etiologies, and there was had good sensitivity (89.5%), specificity (95.9%), and inter-rater reliability (Schwingenschuh et al., 2016).

The demonstration of functional tremors does not exclude another neurological disorders because functional disorders may coexist with other neurological disorders in the same patient. Most electrophysiological studies have only included patients with pure functional tremor. The utility of these methods in distinguishing pure functional tremor from functional overlay is unknown (Schwingenschuh et al., 2016). However, neurophysiology has recently been shown to be helpful in identifying an underlying organic tremor that was masked by a functional tremor (Merchant et al., 2018a).

14. Relevant conflict of interest

All authors: none.

15. Full conflict of interest

G. Deuschl has served as a consultant for Boston Scientific, Cavion, Functional Neuromodulation and received royalties from Thieme publishers. D. Haubenberger is a full-time employee of Neurocrine Biosciences Inc. K.E.Zeuner reports speaker's honoraria from Bayer Vital GmbH, BIAL, AbbVie Allergan and Merz outside the submitted work. She has served as a consultant and received fees from Merz, Ipsen, Alexion and the German Federal Institute for Drugs and Medical Devices (BfArM).R. Elble is an employee of SIU HealthCare; has served as a consultant for Applied Therapeutics, Cadent, Cydan, Jazz, Neurocrine Biosciences, Novartis, Osmotica, Praxis Precision Medicines, and Sage; has served on advisory boards for the International Essential Tremor Foundation and the Neuroscience Research Foundation of Kiwanis International, Illinois-Eastern Iowa District; and has received grants from the Neuroscience Research Foundation of Kiwanis International, Illinois-Eastern Iowa District. J. Becktepe, M. Dirkx, D. Haubenberger, A. Hassan, R. Helmich, M. Muthuraman, P. Panyakaew, P. Schwingenschuh have nothing to declare.

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