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Tremor and Other Hyperkinetic Movements

Review

Tremor: Clinical Phenomenology and Assessment Techniques

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Abstract

Background: Tremors are among the most common movement disorders. As there can be considerable variability in the manner in which clinicians assess tremor, objective quantitative tools such as electromyography, accelerometry, and computerized, spiral analysis can be very useful in establishing a clinical diagnosis and in research settings.

Methods: In this review, we discuss the various methods of quantitative tremor analysis and the classification and pathogenesis of tremor. The most common pathologic tremors and an approach to the diagnosis of tremor etiology are described.

Conclusions: Pathologic tremors are common, and the diagnosis of underlying etiology is not always straightforward. Computerized quantitative tremor analysis is a valuable adjunct to careful clinical evaluation in distinguishing tremulous diseases from physiologic tremors, and can also help shed light on their pathogenesis.

Keywords: Tremor, Parkinson disease, essential tremor, dystonia, orthostatic tremor, motor physiology

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Introduction

Tremor is among the most common movement disorders and is characterized by rhythmic oscillations of a part of the body around one or more joints.[1] Methods of tremor assessment include simple clinical observation, standardized rating scales, objective clinical assessment of drawn figures, and computerized tremor analysis. A broad overview of tremor, and the relative advantages and disadvantages of tremor assessment methods are discussed below. As there are different kinds of tremor with numerous underlying causes, the process of tremor classification and evaluation is of critical importance to establish a correct diagnosis and initiate the most appropriate treatment.

Classification of tremor

Tremor can be most effectively classified based on the circumstances under which it occurs.

Rest tremor can be distinguished from other forms of tremor based on its occurrence when the tremoring body part is completely supported against gravity without voluntary muscle contraction, in contrast to *action tremor*, which occurs with voluntary muscle contraction.[2] Action tremor can be further divided into *postural* or *sustention tremor* (occurring while maintaining a posture against gravity) and *kinetic tremor* (occurring during active movement). Kinetic tremor includes *task-specific tremor* and tremor that is specific to goal-directed movements (*intention tremor*). It can also be associated with situations where there is active muscle contraction against a fixed object (*isometric tremor*). While the tremors encountered in clinical practice are usually involuntary, patients can present with *psychogenic tremor* in isolation or in combination with other neurologic complaints of psychogenic origin, as in psychogenic parkinsonism.[2] In addition to provoking circumstances, other tremor characteristics

have been used to try to classify tremor (such as frequency, amplitude, or distribution). However, such classifications are often problematic as these characteristics can vary greatly within tremor etiologies.

Evaluation of tremor

Though tremor may be the most quantifiable of all movement disorders, there is currently no universally accepted method of rating or measuring tremor.[3,4] There can be considerable variability in the manner in which clinicians assess the presence of tremor and its severity. In an attempt to standardize the evaluation of tremor (particularly for clinical research purposes), a number of rating scales have been developed that optimize comparability between studies and patient populations.[5] One of the earlier tremor scales developed that is still in use today is the Fahn–Tolosa–Marin Tremor Rating Scale (TRS).[6] This 5-point scale rates tremor severity based on tremor amplitude, from 0 (no tremor) to 4 (severe tremor) in each part of the body, and includes assessments of specific abilities and functional disability. A number of other scales have been developed, which include smaller severity gradations[7] or are disease specific.[5,8] Although tremor scales vary regarding reliability and validity,[5,9,10] even the best clinical scale may not be sensitive enough to discern minimal abnormality and subtle changes over time, or objective enough to determine significant responses to therapy. While graphic evidence of tremor activity can be evaluated clinically by examining writing or drawn spirals, these are still interpreted subjectively and are not easily standardized across subjects. Thus, the objective and quantifiable data analysis afforded by computerized assessment of tremor can be an important tool in research and certain clinical settings.[11]

Computerized tremor analysis

Because tremors are quasi-sinusoidal movements, they are amenable to quantitative mathematical analysis and modeling with a high degree of fidelity to the clinical picture. To record tremor activity, accelerometry, electromyography (EMG), and other signals (such as force or gyroscopic measurements) are acquired, digitized through an analog-to-digital board and analyzed. With modern computers and digital signal processing boards, tremors can be analyzed in real time at a high sampling rate or processed off-line. Additional assessments (such as time series analyses) can detect complex synchronization and signal relationships within tremors.

Two of the most important characteristics of tremor assessed by tremor analysis are frequency and amplitude. Tremor frequency, or the amount of oscillations per second, is measured in cycles per second (Hz). If the number of sampled points is N over a period of time T in seconds, then the sampling rate is N/T, the frequency resolution is 1/T Hz and the maximum recordable frequency is N/2T Hz (also known as the Nyquist frequency).[12] Thus, if the highest frequency of concern is 25 Hz (most biological tremors fall in lower frequency ranges), the sampling rate of the recording device must be at least 50 Hz (and preferably several times that) for better signal processing. Low-pass filtering and other techniques can be used to further improve signal-to-noise ratios. Depending on recording circumstances, tremor frequencies can be reliably calculated to within 0.1 Hz and tremor displacement amplitudes can be determined accurately to less than 0.1 mm. It is important to remember, however, that frequency determination alone is not sufficient for a diagnosis as there is considerable frequency overlap between conditions.

While tremors are typically described by their frequency (such as parkinsonian rest tremor ranging from 3 to 6 Hz), patients are usually not greatly bothered by tremor frequency, but rather by the amplitude of their tremor.[13,14] Therefore, with regard to clinical disability and therapeutic effect, amplitude and other waveform characteristics may be more important.[15] The degree of linear or angular displacement of the limb or body part, or the tremor amplitude, is generally measured in millimeters or degrees. Tremor amplitude can be accurately assessed using accelerometers or gyroscopes. Miniature accelerometers can be attached to the involved tremulous parts of the body, typically the limbs and occasionally the head, neck, or trunk, and do not interfere with voluntary or involuntary movements. High-powered microcomputers, now capable of recording and analyzing large amounts of data quickly and efficiently, give almost instantaneous displacement from accelerometric signals. Furthermore, such operations can be modified to also filter out low-frequency noise such as unwanted drift or higher frequency electronic interference. Accelerometric or gyroscopic data can be difficult to appreciate clinically because sinusoidal motion is not easily perceived in accelerometric or rotational units; however, with mathematical integration, displacement of the oscillating body part can be derived from these signals.

EMG provides additional useful information about the activity of muscles involved in the generation of tremor. EMG activity may be recorded using needle, wire electrodes, or more typically surface electrodes overlying active muscles.[16] The EMG can provide information about motor unit recruitment and synchronization,[4,17] and can also elucidate the relationship between involved muscles and tremulous movements, revealing whether antagonist muscles (such as flexors and extensors of the wrist) are working at the same time or alternately to produce tremor. To utilize the EMG most appropriately in tremor analysis, the signal has to be processed by rectification and integration or smoothing to place its frequency profile into the tremor range.[4]

The objective and detailed findings of a tremor analysis test are most helpful when the clinical picture is complicated or when clinical signs are subtle.[18] For example, parkinsonian tremor and essential tremor (ET) can sometimes be difficult to separate clinically, but diagnosis is obviously important to distinguish the appropriate prognosis and treatment.[1,13,19,20] Both conditions occur with increasing age, and both may occur at rest, with postures, or during voluntary movements. EMG-to-movement, side-to-side frequency relationship, EMG topography, reflex responses, tremor amplitude ratios during different clinical tasks, and methods such as time series analyses are ways by which quantified analysis can be diagnostically useful.

Computerized tremor analysis can also shed light on the manner in which tremor is perceived and graded by clinician observers.[21] In evaluating and grading change in tremor severity, the change in tremor amplitude perceived by a clinician is governed by Weber–Fechner laws of psychophysics, in which the size of the discernible change is proportional to the initial tremor amplitude, with a logarithmic relationship between tremor amplitude and perceived change in amplitude, despite the apparent linearity of clinical scales.[21–23] A combined study of tremor analysis data from five different laboratories confirmed this non-linear relationship and demonstrated good correlation between computerized tremor analysis and 4- and 5-point tremor rating scales in this context.[21]

In addition to tremor analysis using accelerometry and EMG, tremor can also be evaluated through the quantification of drawn spirals (Figure 1).

Archimedean spirals drawn on a digitizing tablet can be analyzed in both the x–y plane of the tablet and the z plane of pen pressure perpendicular to the tablet. By mathematically "unraveling" drawn spirals and averaging multiple trials together, tremor characteristics such as frequency, direction, and amplitude can be detected and quantified, as well as an abundance of other variables, including drawing speed and acceleration, loop-to-loop width tightness and variation, and drawing pressure over time.[11] Owing to its portability and ease of data acquisition, which can be analyzed offline, spiral analysis lends itself particularly well to the demonstration and quantification of subtle motor abnormalities in patient cohorts that might not be appreciated using standard clinical rating scales.[24]

Tremor pathogenesis

Physiologic tremor (PT), like all tremors, is generated and mediated both peripherally and centrally. The peripheral component of PT contributes irregular very low amplitudes and variable (8–12 Hz and higher) oscillations depending on the mass, stiffness, and other properties of the tremoring body part. It is a passive response caused by disturbances such as cardioballistics, mild physical perturbations, and subtetanic motor unit firing (too few motor units discharge together to result in anything but imperceptible movement or force).[3,4]

In addition to mechanical factors, short and long loop reflexes influence the peripheral component, although to a lesser degree. Hence, the peripheral component is often termed "mechanical reflex." If the peripheral component can be detected (which is not always the case), inertial loading (weighting) and other mechanical alterations affect it simply by changing limb physical properties.[25] Inertial loading will decrease the mechanical-reflex frequency component in the same manner as weighting slows down a clock pendulum. However, because of non-linearities in the nervous system (spindle stretch responses, muscle properties changes with length, thixotropy, neural membrane firing characteristics, etc.), inertial loading effects are not simple and must be interpreted cautiously. Furthermore, the mechanical-reflex component is not always detectable.

The central component of PT, often referred to as the "central oscillator", contributes weak 8–12 Hz very low-amplitude movements. The central oscillator of PT is not greatly affected by inertial loading or other physical manipulations. Motor units are not entrained (discharging in groups) in PT. When they become entrained, e.g., due to stress, drugs, or cold (as in shivering), PT develops into exaggerated physiologic tremor (EPT). EPT has the same peripheral and central components as PT, but there is greater participation of the stretch reflex and of the 8–12 Hz central oscillator. When EPT becomes clinically symptomatic with posture or movement *without* provoking factors, it becomes phenomenologically similar to ET and may be difficult to separate from EPT early in its course.

Pathologic tremors such as ET, dystonic tremor (DT), or the tremors of Parkinson disease (PD) result in a variety of tremor frequencies from about 1–25 Hz. They are thought to be generated centrally and usually obfuscate their peripheral components (except in neuropathic tremor). The etiology of tremor in PD is poorly understood, but based on recent magnetoencephalography and imaging studies is thought to involve networks of both cortical and subcortical areas.[26,27] While traditionally considered a functional monosymptomatic condition, an accumulation of both epidemiologic and pathologic studies have argued that ET may be a neurodegenerative disease with both an increased risk of non-tremulous co-morbidities[28] and structural pathologic changes in the cerebellum.[29] It is generally believed that the tremors in ET have contributions secondary to abnormal oscillatory activity either within the cerebellum[30] or in the olivocerebellothalamic pathway.[31]

Approach to the diagnosis of tremor

The most practical approach to understanding tremors is to classify them phenomenologically according to the circumstances under which they occur, in conjunction with the clinical history and exam, as well as by appropriate testing when warranted (Table 1).

Rest tremors

Rest tremors most often occur in the setting of PD or parkinsonism. PD rest tremors typically start unilaterally and distally as the classic 3–6 Hz "pill-rolling" sinusoidal oscillations, and progress more proximally as they generalize to both sides, though tremor may occasionally start anywhere (such as in the jaw). Early in the disease, tremor amplitude fluctuates significantly with mental or physical demands and thus is often described as intermittent. Oscillations in wrist extension and flexion, pronation and supination, or finger flexion (producing the pill-rolling quality) can be seen.[4] As with most movement disorders, PD tremor is worsened by stress (which can be useful to bring out tremor during clinical evaluation) and disappears during sleep. Anxiolytics or alcohol can improve symptoms simply by reducing anxiety, which may lead to confusion as ET is specifically responsive to alcohol.

A poly-EMG profile of PD rest tremor typically shows alternating (less commonly synchronous) contraction of agonist and antagonist muscles at a frequency of less than 6 Hz with relatively sinusoidal displacement on accelerometric tracings (Figure 2).

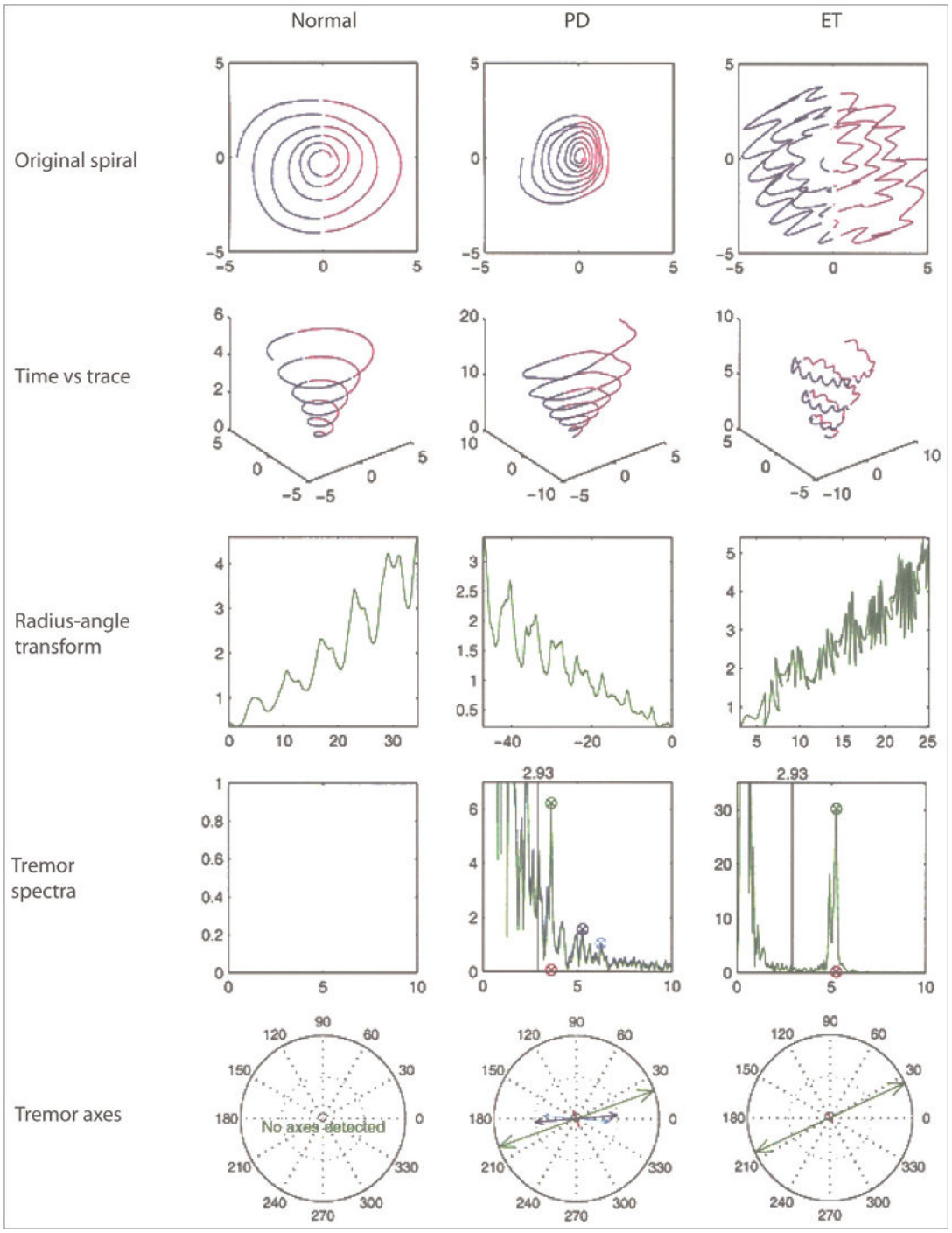

Figure 1. Representative Quantitative Spiral Analyses for Normal Subjects, Parkinson Disease (PD), and Essential Tremor (ET) Patients Demonstrating Tremor Frequency Spectra and Axis. Row 1: Original spiral drawings in 10 × 10 cm outlines with two line colors denoting the left and right sides of the spiral. Row 2: The spirals with dimension of time (seconds) in the vertical axis demonstrating temporal executions of the spirals. Row 3: The graphic representations of spiral unraveling where the x-axis = angle (radians) and the y-axis = radius (cm). Row 4: Spectral analyses of spiral tremor frequencies where the x-axis = frequency (Hz) and y-axis = frequency power. Row 5: Tremor axes, when present, illustrating the predominant direction of spiral tremors.

Table 1. Classification of Tremor Etiology Based on Circumstances of Occurrence

Etiology	Rest Tremor	Action Tremor		Notable Characteristics
		Postural	Kinetic	
Parkinsonism	+++	+	+	3–6 Hz, can re-emerge with posture (re-emergent tremor)
Midbrain (Holmes) tremor	++	+	+	Irregular and large amplitude, variable delayed onset, proximal as well as distal muscles involved
Thalamic tremor	++	++	++	Rare, sometimes delayed onset, can be associated with pain or sensory symptoms
Essential tremor	+	+++	+++	4–12 Hz, can occur at rest in longstanding disease, can have intentional component and be associated with mild ataxia or eye movement abnormalities
Cerebellar tremor		+	++	<5 Hz, predominantly intention tremor, uni- or bilateral, often associated with other cerebellar abnormalities such as dysmetria, overshoot, and past-pointing
Exaggerated physiologic tremor		++	++	Non-pathological; generally between 6 and 12 Hz, can result from anxiety or stress, fatigue, hypothermia, hypoglycemia, or metabolic disorders such as hyperthyroidism
Drug-induced tremor		++	++	Non-progressive, usually symmetric, often has a dose-response relationship with the causative drug and/or is temporally related with drug onset
Orthostatic tremor		+++		>13 Hz, occurs with weight bearing or isometric muscle contraction, variable latent period
Dystonic tremor	+	++	++	Usually <7 Hz or jerky and rhythmic irregular with variable amplitude, accompanied by abnormal (sometimes subtle) posturing, often having a null point and/or "sensory trick"
Neuropathic tremor	+	+	++	3–6 Hz, predominantly affecting more distal muscles, often irregular with variable amplitude, usually accompanied by symptoms of neuropathy
Task-specific (e.g., writing tremor)		+	+++	4–8 Hz, occurring predominantly with a specific task or posture, most common form is primary writing tremor

+, sometimes noted; ++, usually noted; +++, characteristic.

In tremor that is bilateral, tremor frequencies are similar. Some studies have found high coherence between limbs (despite amplitude asymmetry) for brief periods of time,[32] though this is not always observed.[33,34]

While tremor severity does not correlate with the loss of striatal dopamine, and some patients with PD tremor do not improve or even worsen with levodopa,[35] it is generally believed that rest tremors are modulated predominantly centrally by multiple generators within the corticobasal ganglia and corticocerebellar circuitry. Functional neurosurgical treatments that inhibit pathways through the basal ganglia are thought to work by disrupting these circuits.[36]

As ET becomes more severe it may occur at rest;[37] however, this can also sometimes represent coexistent PD or incomplete postural relaxation.[38] ET resting tremor is asymmetric and the frequency

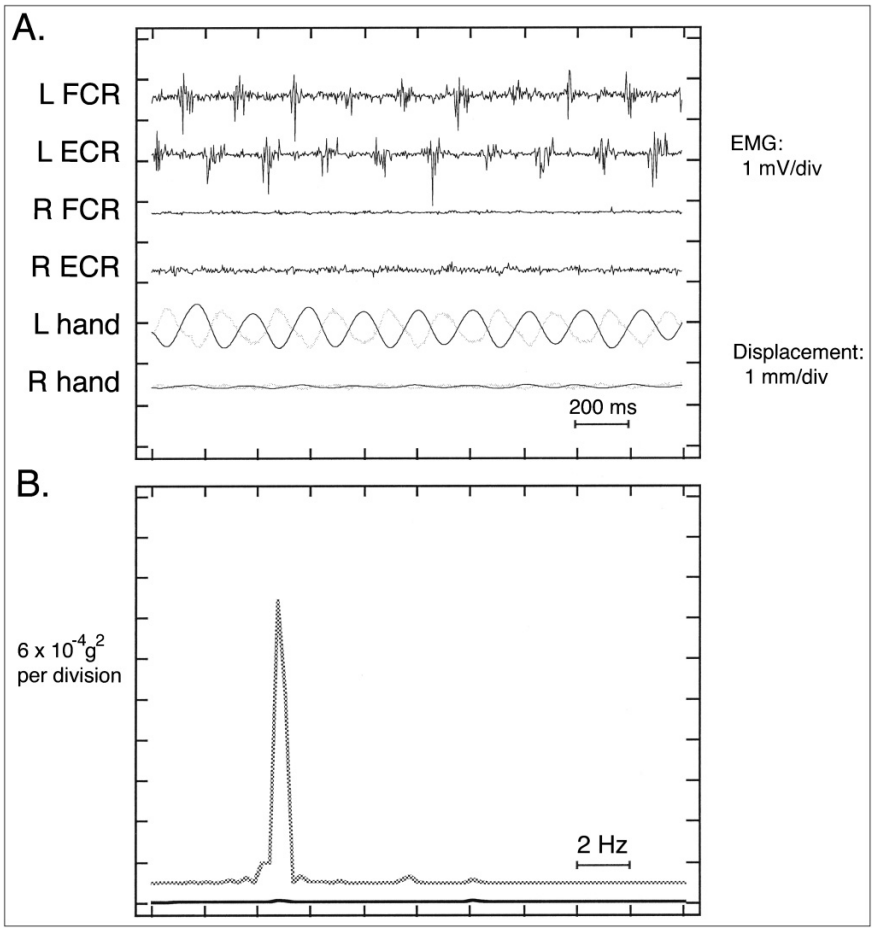

Figure 2. Electromyography (EMG) Profile, Movement Analysis, and Frequency Spectrum of Rest Tremor in a Patient with Parkinson Disease (PD). (A) EMG profile. The first four traces represent surface EMG signal from forearm muscles; ECR, extensor carpi radialis; FCR, flexor carpi radialis. The bottom two traces reflect displacement (darker line) derived from accelerometry. Note the relatively sinusoidal tremor displacement in the symptomatic left hand. (B) Frequency spectrum of tremor displacement demonstrating a peak between 4 and 6 Hz in the symptomatic left (gray line) hand, with a trace peak present in the right (black line) hand.

relationship between sides is variable.[39] Though less commonly seen in clinical practice, other diseases can produce rest tremors as well, though usually not in isolation. Midbrain (rubral or Holmes) tremor and thalamic tremor are occasional causes of rest tremor. Midbrain tremor is caused by lesions of the cerebellothalamic and nigrostriatal pathways and thus consists of a combination of rest, postural, and kinetic components. The tremor at rest is of large amplitude and irregular, and commonly involves both proximal and distal muscles at frequencies of 2–5 Hz.[4,40] Infarction in the midbrain is the most common cause, though tumor, abscess and demyelination are occasionally reported. Thalamic tremor is relatively rare, and causes action and sometimes rest tremor due to lesions most often affecting the ventral lateral posterior nucleus of the thalamus.[41] Though DT and drug-induced tremors are more commonly thought of as action tremors, they can occur at rest, usually along with an action component.

Action tremors

Most pathologic tremors are predominantly action tremors, whether kinetic or postural (or often a combination of both). Unlike rest tremor, the diagnostic possibilities of action tremor are broader, and discussion based on etiology is more appropriate.

Action tremor in PD

Patients with PD can exhibit a variable-onset delayed tremor when holding up an outstretched arm, with a frequency typical of PD rest tremor. This is in contrast with the postural tremor of ET, which has no delay in onset. It is commonly thought of as re-emergent PD rest tremor, though a case of such tremor without rest tremor has been reported.[42] In addition, higher frequency 5–8 Hz lower amplitude action tremors are not uncommon in PD and can be difficult to distinguish from ET.[4] Single photon emission computed tomography imaging of the dopamine transporter has been approved in the United

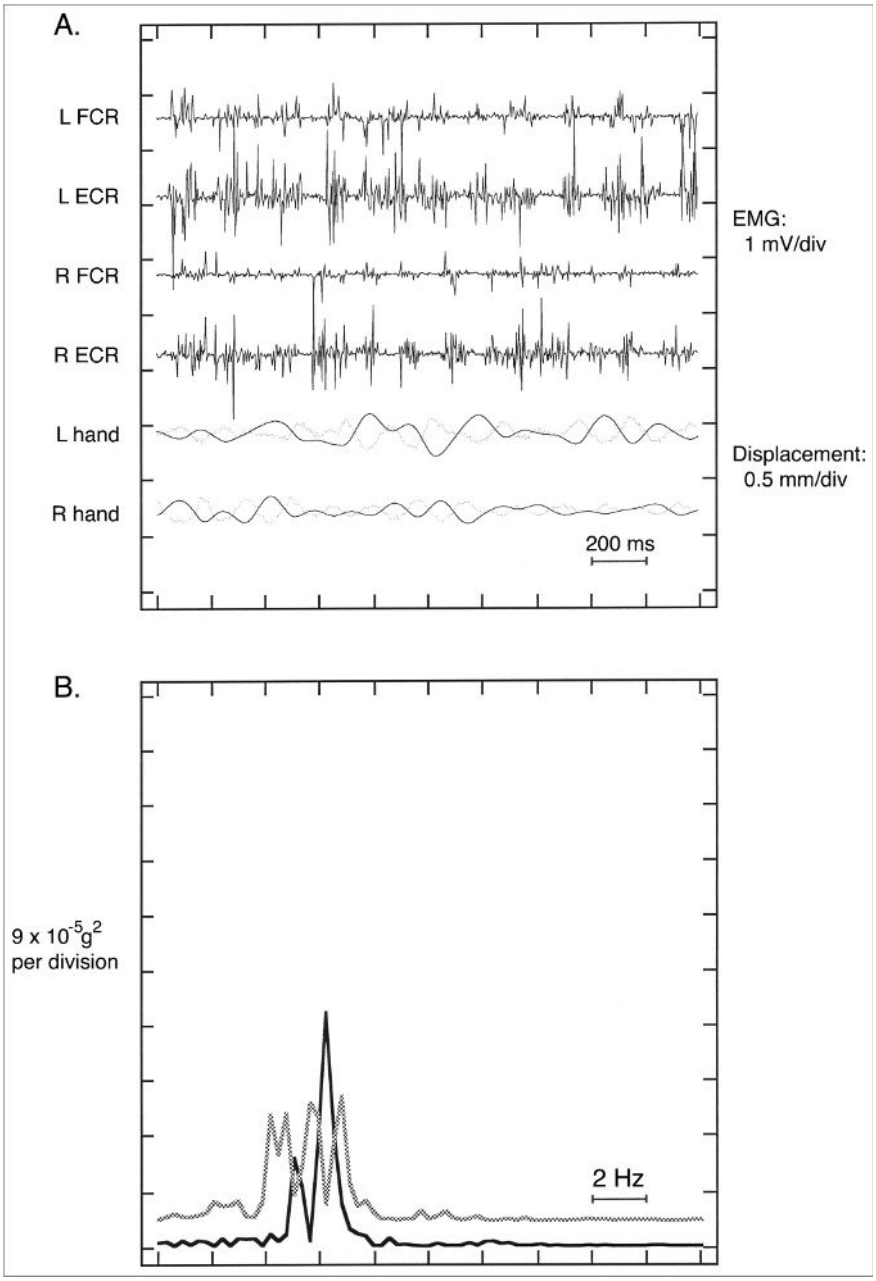

Figure 3. Electromyography (EMG) Profile, Movement Analysis, and Frequency Spectrum of Postural Tremor in a Patient with Essential Tremor (ET) with Arms Extended. (A) EMG profile. The first four traces represent surface EMG signal from forearm muscles; ECR, extensor carpi radialis; FCR, flexor carpi radialis. The bottom two traces reflect displacement (darker line) derived from accelerometry (B) Frequency spectrum of tremor displacement demonstrating a broad peak between 4 and 8 Hz in both hands.

States of America to help differentiate these entities, and computerized tremor analysis can also be useful in this regard.

Essential tremor

ET is the most prevalent adult movement disorder. It is often familial and transmitted in an autosomal dominant pattern with high penetrance.[43] While advancing age is the most obvious risk factor, ET can occur in the pediatric age group as well.[44] Figure 3 shows a typical EMG profile and frequency spectrum.

ET is generally a slowly progressive, clinically monosymptomatic disorder marked by initially low-amplitude tremors (which can increase dramatically as the disease progresses) of mid to high frequency (4–12 Hz that decreases with age) and is most prominent in the hands, though other body parts can be involved.[4] The amplitude of

kinetic tremor (which is invariably present) is generally greater than that of postural tremor.[45] A worsening of kinetic tremor as the hand approaches a target (intention tremor) can be seen.[30] Head tremor (commonly in the horizontal plane) can develop or rarely be present in isolation, and a jaw tremor (in contrast to the lower lip tremor typically associated with PD) can be seen in some cases.[30] Unlike tremor in PD, it is more irregular and more bilaterally symmetric, and it does not occur as a hemibody tremor lateralized to one arm and leg. Cogwheeling is often found secondary to tremor and should not be confused with the rigidity seen in PD patients. The amelioration of tremor with alcohol is common and can help establish the diagnosis, and moderate use of alcohol limited to occasional social settings is usually not discouraged. However, alcohol clearly should not be used in the chronic treatment of ET, and the risk of dependence and abuse in ET has not been completely addressed by formal studies.[46]

Cerebellar tremor

Cerebellar postural and action tremors are irregular and often of high amplitude, causing severe functional disability. With no rest component, patients may appear normal until they initiate movement or assume a steady posture, and tremor is most pronounced with intention.[47] Irregular postural tremor of the head and rhythmic postural sway (truncal tremor) may also occur. As with all tremors, the frequency of cerebellar tremor depends upon the part of the body that is affected.[4] Tremor frequencies range from 3–8 Hz in the upper extremities, around 1–3 Hz in the lower extremities, and 2–4 Hz in the trunk. Injury to the deep cerebellar nuclei and cerebellar outflow tracts are likely involved in tremor production. The benefits of both pharmacologic and surgical treatments have been limited.[4,48]

Orthostatic tremor

The term orthostatic tremor (OT) was first used in 1984[49] and was previously referred to as "shaky leg syndrome". In this relatively uncommon but distinct disorder, patients find it increasingly difficult to stand still due to sensations variably described as tremor, unsteadiness, and/or pain. Tasks such as waiting in line or doing dishes become troublesome, and patients find themselves needing to walk in place, continuously shift their weight from one leg to the other, or lean against a wall in order to reduce discomfort.[50] OT may also be associated with muscle cramps,[51] and patients will often describe subjective tremor elsewhere in the body, such as the lips, jaws, or hands. Significant disability and depression with substantial curtailing of activities can occur in severe cases.

OT is more common in women, with a mean age of onset in the early sixties, and is generally considered to be sporadic, though associations with various other neurologic disorders have been reported, including ET, PD, cerebellar degeneration, progressive supranuclear palsy, and pontine lesions.[52–54] Familial occurrence is uncommon, though EMG-confirmed OT in three brothers has been reported.[53,55]

The diagnosis of OT should be suspected in any patient describing pain or other unpleasant sensations shortly after standing that is relieved by sitting or walking. Auscultation of the gastrocnemius muscles can sometimes reveal a characteristic of barely audible noise akin to the sound of a helicopter.[56] The diagnosis is confirmed by pathognomonic surface EMG recordings revealing rhythmic activation of lower limb muscles at sharply peaked frequencies between 14 and 18 Hz, and sometimes higher (Figure 4).

Frequency spectra consistently show a high degree of coherence between limbs, unlike that in any other form of tremor.

The etiology of OT is unclear; while it was initially considered a task-specific tremor, upright body position has been shown to be less important than weight-bearing and the sensation of postural instability, both of which may give rise to the clinical disorder. It has been demonstrated in all limbs in OT patients with weight bearing[57] and isometric contraction,[58] and high-frequency highly coherent tremor has been produced in normal subjects made to feel unsteady through postural manipulation or galvanic stimulation, suggesting an exaggerated response to postural instability as playing a role.[59] These observations, combined with its demonstration in cranially innervated muscles[60] and the resetting of tremor phase induced with transcranial magnetic stimulation[61] support a supraspinal central generator of the tremor. Treatment of OT is often disappointing, and improvement has been reported mostly with clonazepam, but occasionally with phenobarbital, primidone, or valproate.[62] Improvement with deep brain stimulation (DBS) of the ventrointermediate nucleus (VIM) has also been described.[63,64]

Dystonic tremor

DT occurs in a body part affected by dystonia. It is typically postural or task related, with an irregular or jerky rhythmic low- to mid-frequency tremor secondary to co-contraction of agonist and antagonist muscles. Frequencies range from 1 to 6 Hz during dystonic contractions, with higher frequencies similar to ET seen during voluntary movements.[4] Tremor associated with dystonia (occurring in a clinically non-dystonic body part in a patient with dystonia) can also occur.[47] Characteristic of DT is the null point, a position in which the tremor almost fully abates.[65] It may initially be present during specific action but can generalize to occur with any task. DT of the head or hand can sometimes be confused with ET or PD, and patients with DT have been postulated to account for some of the instances of patients with parkinsonism who have normal dopamine neuroimaging (scans without evidence of dopaminergic deficit (SWEDDs), or scans without evidence of dopaminergic deficit).[66] Careful evaluation for subtle dystonic posturing and the presence of a null point and/or geste antagoniste (a tactile or proprioceptive sensory trick that reduces the abnormal posture), as well as attention to tremor quality (jerky versus smooth), are helpful in making the correct diagnosis.[47] In patients with head tremor, it is also helpful to remember that the typical head tremor seen in ET rarely occurs in the absence of coexistent hand tremor.[30]

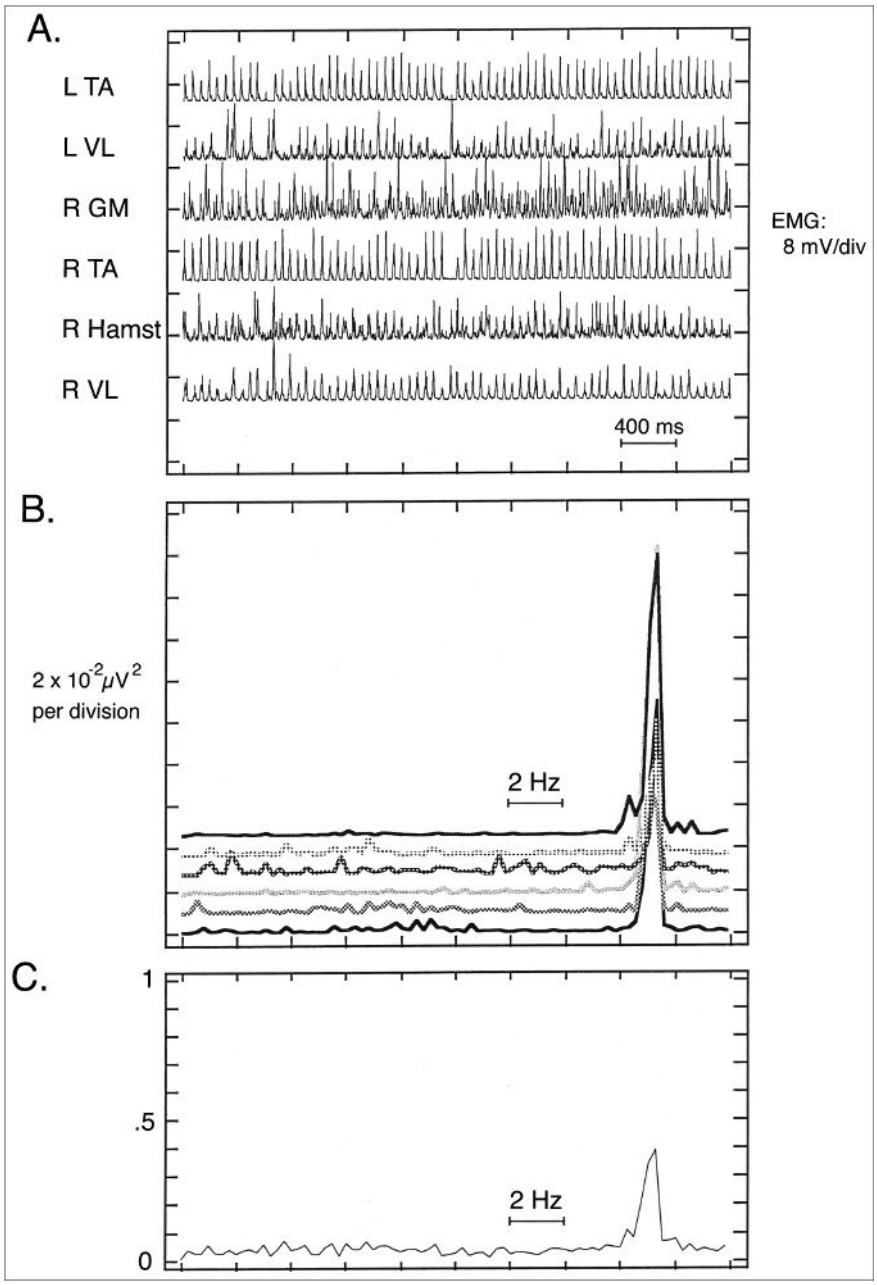

Figure 4. Electromyography (EMG) Profile and Frequency Spectrum of A Patient with Orthostatic Tremor While Standing. (A) EMG profile. GM, gastrocnemius; Hamst, hamstrings; TA, tibialis anterior; VL, vastus lateralis. (B) Frequency spectra demonstrating a sharp peak at 17.3 Hz in all muscles recorded. (C) Note the high coherence between frequency spectra of the EMG signals in the legs.

Neuropathic tremor

Neuropathic tremor is thought to arise secondary to central processing of mistimed and distorted peripheral input that occurs with neuropathic disease.[67] It is usually irregular and distal, and can be asymmetric or relatively symmetric, with frequencies in the upper limbs ranging from 3 to 6 Hz. Figure 5 demonstrates the distal low frequency tremor that developed subacutely in a patient with sensorimotor neuropathy with demyelinating and axonal features. Neuropathic tremor can physiologically mimic a number of other tremor disorders, and the most helpful clues to the diagnosis are the coexistence of neuropathic symptoms.[4] It can occur at rest, with posture, or during movement and can develop with multiple neuropathies, such as anti-myelin-associated glycoprotein

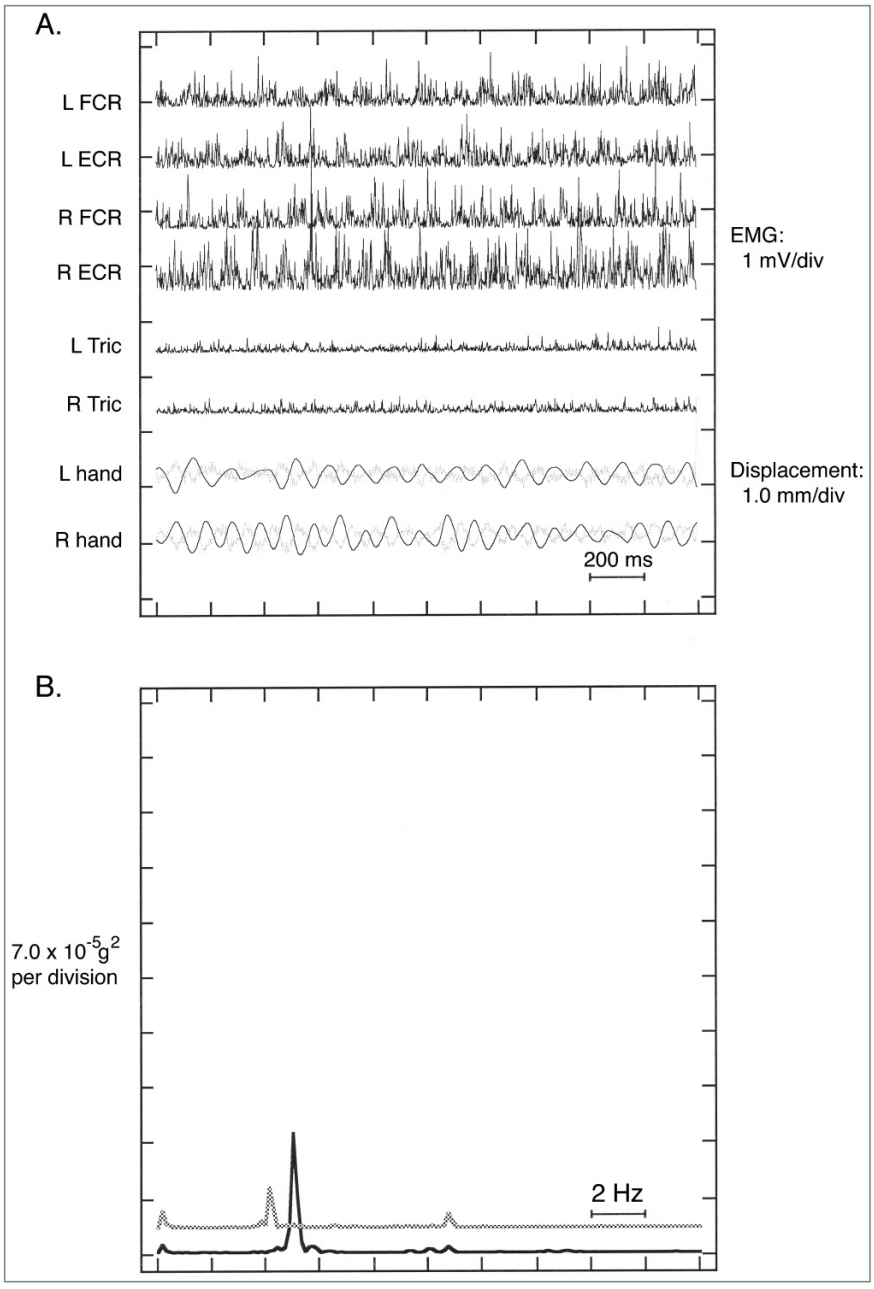

Figure 5. Electromyography (EMG) Profile, Movement Analysis, and Frequency Spectrum of a Patient with Neuropathic Tremor Accompanied by Bilateral Sensory Loss and Weakness. EMG and nerve conduction studies demonstrated sensorimotor neuropathy with both demyelinating and axonal features. Note the distal low-frequency tremor driven primarily by wrist flexors and extensors with little proximal limb involvement. (A) EMG profile. The first six traces represent surface EMG signal from arm muscles. ECR, extensor carpi radialis; FCR, flexor carpi radialis; Tric, triceps. The bottom two traces reflect displacement (darker line) derived from accelerometry. (B) Frequency spectrum of tremor displacement demonstrating peaks between 4 and 6 Hz.

(anti-MAG) neuropathy.[68] Most patients with neuropathic tremor are without central nervous system disease, and the tremor subsides with treatment of underlying neuropathy. Beta-blockers and other drugs used in ET have been reported to be helpful for neuropathic tremor, and success with VIM DBS has also been reported.[69]

Task-specific tremor

Tremor (not associated with abnormal postures or muscle spasm) that occurs predominantly during the execution of a specific (and often skilled) task is considered a task-specific tremor.[43] While the 4–8 Hz tremor of primary writing tremor (PWT) is the most common example

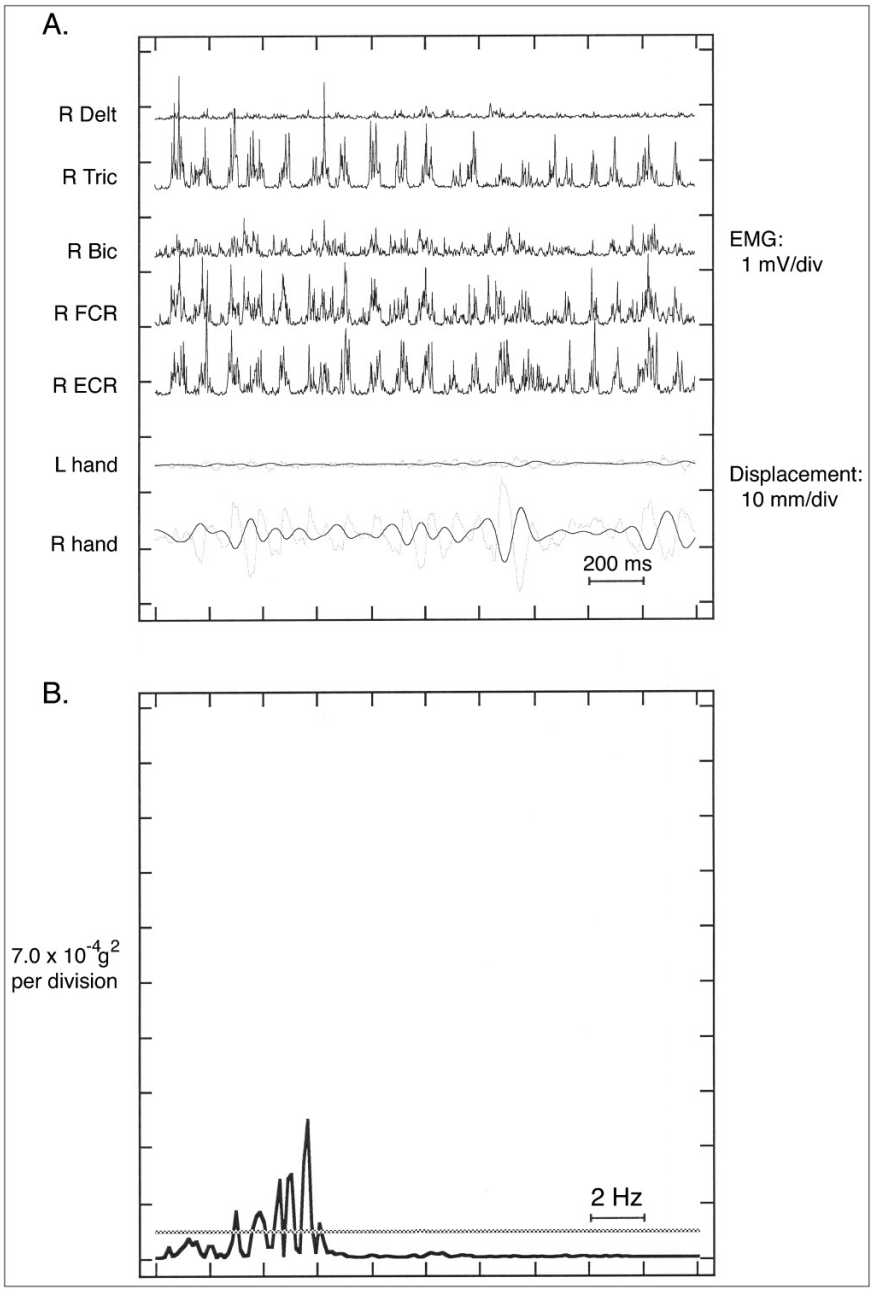

Figure 6. Electromyography (EMG) Profile, Movement Analysis, and Frequency Spectrum of a Patient with Primary Writing Tremor while Writing with the Dominant Hand. Co-contraction of agonist and antagonist muscles below the deltoid is evident, though alternating contraction of agonist and antagonist muscles may be a more commonly seen pattern. (A) EMG profile. The first five traces represent surface EMG signal from forearm muscles. ECR, extensor carpi radialis; FCR, flexor carpi radialis. The bottom two traces reflect displacement (darker line) derived from accelerometry (B) Frequency spectrum of tremor displacement demonstrating peaks between 4 and 6 Hz.

of a task-specific tremor, it can be found in musicians, athletes, and other professionals who are highly trained, such as surgeons or dentists. PWT can be sporadic or inherited in an autosomal dominant manner, and its etiology is controversial; it has been proposed to be a variant of DT, ET, and its own distinct entity.[70] Poly-EMG profiles most commonly show alternating contraction of agonist and antagonist muscles, although various other contraction patterns can be seen as well. Figure 6 shows co-contraction of agonist and antagonist muscles and excessive muscle activity resulting in 4–5 Hz irregular tremor in a patient with primary writing tremor of 10 years' duration.[4]

Drug-induced tremor

A wide variety of pharmacologic agents with differing mechanisms of action can cause tremor as a side effect.[4] In general, they are

non-progressive, often temporally related to the onset of a medication, and worsen with increasing medication dose.[71] Drug-induced rest tremor can occur in isolation or as part of drug-induced parkinsonism secondary to the use of antipsychotics, and can be clinically indistinguishable from PD tremor.[72] In addition to neuroleptics, any medication which can cause secondary parkinsonism, such as lithium carbonate, valproate, or serotonin specific reuptake inhibitors, can induce a rest tremor.[73,74]

Many of these medications can cause an action tremor as well. Lithium is a frequent offender, causing tremor at both toxic and therapeutic levels.[75,76] High blood levels of lithium are not necessary to produce tremor,[77,78] and no correlation has been found between blood lithium levels and patient complaints of tremor.[79] Non-toxic lithium tremor can occur acutely within the first week of starting therapy,[80] or may develop within weeks[81] or months after starting the medication.[78] Valproate can cause a fine, 6–9 Hz rhythmic postural tremor, similar to the action tremor, which can occur with tricyclic antidepressants, and can mimic ET.[71] Treatment with propranolol can be beneficial.[82] Other tremorogenic medications include anti-arrhythmics, bronchodilators, and chemotherapeutic agents.[83,84] Drugs of abuse such as alcohol, cocaine, and amphetamines can also cause tremor, due to acute intoxication, chronic use, or withdrawal.[85] Similar effects can be seen with heavy caffeine use.

Psychogenic tremor

Psychogenic tremors can occur as a manifestation of an underlying psychiatric disorder such as somatoform or factitious disorder, or can occur in cases of malingering.[86] The diagnosis is based on unusual phenomenology and other diagnostic clues, such as abrupt onset, inconsistencies in tremor pattern and characteristics, spontaneous remissions, response to placebo, and distractibility.[47,87,88] Relatively consistent physiologic findings include an increase in tremor amplitude with inertial loading (Figure 7), large fluctuations in frequency and amplitude, co-activation of antagonist muscles at the onset of tremor, and the absence of finger tremors.[89–91] Coexistent non-physiologic signs such as weakness or sensory abnormalities and underlying psychopathology can also help to suggest the diagnosis. Because it may be difficult to approach patients with a diagnosis of psychogenic tremor, clinicians are often reluctant to discuss the possibility of psychogenicity. However, if correctly identified, psychogenic tremor due to a somatoform disorder is potentially curable through a coordinated effort between neurologists and psychiatrists.[92] It is important to remember that the diagnosis of psychogenic tremor can only be made by a neurologist, while the role of the psychiatrist is to explore underlying psychodynamics and the degree of insight, guide psychopharmacologic treatments, and provide the continued psychotherapy critical for improvement.[73]

Other types of tremor

Some disorders, such as asterixis, epilepsia partialis continua, and rhythmic forms of myoclonus such as palatal myoclonus, are often misinterpreted as tremor. Physiologically, myoclonic EMG bursts do not have gradual rise times and are not sinusoidal, and are separated by discrete periods of muscle silence.[3] Cortical tremor is thought to be

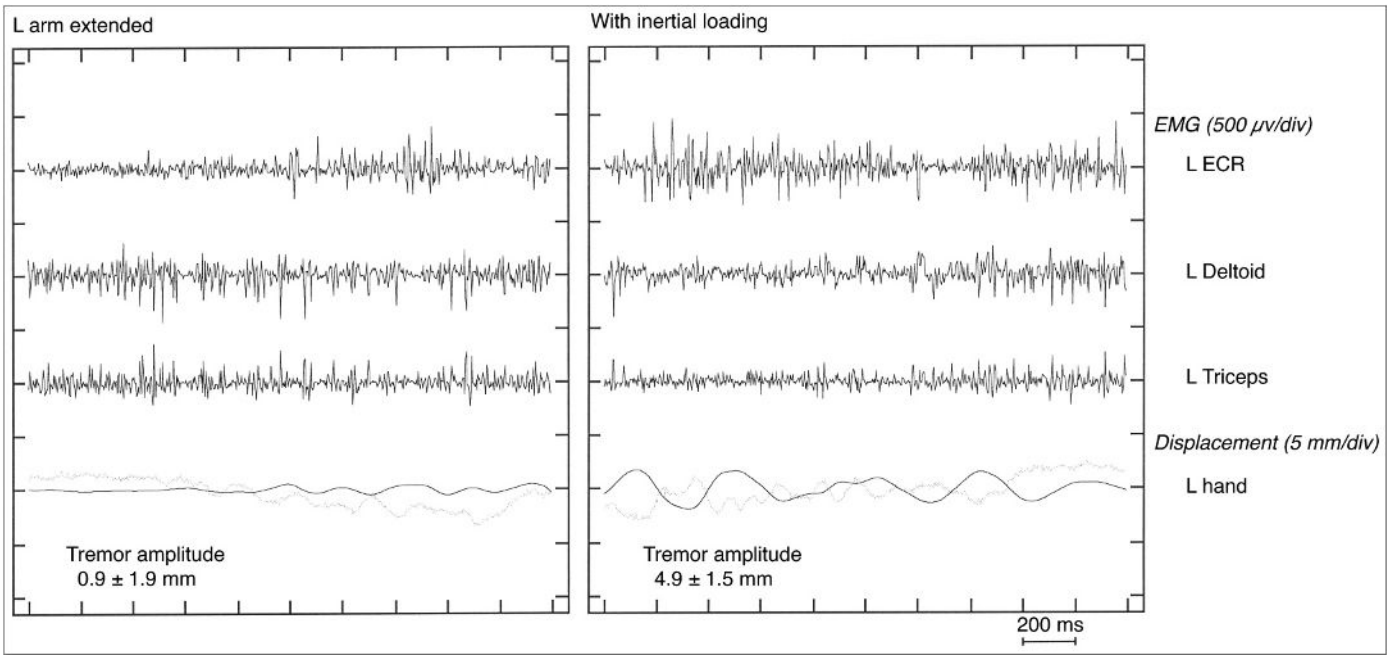

Figure 7. Electromyography (EMG) Profile and Movement Analysis of a Patient with Psychogenic Tremor of the Left Arm with the Arm Extended (left) and with Inertial Loading of the Extended Left Hand (right). Note the almost fivefold increase in tremor amplitude as shown by an increase in mean displacement from 0.9 to 4.9 mm.

a variant of action-induced myoclonus in the setting of cortical myoclonus.[93] It is characterized by distal short duration (generally less than 50 ms) rhythmic irregular bursts on EMG with synchronous activation of agonist and antagonist muscles and alternating periods of near silence. Peak EMG burst frequency is 9–18 Hz with an associated cortical potential on EEG back-averaging.[91,94]

Summary

While clinical assessment remains the most commonly used method of diagnosing and examining tremor, the techniques of computerized quantitative analysis using accelerometry, EMG, and spiral analysis can be powerful tools in the assessment of tremor in both clinical and research paradigms. A combination of careful clinical evaluation, response to therapy, and computerized analysis best helps distinguish the various pathologic tremors and shed light on their pathogenesis.

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