Contemporary Clinical Neuroscience

Giuliana Grimaldi
Mario Manto *Editors*

Mechanisms and Emerging Therapies in Tremor Disorders

Second Edition

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Foreword

Tremor is one of the most common movement disorders, a manifestation of several neurological disorders, but it can also be secondary to several medical conditions. This book deals with the various common and uncommon types of tremors. Clinical features, differential diagnosis, pathogenesis, pathophysiology and treatment of the different types of tremors are extensively reviewed.

The book begins with a chapter describing the classification of tremor, its clinical features and etiology and provides an overview of the pathophysiological mechanisms underlying tremors. The role of the cerebello-thalamo-cortical circuit is emphasized, and the concept of a sensorimotor network with multiple interacting nodes causing tremors is discussed. The electrophysiological properties of neuronal membranes in thalamic neurons and in the inferior olive neurons are discussed in the second chapter. Oscillations in the thalamo-cortical and in the cerebellar pathways are relevant for the pathogenesis of tremor in ET; oscillations in a network that include the subthalamic, the globus pallidum, the thalamus and the cortical areas are relevant for PD tremor. Drugs commonly used for treating ET support the importance of membrane oscillations in the pathophysiology of tremor. The importance of genetics in the pathogenesis of tremors is upheld in the third chapter; several examples of hereditary tremor disorders are provided and discussed. The heterogeneity of the diseases characterized by tremors is reflected by the heterogeneity of genes and pathways causing such diseases. In Chap. 4, the authors describe the effects of lesions in the Guillan-Mollaret triangle, suggesting that lesions of the triangle may cause different types of tremors.

The role of the mechanical-reflex component and of central mechanisms underlying physiological tremor, which is best seen with motion transducers, is dealt with in Chap. 5. Rest tremor, defined as an involuntary oscillation while the body segment is at rest, is described in Chap. 6. Rest tremor, mainly present in patients with Parkinson's disease (PD), can also be present in other types of tremors, including advanced cases of ET. In PD, the re-emergent tremor, which is a postural tremor that appears after a delay of a few seconds, is considered a subtype of rest tremor. The most convincing evidence suggests that rest tremor is due to the interaction between the basal ganglia and the cerebello-thalamo-cortical circuit, driven by

impaired dopaminergic projections. Demonstrating a disynaptic projection from the STN to the cerebellum via the pons and from cerebellar nuclei to the striatum via thalamic nuclei supports this hypothesis. The chapter ends with a review of the possible pharmacological and surgical therapy for rest tremors. The clinical and pathophysiological characteristics of postural tremor in healthy individuals and in people with physiological and essential tremors are discussed in Chap. 7, together with the relationship between ET and PD postural tremor. Whether postural PD tremor results from the activation of neural circuits generating rest PD tremor or is due to the activation of neural networks involved in ET remains unclear. Isometric tremor can occur in isolation but is most frequently associated with other types of action tremor and results from muscle contractions when holding an object. Chapter 8 describes the clinical characteristics, pathophysiology and treatment of isometric tremor in various clinical syndromes. Chapter 9 deals with kinetic, rhythmic and oscillatory movements during guided voluntary movements. Kinetic tremors can be present in patients with physiological tremor, essential tremor, dystonic and other pathological tremors. The etiology of ET (genetic, environmental or a combination of both factors) is a research area that still needs active investigation. Studies on the pathophysiology suggest that tremor in ET may result from functional changes in brain circuitries, with the cerebellum being involved; however, it must be said that other studies identified structural/cellular changes in the ET brain, most on the Purkinje and connected neuronal populations. ET may be a cerebellar degenerative disorder. Other forms of kinetic tremors are also discussed in this chapter. Dystonic tremor and the discussion on the relationship between dystonia and tremor are tackled in Chap. 10. The involvement of the cerebellum in the pathogenesis of all tremor syndromes and the different types of lesions in the cerebellum causing tremors are discussed in Chap. 11. Orthostatic tremor, mainly considered an idiopathic condition, is characterized by tremors of the legs and trunk, present on standing and improving on walking or sitting. Neurophysiological and functional imaging studies, as discussed in Chap. 12, suggest a key role of the cerebellum in its pathophysiology, together with involvement of motor and sensory cortical areas. Orthostatic tremor might be a family of diseases, having in common lower limbs tremor, but further characterized by etiological and clinical heterogeneity.

As would be the case with other types of movement disorders, tremors can follow a trauma. Chapter 13 discusses the role of central and peripheral trauma causing tremor and other types of movement disorders. Many rare conditions can produce tremors in childhood and Chap. 14 describe all these conditions, also dealing with the differential diagnosis with other types of movement disorders. In Chap. 15, tremors due to metabolic causes are reviewed. The phenomenology of metabolic tremors, associated neurologic abnormalities and therapies are discussed. Treatable causes are emphasized. Chapter 16 deals with general clinical features that need to be considered to diagnose tremor correctly. A correct approach should consider the location of the tremor, the activating features, the phenomenology of tremor, the associated neurologic signs and, when necessary, ancillary testing such as imaging and electrophysiology. Signal processing methods in the analysis of tremors, mostly

spectral analysis, can be useful for clinical and scientific purposes (Chap. 17), together with the investigation of white matter pathways and the investigation of the microstructural integrity of grey matter structures (Chap. 18). Noradrenergic activity may modulate tremors at different anatomical levels, both peripherally and centrally. The role played by the noradrenergic system in the pathophysiology of physiological tremor, PD tremor and ET tremor is reviewed in Chap. 19. Metabolic brain imaging with [18F]-fluorodeoxyglucose ([18F]-FDG) positron emission tomography (PET) in PD tremors is discussed in Chap. 20. The use of deep brain stimulation for treating common and uncommon tremors is discussed in Chap. 21; the contribution of DBS in advancing our knowledge of the pathophysiology of tremors is also emphasized. Wearable technology as a potential alternative approach for tremor management and tremor suppression mechatronic systems for the upper limb is discussed in Chap. 22. Chapter 23 describes tremors caused by drugs, with most drugs causing postural or kinetic tremors, although rest tremors with parkinsonism may also occur after drug use. A careful medical history is needed, especially regarding the temporal relationship with initiating the drug.

This book encompasses all the medical aspects of tremor, and all the information are updated. This book will be essential for all the researchers actively involved in research activities on tremors and neurologists who see patients with tremors in their clinics. The editors and authors of this important book should be congratulated for their excellent job in writing this book.

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Contents

Chapter 1
Definition of Tremor

Giuliana Grimaldi and Mario Manto

Abstract Tremor is generally defined as a rhythmic shaking of a body part (Deuschl et al., Ad Hoc Scientific Committee Mov Disord 13(suppl 3):2–23, 1998; Findley and Capildeo, Movement disorders: tremor. Macmillan, London, 1984). Tremor is a nonlinear and nonstationary phenomenon, often made of a roughly sinusoidal oscillatory movement, usually nonvoluntary. Within-subject fluctuations represent an inherent property of tremor. Tremor is readily apparent in most cases. The oscillation is composed of a back-and-forth movement (McAuley and Marsden, Brain 123:1545–1567, 2000), where "back-and-forth" means that there is a relatively symmetric velocity profile in both directions about a midpoint of the movement, with the velocity profile of oscillations appearing sinusoidal (Sanger et al., Mov Disord 25(11):1538–1549, 2010). Tremor is now classified along two axes: Axis 1 refers to the clinical features (historical features, tremor characteristics, and associated signs) and laboratory tests, and Axis 2 refers to the etiology (acquired, genetic, or idiopathic) (Bhatia et al., Mov Disord 33(1):75–87, 2018). Tremor syndromes are defined within Axis 1.

Keywords Rhythmic · Rest · Postural · Kinetic · Action · Movement disorders · Thalamus · Basal ganglia · Inferior olive · Cerebellum · Consensus statement · Connectomics

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1.1 Introduction

Tremor is generally defined as a rhythmic shaking of a body part (Deuschl et al. 1998; Findley and Capildeo 1984). Tremor is a nonlinear and nonstationary phenomenon, often made of a roughly sinusoidal oscillatory movement, usually nonvoluntary. Tremor is readily apparent in most cases. The oscillation is composed of a back-and-forth movement (McAuley and Marsden 2000), where "back-and-forth" means that there is a relatively symmetric velocity profile in both directions about a midpoint of the movement, with the velocity profile of oscillations appearing sinusoidal (Sanger et al. 2010).

Tremor is one of the most common movement disorders encountered during daily practice (Louis et al. 1995). Its incidence and prevalence increase with aging. The prevalence in people over 60 years has been estimated to be 4.6% (Louis and Ferreira 2010). In this sense, and given the aging of the population, tremor disorders are a matter of interest for the society in general and for the scientific community in particular.

Tremor causes functional disability and social inconvenience, disturbing daily-life activities and also contaminating other specific motor activities. Nevertheless, a nonnegligible number of patients, especially those with a mild tremor, do not ask for medical advice if tremor does not impede daily-life activities.

The consensus statement on the classification of tremor has clarified the nosology of tremor and considers two axes (Bhatia et al. 2018; Fig. 1.1):

1. *Axis 1* refers to the clinical features. It includes historical features (age of onset, family history, evolution with time, exposure to drugs or toxins), tremor characteristics (distribution, activation condition, frequency), and associated systemic/neurological signs and laboratory results (electrophysiology including electromyographic recordings and structural imaging with CT/MRI to identify lesions). Functional imaging studies (including dopamine and serotonin transporter imaging) and fluid biomarkers (metabolic blood tests, genetic tests, etc.) may be used and point toward an etiology of Axis 2.
2. *Axis 2* refers to the etiology (acquired, genetic, or idiopathic). Axis 1 characterization will often lead to a syndrome or phenotyping presentation that will end in the identification of an etiology. This is an important step toward a consensual phenotyping of tremor, taking into account that a syndrome may have multiple etiologies and a given etiology may produce several syndromes. It is important to note that the follow-up and re-evaluation of patients are critical for Axis 1 determination. Furthermore, additional signs may develop after years or even decades.

Regarding the age of onset, the consensus statement suggests to categorize patients in six groups: infancy (birth to 2 years), childhood (3–12 years), adolescence (13–20 years), early adulthood (21–45 years), middle adulthood (46–60 years), and late adulthood (above 60 years). In terms of distribution, tremor can be focal (one body region: voice, head, jaw, one limb, etc.), segmental (two or more contiguous parts: head and arm, arm and leg, bibrachial, bicrural, etc.), take the presentation of a hemibody tremor, or generalized (upper and lower body).

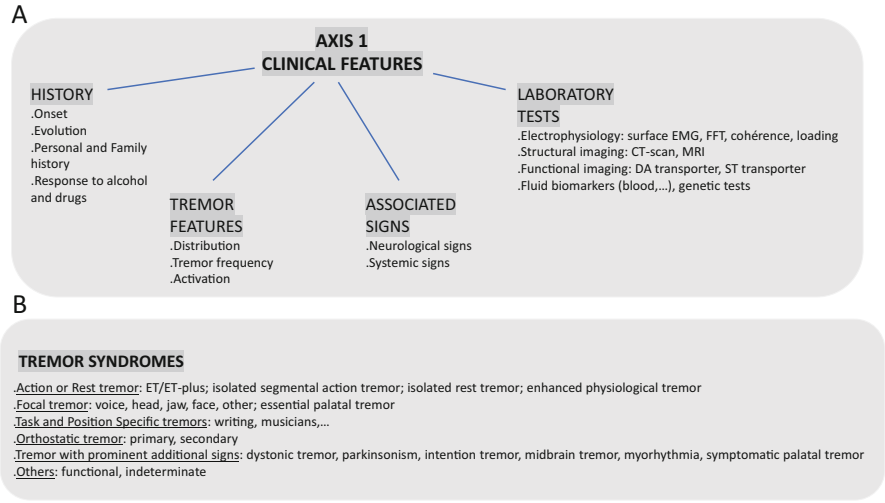

Fig. 1.1 **(a)** Clinical features of tremor for a given patient. **(b)** Tremor syndromes. (Adapted from Bhatia et al. 2018)

Tremor may thus present with different clinical features and different parameters. Rest tremor occurs in a body part not activated voluntarily and should be assessed when the patient tries to relax. It may require a complete support of the body. *Action tremor* occurs when the patient is maintaining a position against gravity (*postural tremor*, which is position independent or position dependent) or during a movement (*kinetic tremor*) (Bhatia et al. 2018; Grimaldi and Manto 2008). *Kinetic tremor* is subdivided into a *simple kinetic tremor* (tremor is about the same throughout the movement) and *intention tremor* (tremor increases near the target). Although the terminology of action tremor and kinetic tremor is frequently used in an interchangeable manner, the meaning is different (Bhatia et al. 2018).

Numerous neurological diseases are associated with a form of tremor falling within these categories (Table 1.1). *Task-specific tremor* appears while attempting to perform a specific task such as writing.

Tremor frequency is usually not very helpful because most tremors occur in the frequency range of 4–8 Hz. However, in some instances the frequency is particularly relevant:

- Myorhythmias and palatal tremors show a frequency below 3.5 Hz.
- Primary orthostatic tremor has a typical frequency between 13 and 19 Hz.

According to the presence of associated signs, Axis 1 considers that tremor can be subdivided into the following:

- *Isolated tremor:* no other sign.
- *Combined tremor*: other neurological signs (dystonia, rigidity, myoclonic jerks, etc.) or systemic signs (Kayser-Fleischer ring).

Table 1.1 Main disorders associated with tremor according to the clinical presentation

Clinical presentation	Diseases
Rest tremor	Parkinson's disease[a]
	Drug-induced Parkinsonism
	Stroke
	Post-traumatic tremor
Action tremor: postural	Essential tremor[b]
	Enhanced physiological tremor
	Cerebellar diseases
	Multiple sclerosis
	Post-traumatic tremor
	Metabolic diseases (Wilson's disease, hyperthyroidism)
	Peripheral neuropathy (acute, chronic)
	Drug-induced (valproate, bronchodilators, lithium, neuroleptics, etc.)
	Withdrawal syndromes (ethanol)
	Toxins (mercury, lead, toluene, etc.)
Action tremor: kinetic tremor	Cerebellar diseases
	Essential tremor[a]
	Multiple sclerosis

Adapted from Grimaldi and Manto (2008)

[a]Some patients with Parkinson's disease show a pure postural tremor (not re-emergent) with a higher frequency than the rest component and poorly responsive to levodopa

[b]Two forms are considered: ET (isolated tremor syndrome of bilateral upper limb action tremor, with duration of at least 3 years) and ET-plus (ET associated with other neurological signs: rest tremor, additional "soft signs"). The new classification of tremor based on two axes allows one syndrome to evolve into another over time

1.2 Types of Tremor

A list of the main types of tremor encountered during daily practice with a brief definition is proposed here according to the English literature published between 1995 and 2021 and limited to human studies (sources: Medline, Scopus). Detailed descriptions are provided along the book's chapters. Table 1.2 summarizes their main features for the commonest forms.

Physiologic tremor is an involuntary rhythmical movement of upper limb segments typically in the frequency range of 8–12 Hz, occurring in healthy subjects. The amplitude is often small and is barely seen with the naked eye (Cathers et al. 2006).

Enhanced physiologic tremor is a visible high-frequency postural tremor, which can be associated with several metabolic conditions (mainly thyrotoxicosis or hypoglycemia), drugs administration, caffeine intake, and muscle fatigue (Grimaldi and Manto 2008).

Table 1.2 Principal types of tremor

Tremor type	Amplitude	Frequency (Hz)	Distribution	Precipitants
Physiologic tremor	Small, barely seen with the naked eye	8–12	Proximal and distal	
Enhanced physiologic tremor	Visible; mild	8–12	Proximal and distal	Any posture
Rest tremor	Mild to severe	3–6	Distal/asymmetrical	Rest Mental activities
Postural/action tremor	Mild to severe	4–12	Proximal and distal	Any posture
Kinetic/action tremor	Mild to severe	2–7	Proximal > distal	Execution of a movement
Isometric tremor	Mild to severe	Variable	Body region in isometric contraction	Isometric muscle contraction
Postural/action tremor in cerebellar diseases				
Asthenic cerebellar tremor	Mild to severe	Irregular	Proximal and distal	Fatigue/weakness
Precision cerebellar tremor	Mild to severe	2–5	Distal	Accurate placements
Cerebellar axial postural tremor	Mild to severe	2–10	Proximal > distal	Any posture
Cerebellar proximal exertional tremor	Mild to severe	3–4	Proximal > distal	Prolonged exercise
Midbrain tremor				
Rest postural and kinetic	Mild to severe	2–5	Proximal > distal	Any posture
Orthostatic tremor				
Isometric tremor	Mild to severe	13–18	Legs and trunk	Isometric contraction of the limb muscles
Dystonic tremor				
Postural and kinetic/action	Unsteady	4–9	Asymmetrical	May increase with movement

Rest tremor occurs while the body segment is maintained at rest and may disappear with action. It is typically asymmetrical, starting distally in the arms, with a frequency range of 3–6 Hz. Usually, rest tremor in the upper limbs reminds a "pill rolling" movement at the level of the hands.

Postural tremor (a form of action tremor) is triggered by postural tasks. Its frequency is usually between 4 and 12 Hz. Tremor appears immediately and often increases in amplitude after a few seconds in the line of gravity.

Postural tremor in cerebellar disease can be further described as (a) *precision tremor*, with a frequency of 2–5 Hz, occurring during the execution of precision tasks and involving the distal musculature; (b) *asthenic tremor*, precipitated by fatigue; (c) *axial postural tremor*; and (d) *midbrain tremor* (Brown et al. 1997) (see also below).

Kinetic tremor appears during the execution of a movement and is usually maximal as the limb approaches the target (Holmes 1939). It has a frequency between 2 and 7 Hz in the large majority of cases. Kinetic tremor tends to involve predominantly the proximal musculature (Gilman et al. 1981; Lechtenberg 1993) and oscillations are usually perpendicular to the main direction of the intended movement. It is reduced by addition of inertia (Chase et al. 1965; Hewer et al. 1972).

Cerebellar tremor is a tremor associated with cerebellar disorders. It is mainly composed of low-frequency oscillations. There is usually a kinetic component often associated with a concomitant postural tremor (Rondot and Bathien 1995). Action tremor is common in cerebellar disorders. Tremor may be bilateral, but in case of cerebellar unilateral lesions oscillations are observed ipsilaterally to the cerebellar lesion. According to the consensus statement definition, *intention tremor syndromes* consist of intention tremor at a frequency below 5 Hz, with or without other localizing signs (Bhatia et al. 2018).

Isometric tremor occurs when a voluntary muscle contraction is opposed by a rigid stationary object (Findley and Koller 1995).

Orthostatic tremor is a high-frequency tremor (13–18 Hz) predominantly in the legs and trunk, triggered during isometric contraction of the limb muscles or during standing (Piboolnurak et al. 2005).

Dystonic tremor is mainly a postural and sometimes kinetic tremor in a body part affected by dystonia. Its frequency is typically irregular, varying from 4 to 9 Hz. Amplitude is unsteady. It is usually asymmetrical and often remains localized, although shaking can extend to other body segments or the entire body (Bhidayasiri 2005). Dystonic tremor may be enhanced by a goal-directed movement. Tremor may anticipate a genuine dystonia by several years, which can be a source of diagnostic difficulties (Rivest and Marsden 1990). Dystonic tremor is likely underdiagnosed. *Dystonic tremor syndromes* are tremor syndromes combining tremor and dystonia as the leading neurological signs. If dystonia and tremor are found in different body parts, this is called *tremor associated with dystonia* (Bhatia et al. 2018).

The most common form of *task-specific tremor* is primary writing tremor, which occurs during writing. Several authors consider that primary writing tremor is a dystonic tremor.

Midbrain tremor (also called *Holmes tremor*) is characterized by a combination of 2–5 Hz rest, postural, and kinetic tremor (Hopfensperger et al. 1995). It affects predominantly proximal segments in upper limbs.

Thalamic tremor presents as a postural and kinetic tremor occurring several weeks or months after a thalamic lesion involving posterior nuclei (Kim 2001). Dystonic features may be associated.

Rhythmic cortical myoclonus (*cortical tremor*) presents as an action tremor. It may be associated with myoclonus and seizures (Ikeda et al. 1990).

Palatal tremor (also called palatal myoclonus) may be symptomatic or essential. Symptomatic palatal tremor is due to rhythmic contractions of the levator veli palatini muscle and is often unilateral. It may persist during sleep. It is usually associated with a lesion of the posterior fossa (see also Guillain–Mollaret triangle). Essential palatal tremor is bilateral. Patients may perceive an ear click due to contractions of the tensor veli palatini muscle (closing Eustachian tube).

Psychogenic tremor (now called *functional tremor*, the most common functional movement disorder) has usually a frequency between 4 and 11 Hz, often varying with time. Women are more commonly affected and account for two-thirds of the patient population, males presenting later in life. It is characterized by an inconsistency of symptoms (variability in frequency, distractibility) (Bhatia et al. 2018). Observing the patient at rest and during neurological examination is associated with an increase in severity and complexity of movements (Schwingenschuh and Espay 2022). Tremor shows incongruent features (frequency entrainment: tremor takes the frequency of a repetitive movement elsewhere in the body; ballistic suppression: brief arrest of tremor with execution of a ballistic movement in the opposite limb; antagonistic coactivation: co-contraction of antagonistic muscles immediately before to reemergence of tremor) (Fahn and Williams 1988; Schwingenschuh et al. 2011). It may have a sudden onset, with frequent remissions, and may respond to placebo or suggestion. Search for a psychiatric disorder is required. Functional tremor may be mischaracterized as malingering.

Indeterminate tremor syndrome refers to a patient who does not fit into an established syndrome or who requires further follow-up (Bhatia et al. 2018).

Some patients with tremor exhibit subclinical or clinically evident neuropsychological changes. For instance, patients with essential tremor may show impairments in executive functions, language, and visuospatial abilities (Higginson et al. 2008). Very often, the consequences of these deficits are underestimated in clinical settings.

1.2.1 Differential Diagnosis Between Tremor and the Other Involuntary Disorders

The repetitive and stereotyped feature of oscillations allows to distinguish tremor from other involuntary movement disorders, such as chorea, athetosis, ballism, tics, and myoclonus (Table 1.3) (Bhidayasiri 2005). However, comorbidity is not rare.

Table 1.3 Differential diagnoses of involuntary movements

	Definition/features	Diseases commonly associated with the movement disorder
Tremor		
Rest Action Kinetic	*See text*	Parkinson's disease Essential tremor Cerebellar tremor
Dystonia	Prolonged muscle contractions leading to abnormal postures; may be repetitive; twisting movements	Drug-induced Genetic Idiopathic
Chorea	Irregular; often hidden in voluntary movement; generates a dance-like movement	Huntington's disease
Athetosis	Continuous slow hyperkinesia of distal segments of limbs; causes an octopus-like movement	Stroke
Ballism	Fast and ample movement of proximal segments of limbs; gives a "throw away"-like movement; more severe in upper limbs	Stroke Inflammatory diseases
Tics	Fast and short hyperkinetic movements usually with a facial or head topography	Gilles-De-La-Tourette Syndrome
Myoclonus	Sudden, short (20–150 ms) movement; may cause a pseudo-repetitive muscular contraction	Essential myoclonus Myoclonic epilepsy Symptomatic myoclonus

From Grimaldi and Manto (2008)

Indeed, tremor may coexist with other involuntary movements, as for the dystonic tremor.

1.2.2 Sources of Tremor

The sources of tremor can be summarized into three groups: mechanical, reflex, and central oscillations (see also Chap. 6). Tremor may be generated by the central and/or peripheral nervous system, with complex interactions. In some neurological disorders, the central generator is obvious, but in other cases, its identification is a real challenge. Indeed, a myriad of structures are all involved in tremorogenesis: joints and muscles obeying the laws of physics (inertia, damping, etc.); spinal cord; and segments at the supra-spinal level including the brainstem, basal ganglia, cerebral cortex, as well as the cerebellum, which is considered to be a major site for tremorogenesis (Grimaldi and Manto 2008; Fig. 1.2). Rest tremor is often believed to be generated mainly in the basal ganglia loop, whereas the postural

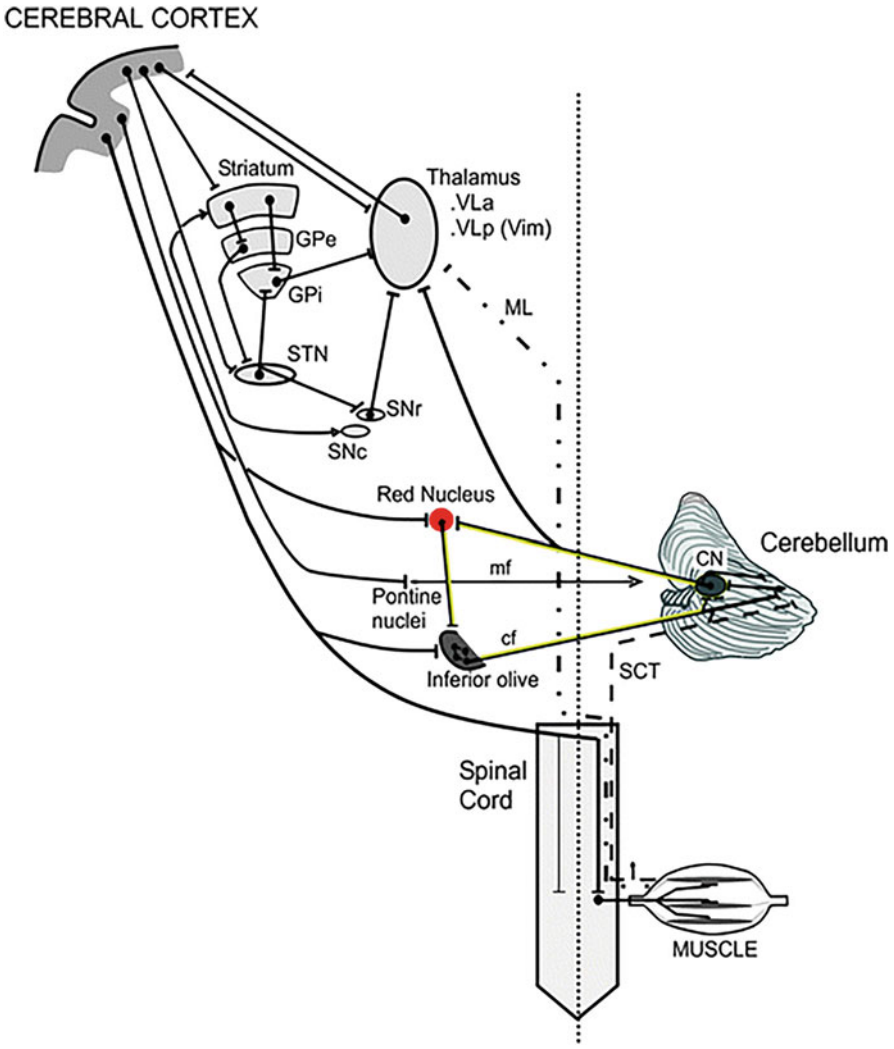

Fig. 1.2 Motor pathways and main loops involved in tremor genesis. Corticosubcortical loops including (**a**) the basal ganglia–thalamocortical motor circuit involving the sensorimotor cortex, and (**b**) the Guillain–Mollaret triangle (including red nucleus, inferior olive, and contralateral cerebellar nuclei). The internal globus pallidus (GPi) and substantia nigra pars reticulata (SNr) tonically inhibit the thalamocortical neurons. Thalamic neurons have a firing mode varying with the membrane potential and are prone to oscillations. Cerebellar afferences include the climbing fibers (cf) from the contralateral inferior olive, the mossy fibers (mf) from the crossed pontocerebellar tract, and the direct spinocerebellar tract (SCT: Flechsig tract or dorsal spinocerebellar fasciculus; the crossed spinocerebellar tract is not illustrated), which conveys proprioceptive information. Neurons of the inferior olive are electrotonically coupled via gap junctions and are endowed with voltage-dependent ionic conductances explaining oscillatory properties. Cerebellar nuclei (CN; mainly interpositus and dentate nuclei) project contralaterally to red nucleus and thalamic nuclei, providing an excitatory activity to these targets. Cerebellar nuclei exert an inhibitory activity on the contralateral inferior olive via the nucleoolivary tract (NOT; not illustrated). The disynaptic projections from the STN to the cerebellum via the pons and from cerebellar nuclei to striatum via thalamic nuclei are not illustrated. Segmental spinal loops are not illustrated (see Chap. 5). *ML* medial lemniscus, *SNc* substantia nigra (pars compacta), *STN* subthalamic nucleus, *VLa* ventrolateral thalamus (anterior), *VLp* ventrolateral thalamus (posterior)

and kinetic tremor are likely generated by the olivo-cerebello-thalamo-cortical loop, which includes the so-called Guillain–Mollaret triangle (cerebello-rubro-olivary projections). It is now accepted that the key system implicated in the pathogenesis of many tremors is the cerebello-thalamo-cortical circuit and the current view considers tremor in a sensorimotor network dynamic perspective with multiple interacting nodes (Helmich 2018; Erro et al. 2022). For instance, parkinsonian tremor is presumed to result from increased interactions between basal ganglia and the cerebello-thalamo-cortical circuit, driven by impaired dopaminergic projections, with a contextual effect such as psychological stress (Helmich 2018). Another example is the increased cerebellar drive in ET. Both structural (physical connections between different nodes through reconstruction of axonal fibers) and functional (operational relationships between regions of the brain with respect to time and stimuli) connectivity studies are increasingly used (Nieuwhof et al. 2021). The inter-node coupling between given sets of regions is often impaired in several forms of tremor, and for some tremor selective brain regions are predominantly acting together, as observed between the VIM and cerebral cortex in the dopamine-responsive tremor of Parkinson's disease. In functional tremor, abnormal patterns of connectivity between the limbic and motor networks have been observed; alterations in functional connectivity in networks involved in emotion processing and theory of mind might underlie tremor (Baizabal-Carvallo et al. 2019). Together with the identification of the sites of structural alteration, psychophysical measurements, and adaptative brain stimulation techniques, studies of connectomics lead to advances by revealing oscillating sites, modulatory effects, and compensatory mechanisms (van den Berg and Helmich 2021; Wong et al. 2020).

References

Baizabal-Carvallo JF, Hallett M, Jankovic J. Pathogenesis and pathophysiology of functional (psychogenic) movement disorders. Neurobiol Dis. 2019;127:32–44.

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM, Deuschl G, Tremor Task Force of the International Parkinson and Movement Disorder Society. Consensus Statement on the classification of tremors from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33(1):75–87.

Bhidayasiri R. Differential diagnosis of common tremor syndromes. Postgrad Med J. 2005;81:756–62.

Brown P, Rothwell JC, Stevens JM, Lees AJ, Marsden CD. Cerebellar axial postural tremor. Mov Disord. 1997;12(6):977–84.

Cathers I, O'Dwyer N, Neilson P. Entrainment to extinction of physiological tremor by spindle afferent input. Exp Brain Res. 2006;171(2):194–203.

Chase RA, Cullen JK Jr, Sullivan SA, et al. Modification of intention tremor in man. Nature. 1965;206(983):485–7.

Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13(suppl 3):2–23.

Erro R, Fasano A, Barone P, Bhatia KP. Milestones in tremor research. Mov Disord Clin Pract. 2022;9:429–35.

Fahn S, Williams DT. Psychogenic dystonia. Adv Neurol. 1988;50:431–55.

Findley LJ, Capildeo R. Movement disorders: tremor. London: Macmillan; 1984.
Findley LJ, Koller WC. Handbook of tremor disorders. New York: Marcel Dekker; 1995.
Gilman S, Bloedel JR, Lechtenberg R. Disorders of the cerebellum. Contemporary neurology series. Philadelphia: Davis; 1981.
Grimaldi G, Manto M. Tremor: from pathogenesis to treatment. San Rafael: Morgan & Claypool; 2008.
Helmich RC. The cerebral basis of Parkinsonian tremor: a network perspective. Mov Disord. 2018;33:219–31.
Hewer RL, Cooper R, Morgan MH. An investigation into the value of treating intention tremor by weighting the affected limb. Brain. 1972;95:579–90.
Higginson CI, Wheelock VL, Levine D, King DS, Pappas CT, Sigvardt KA. Cognitive deficits in essential tremor consistent with frontosubcortical dysfunction. J Clin Exp Neuropsychol. 2008;30(7):1–6.
Holmes G. The cerebellum of man. The Huglings Jackson memorial lecture. Brain. 1939;62:1–30.
Hopfensperger KJ, Busenbark K, Koller WC. Midbrain tremor. In: Findley LJ, Koller WC, editors. Handbook of tremor disorders. New York: Marcel Dekker; 1995. p. 455–9.
Ikeda A, Kakigi R, Funai N, Neshige R, Kuroda Y, Shibasaki H. Cortical tremor: a variant of cortical reflex myoclonus. Neurology. 1990;40:1561–5.
Kim JS. Delayed onset mixed involuntary movements after thalamic stroke: clinical, radiological and pathophysiological findings. Brain. 2001;124:299–309.
Lechtenberg R. Signs and symptom of cerebellar diseases. In: Lechtenberg R, editor. Handbook of cerebellar diseases. New York: Marcel Dekker; 1993.
Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010;25:534–41.
Louis ED, Marder K, Cote L, et al. Differences in the prevalence of essential tremor among elderly African Americans, whites, and Hispanics in northern Manhattan, NY. Arch Neurol. 1995;52:1201–5.
McAuley JH, Marsden CD. Physiological and pathological tremors and rhythmic central motor control. Brain. 2000;123:1545–67.
Nieuwhof F, Toni I, Dirkx MF, Gallea C, Vidailhet M, Buijink AWG, van Rootselaar AF, van de Warrenburg BPC, Helmich RC. Cerebello-thalamic activity drives an abnormal motor network into dystonic tremor. Neuroimage Clin. 2021;33:102919.
Piboolnurak P, Yu QP, Pullman SL. Clinical and neurophysiologic spectrum of orthostatic tremor: case series of 26 subjects. Mov Disord. 2005;20(11):1455–61.
Rivest J, Marsden CD. Trunk and head tremor as isolated manifestations of dystonia. Mov Disord. 1990;5:60–5.
Rondot P, Bathien N. Cerebellar tremors: physiological basis and treatment. In: Findley LJ, Koller WC, editors. Handbook of tremor disorders. New York: Marcel Dekker; 1995.
Sanger TD, Chen D, Fehlings DL, Hallett M, et al. Definition and classification of hyperkinetic movements in childhood. Mov Disord. 2010;25(11):1538–49.
Schwingenschuh P, Espay AJ. Functional tremor. J Neurol Sci. 2022;435:120208.
Schwingenschuh P, Katschnig P, Seiler S, Saifee TA, Aguirregomozcorta M, Cordivari C, Schmidt R, Rothwell JC, Bhatia KP, Edwards MJ. Moving toward “laboratory-supported” criteria for psychogenic tremor. Mov Disord. 2011;26(14):2509–15.
van den Berg KRE, Helmich RC. The role of the cerebellum in tremor - evidence from neuroimaging. Tremor Other Hyperkinet Mov (N Y). 2021;11:49.
Wong JK, Middlebrooks EH, Grewal SS, Almeida L, Hess CW, Okun MS. A comprehensive review of brain Connectomics and imaging to improve deep brain stimulation outcomes. Mov Disord. 2020;35(5):741–51.

Chapter 2
Membrane Mechanisms of Tremor

Hemani Ticku, Neel Fotedar, and Aasef G. Shaikh

Abstract Tremor is one of the most common hyperkinetic movement disorders. Tremors can be of many different types, and the etiopathogenesis is very diverse and heterogeneous. Sometimes, an underlying structural abnormality, that explains the tremor, can be identified but in most cases, the pathophysiology remains unclear. For example, acquired pendular nystagmus (APN), which is the tremor equivalent of eyes, is thought to be a result of neural integrator instability, seen in central nervous system disorders with demyelination (Das et al., Exp Brain Res 133:189–197, 2000). Oculopalatal tremor (OPT) is associated with hypertrophic degeneration of the inferior olive and resultant synchronized inferior olivary output acting as a pacemaker for the ocular oscillations (Shaikh et al., Brain 133:923–940, 2010). On the other hand, essential tremor, which is the most common type of tremor disorder, does not have clear anatomical and physiological correlates, although it has been proposed that essential tremor might be a cerebellar degenerative disorder (Louis and Lenka, Tremor Other Hyperkinet Mov (N Y) 7:473, 2017). However, regardless of the underlying etiology, it has been hypothesized that pathological neuronal membrane oscillations, resulting from membrane hyperexcitability, are at the core of many tremor disorders (Shaikh et al., J Transl Med 6:68, 2008a).

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2.1 Background

Tremors comprise of a heterogeneous group of hyperkinetic movement disorders, where the underlying pathophysiology is not always clear. In some cases, there is a clear underlying anatomical substrate, e.g., hypertrophic degeneration of the inferior olive, as seen in oculopalatal tremor (OPT), but in others, the pathophysiology remains unclear, e.g., essential tremor (ET). Recent literature has shown that pathological oscillations arising at the level of neuronal membrane, related to hyperexcitability, could contribute to tremor pathophysiology. For example, membrane hyperexcitability has been implicated in essential tremor (Shaikh et al. 2008a). Drugs commonly used in the treatment of tremor disorders such as propranolol, gabapentin, or primidone have membrane stabilizing properties, thus lending credence to this hypothesis (O'Suilleabhain and Dewey Jr 2002; Zesiewicz et al. 2005).

2.2 Outline

In this chapter, we will review relevant literature as it pertains to the electrophysiological properties of neuronal membranes and their subsequent role in the pathogenesis of various tremor disorders. We will also explore the pathophysiology of neuronal membrane oscillations and their relationship to the intrinsic membrane properties and the mechanism of tremor generation secondary to these oscillations. We will also discuss the various pharmacological treatment options available for tremor disorders such as gabapentin, propranolol, or primidone and how these treatment options support the hypothesis of the critical role played by intrinsic membrane properties in tremor generation. Even though we will focus on the role played by the neuronal membrane in tremor generation throughout this chapter, we must emphasize that we are, in no way, excluding the importance of underlying anatomical and physiological abnormalities in the generation of tremors. Our view is that a combination of both anatomical and neuronal membrane abnormalities leads to tremor generation.

2.3 Membrane Mechanisms of Essential Tremor

A simplistic schematic of the primate motor system and the potential sources of tremor generation is shown in Fig. 2.1. A critical factor in determining the tremor

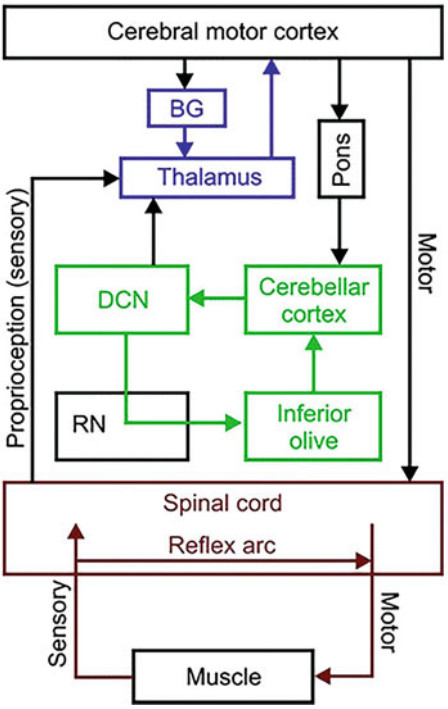

Fig. 2.1 Illustration of a schematic summary simplified diagram of primate motor system highlighting three possible circuits that are known to cause tremor. The *brown circuit* illustrates possible peripheral tremor generator, which include mechanical system comprised of muscle, tendon, and joint. The afferent pathway of the mechanical system is made of sensory neurons that synapse at spinal cord, send proprioceptive signals to thalamus, and also influence the interneuron that project locally to the motor neuron. *Blue circuit* illustrates thalamocortical circuit for central tremor generation. The *blue box* (thalamus) contains reciprocally innervating thalamocortical and thalamoreticular neurons—the reciprocal innervations are fundamental for generation of tremor. Basal ganglia receive cortical input through striatum and their output nuclei is globus pallidus. The latter normally inhibits the oscillations in the circuit of reciprocally innervating thalamic neurons. Synchronized inferior olive oscillations transmitted in olivocerebellar circuit, shown in *green*, is third source of tremor. Normally this circuit has cardinal role in motor learning

frequency is the mass of the body part involved and its biophysical properties (Elble and Koller 1990). The thalamocortical (TC) pathway (blue pathway in Fig. 2.1) plays an important role in the pathogenesis of essential tremor. This is supported by studies showing the effect of thalamic lesion on the tremor (Koller et al. 2000; Pahwa et al. 2000) and the studies showing strong coherence between thalamic oscillations and tremor frequency (Hua and Lenz 2004; Hua et al. 1998). The other important pathway that has been shown to play a role in the pathogenesis of essential tremor is the olivocerebellar pathway (shown in green color in Fig. 2.1). This pathway consists of the inferior olivary neurons projecting to the cerebellar Purkinje neurons, which in turn project to deep cerebellar nuclei. Synchronized

activity of neurons in this circuit plays an important role in motor learning and timing (Apps and Garwicz 2005; Wolpert et al. 1998). Studies have shown increased activity in this pathway in patients with essential tremor (Louis et al. 2004; Deuschl and Elble 2000; Jenkins and Frackowiak 1993). In addition, the animal models of tremor generated by harmaline also show increased synchronization of the inferior olivary neurons (Lamarre et al. 1971; Lamarre and Mercier 1971; de Montigny and Lamarre 1973; Llinás and Volkind 1973).

In the next subsections, we will address the pathophysiology of oscillations in the thalamocortical and olivocerebellar networks and the factors that predispose them to tremor generation. It has been well established that the inferior olivary neurons and thalamic neurons are predisposed to spontaneous rhythmic firing (like a pacemaker) because of their intrinsic membrane properties (Jahnsen and Llinás 1984; Park et al. 2010; Llinás and Yarom 1986).

2.3.1 Membrane Oscillations in Thalamic Neurons

Thalamic neurons have a unique property to fire spontaneous action potentials. This is because of the presence of certain voltage-activated ion conductances like low-threshold calcium currents (I_T), hyperpolarization-activated mixed cation currents (I_H), 4-aminopyridine-sensitive potassium currents (I_A), and calcium-dependent potassium currents ($G_{K[Ca]}$) (Jahnsen and Llinás 1984).

There are two membrane properties of thalamic neurons that could generate spontaneous oscillations and hence play a critical role in tremor generation: (1) when partially depolarized, the membrane fires a "burst" of low-threshold spikes; (2) when the membrane is further depolarized, the neuron enters a state of "tonic" sustained firing (Jahnsen and Llinás 1984; McCormick and Pape 1990). The frequency of the oscillations is determined by the resting membrane potential of the neuron.

When the neuron is depolarized to approximately −46 mV, a high-frequency oscillation emerges (9–11 Hz) (Jahnsen and Llinás 1984; Fig. 2.2a). This amount of depolarization first activates a slow sodium conductance, followed by a fast sodium current, which generates the action potential and the following after-hyperpolarization (AHP) (Jahnsen and Llinás 1984). This after-hyperpolarization returns the membrane potential to a subthreshold state for ~100 ms and it is this "refractory" period that determines the frequency of the oscillations (9–11 Hz). The after-hyperpolarization is a result of voltage- and calcium-dependent potassium current (Hotson and Prince 1980; Llinás and Sugimori 1980; Llinás and Yarom 1981). This particular sequence of ion conductances responsible for the 9–11 Hz oscillations is shown in Fig. 2.2a. This amount of hyperpolarization is not strong enough to de-inactivate I_T and I_H low-threshold spikes. About 6 Hz oscillations emerge when the membrane is hyperpolarized beyond −55 mV. This level of hyperpolarization leads to a prolonged after-hyperpolarized state because of inhibitory postsynaptic potentials (IPSPs) and a prolonged I_A current (reflected in the gray zone in Fig. 2.2b). This hyperpolarization eventually de-inactivates

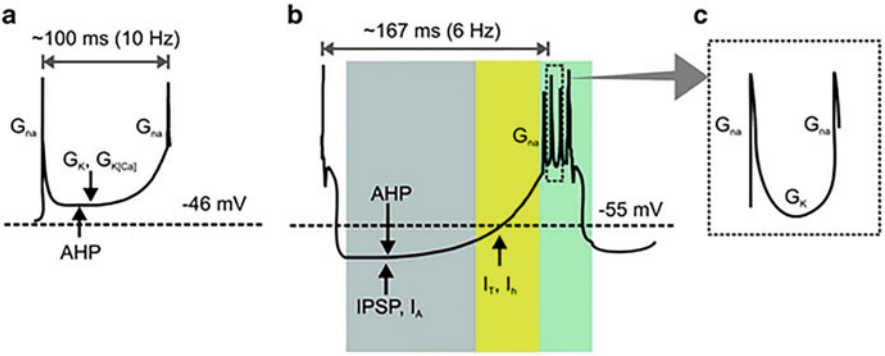

Fig. 2.2 Illustration of the underlying ion currents responsible for two oscillatory attributes of the thalamic neurons. (**a**) Action potential spike is generated by fast-acting sodium currents (G_{Na}). The spike is [followed by] voltage-sensitive potassium current (G_k) and calcium-dependent potassium current ($G_{K[Ca]}$), causing after-hyperpolarization. After-hyperpolarization (AHP) typically brings membrane to threshold for fast spike, but not further negative than −55 mV. The threshold is sufficient for subsequent spike in approximately 100 ms, causing 10 Hz spikes. (**b**) Strong hyperpolarization simulating inhibitory postsynaptic potential (IPSP) brings membrane potential further negative than −55 mV, de-inactivating 4-aminopyridine-sensitive potassium current (I_A) to further prolong the duration of the hyperpolarized state. The latter then de-inactivates low-threshold calcium current (I_T) and hyperpolarization-activated mixed cation current (I_H) triggering a rebound spike of action potential (post-inhibitory rebound). (**c**) Zoomed in view of the "burst" of action potentials due to post-inhibitory rebound (PIR)

I_T and I_H currents (pacemaker currents) (reflected in yellow zone in Fig. 2.2b) (Jahnsen and Llinás 1984; Pape and McCormick 1989; McCormick and Pape 1990). The de-inactivation of these channels leads to membrane depolarization, which in turn produces a "burst" of action potentials. This phenomenon is known as post-inhibitory rebound (PIR; see light blue zone in Fig. 2.2b). Within each burst, action potentials are followed by brief hyperpolarizations secondary to voltage-dependent potassium current (dashed black box in Fig. 2.2b, c). Extracellular potassium concentration determines the rate of depolarization that follows hyperpolarization after each action potential, e.g., decreased extracellular potassium concentration leads to faster depolarization, thus taking shorter amount of time to reach the threshold for next action potential, hence increasing the number of action potentials within each burst. Multiple factors, including the levels of I_H and I_T, play a critical role in determining the extracellular levels of potassium, the strength of each burst, and subsequent PIR. Typical duration of a burst is ~20–30 ms (Jahnsen and Llinás 1984). Each burst is followed by a refractory period, characterized by a strong hyperpolarization beyond −55 mV, which then activates the same cascade of events again. It is clear how a periodic inhibitory stimulus can produce a sustained 6 Hz oscillation of the PIR. The frequency is ~6 Hz because the inactivation time of I_T current is longer (Jahnsen and Llinás 1984).

2.3.2 Membrane Oscillations in the Inferior Olive Neurons

The oscillatory behavior of the olivary neurons is similar to that of thalamic neurons. The olivary neurons can oscillate at ~9–10 Hz frequency just like thalamic neurons (Llinás and Yarom 1986). These oscillations consist of sequential action potentials, each one of which is followed by a brief after-hyperpolarization. The second type of oscillatory behavior at a lower frequency can occur when the membrane is more strongly hyperpolarized, resulting in de-inactivation of I_H and I_T currents, followed by a burst of action potentials and subsequent PIR (Llinás and Yarom 1986).

In addition, the inferior olivary neurons also show a distinct third type of oscillatory behavior, which consists of subthreshold 3–6 Hz sinusoidal resting membrane potential oscillations (Llinás and Yarom 1986). The depolarizing shifts produced by these oscillations are typically not strong enough to fire action potentials, except when the membrane is hyperpolarized. In that case, these subthreshold oscillations can lead to low-threshold currents (e.g., I_T) that are often followed by a burst of action potentials (Llinás and Yarom 1986). The amplitude and frequency of these oscillations are independent of transmembrane voltages during the resting neuronal state. These oscillations can be abolished by antagonists of I_T, but they remain unaffected by fast sodium current attenuation (Llinás and Yarom 1986).

2.3.3 Thalamic and Inferior Olive Oscillations and Relation to Harmaline Model of Tremor

Harmaline-induced tremor has been a very popular animal experimental model of essential tremor (Lamarre et al. 1971; Lamarre and Mercier 1971; de Montigny and Lamarre 1973; Llinás and Volkind 1973). Harmaline increases the de-inactivation of I_T and I_H currents and increases the membrane excitability to produce 3–6 Hz spike trains of action potentials (Llinás and Yarom 1986). In addition, it also potentiates the subthreshold sinusoidal oscillations and further increases the propensity to produce action potentials in otherwise "silent" neurons (Llinás and Yarom 1986).

In harmaline animal models, inferior olive is a major site of action as evidenced by multiple factors such as attenuation of the tremor after inferior olive destruction by 3-acetylpyridine, increased c-fos level in the inferior olive after harmaline administration (c-fos is a marker of neuronal activation), and rhythmic burst activity recorded from inferior olive after direct local injection of harmaline (Louis and Lenka 2017).

2.3.4 Synchronization of Isolated Neuronal Oscillations

Isolated neuronal oscillations are not sustainable and cannot generate tremor (Fig. 2.3a). In this section, we will describe how groups of neurons can be coupled to sustain their oscillations and generate enough motor drive to produce a tremor.

The oscillatory behavior produced by a strong hyperpolarizing signal to bring the membrane potential beyond −55 mV, thus causing de-inactivation of I_T, I_H, and 4-aminopyridine-sensitive potassium currents leading to PIR, will dissipate over time in absence of sustained repetitive inhibitory stimuli (Fig. 2.3a). In addition to sustaining the oscillatory behavior, an ensemble discharge from a group of neurons is necessary to generate enough drive to move a body part. The following subsections will discuss the neuronal coupling in thalamic and inferior olivary neurons.

2.3.4.1 Neuronal Coupling in Thalamus

A schematic showing the principle of reciprocal inhibition between agonist and antagonist neurons is shown in Fig. 2.3b. This coupling is required to generate sustained oscillations in the thalamic circuit (Sherrington 1908). In the thalamus, these reciprocal feedback connections exist between thalamocortical (TC) relay neurons and thalamic reticular (TR) neurons. The TC neurons send glutamatergic excitatory projections to the TR neurons, which in turn send GABAergic inhibitory projections back onto the TC neurons (Pinault 2004; Guillery and Harting 2003). The TR neurons also send inhibitory collaterals onto neighboring TR neurons (Pinault 2004; Guillery and Harting 2003). This reciprocal innervation can generate PIR with a strong burst, which can provide adequate input to the downstream neurons to produce prompt and high-speed ballistic movements.

But this characteristic of reciprocal innervation also renders these circuits unstable and prone to oscillations (Shaikh et al. 2007, 2008a; Ramat et al. 2005; Fig. 2.3b). A simple illustration of two reciprocally inhibitory neurons (neuron A and neuron B) with membrane properties suitable to produce PIR is shown in Fig. 2.3c. When neuron A is activated, it will send an inhibitory signal to neuron B. The strong hyperpolarization in neuron B would subsequently lead to PIR. This burst of action potentials in neuron B would then send an inhibitory signal back to neuron A (reciprocal inhibition), hyperpolarizing it enough to produce a PIR in neuron A. Thus, this reciprocal inhibitory relationship between neurons A and B can lead to a sustained PIR oscillation (Fig. 2.3c). Coupling between multiple neurons allows for synchronization across larger groups of neurons, thus generating enough drive to produce a tremor.

2.3.4.2 Experimental and Computational Evidence of Thalamic Coupling as a Cause of Tremor

As is shown in Fig. 2.3b, a strong external source of inhibition can keep a "check" on inherently unstable circuits prone to oscillations (Shaikh et al. 2007, 2008a). In the case of thalamic circuits, this source of inhibition is globus pallidus internus (GPi). The GPi has strong GABAergic projections that provide tonic inhibition to the downstream thalamic neurons (Parent and Hazrati 1995; Takada and Hattori 1987).

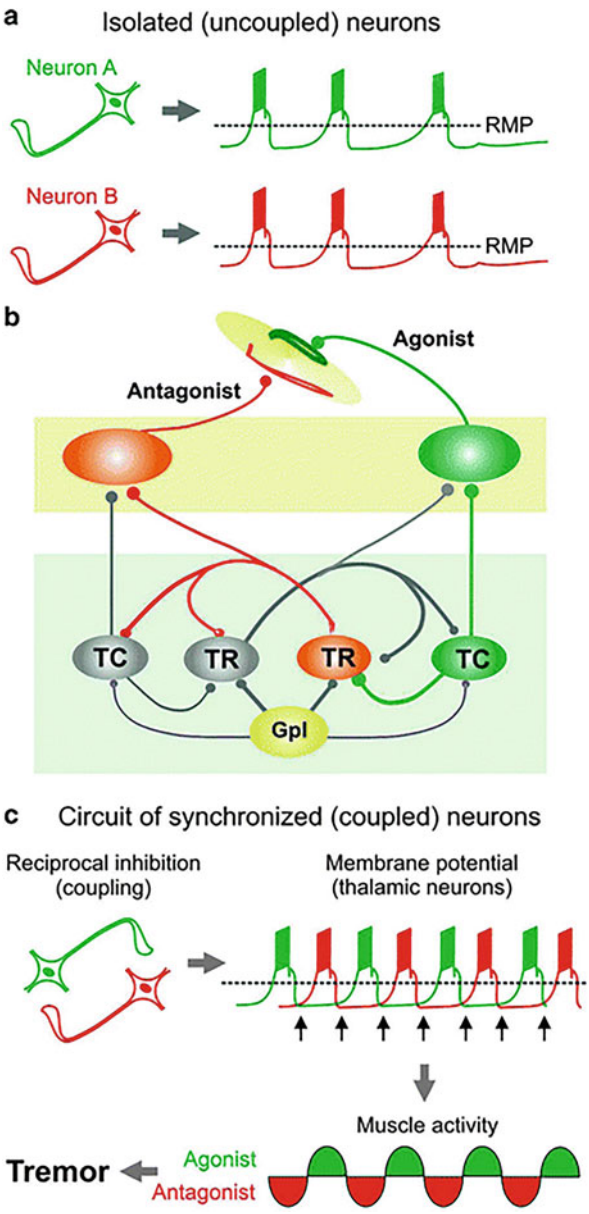

Fig. 2.3 (**a**) Caricatures of repetitive bursts from two thalamic neurons are illustrated. Due to membrane ion channel profile, the action potential in the given neuron is followed by after-hyperpolarization. When the strength of after-hyperpolarization is sufficient to bring the membrane potential more negative than −55 mV, there is de-inactivation of 4-aminopyridine-sensitive potassium current, low-threshold calcium current (I_T), and hyperpolarization-activated cation current (I_H). As a result there is rebound burst, post-inhibitory rebound. As illustrated in this panel, in absence of consistent, repetitive burst of inhibition, the bursting oscillatory behavior of

This led to the so-called GABA hypothesis of tremor. Studies in GABA mutant mice showed that abolishing the GABAergic inhibition could produce a tremor phenotype (Kralic et al. 2005). Boecker et al. showed decreased GABA function and increased availability of GABA receptors in cerebellum and the thalamus in a recent 11C-flumazenil PET study, thus lending further support to the "GABA hypothesis" (Boecker et al. 2010). But this hypothesis is not universally accepted and remains controversial. Human genetic studies have not found any significant differences in frequencies of allelic variants in GABA receptor genotypes between ET patients and controls (García-Martín et al. 2011). Another study of patients with familial ET failed to detect any pathogenic variants in the GABRA1 gene, which encodes for GABA-A receptor alpha-1 polypeptide (Deng et al. 2006).

A novel hypothesis was proposed by Shaikh et al. in 2008 for the pathophysiology of essential tremor (Shaikh et al. 2008a). This hypothesis posits that in presence of increased intrinsic membrane excitability, "normal" inhibition has a reduced effect in preventing circuit oscillations (Shaikh et al. 2008a). This hypothesis, essentially, eliminates the need for a GABA deficit as a prerequisite for thalamic circuit oscillations. It has been proposed that increased activation kinetics of I_H or I_T due to alterations in the intracellular levels of second messengers or other regulators can increase the neuronal excitability (McCormick and Pape 1990; Shaikh and Finlayson 2005; Wainger et al. 2001; Lüthi and McCormick 1999). Computational models of thalamic neurons with physiologically realistic membrane properties and anatomically realistic neural connections are compatible with a role for neuronal hyperexcitability in the pathogenesis of essential tremor (Shaikh et al. 2008a). This model rests on two main characteristics: (1) increased neural excitability secondary to increased I_H and/or I_T currents; and (2) inherently unstable circuit prone to oscillations because of reciprocal innervation and the property of PIR (Shaikh et al. 2008a). Experimental support for this hypothesis comes from the studies showing reduction of tremor in $GABA_A$ receptor null mice and harmaline animal models with an experimental drug NNC 55-0396, which is a potent I_T blocker (Shaikh et al. 2008a; Quesada et al. 2011).

Fig. 2.3 (continued) these neurons dissipates. Furthermore, resultant spikes from an isolated neuron are not sufficient to generate adequate force generating tremor. These spikes would dissipate over time in absence of repetitive external impulse. (**b**) This panel illustrates the circuit of reciprocally innervating neurons controlling movements. As illustrated, thalamocortical (TC) neurons and thalamic reticular (TR) neurons make a circuit of reciprocally innervating neurons. Unless inhibited or hyperexcited, the reciprocally innervating circuit can oscillate. The oscillations are normally inhibited by the globus pallidus internus (GPi) neurons. (This panel is modified from Shaikh et al. (2008a)). (**c**) The thalamic reticular and thalamocortical neurons form reciprocally inhibitory circuit and thus couple with each other forming multiple synchronized patches. Here, in example of two inhibitory neurons A and B, due to reciprocal inhibition, a burst in neuron A is followed by a burst in neuron B (due to inhibition from neuron A). The burst in neuron B then results in burst in neuron A; hence, train of bursts in two mutually inhibitory neurons starts. When these neurons are designated to innervate agonist and antagonist muscles, respectively, alternating firing of agonist and antagonist muscle pairs cause tremor

2.3.4.3 Other Causes of Thalamic Neuronal Excitability in Essential Tremor

In some essential tremor patients, the hyperexcitability is a result of loss of inhibition because of pathology involving the cerebellar Purkinje neurons (Axelrad et al. 2008; Louis and Vonsattel 2008; Louis 2010). The dentate-thalamic projection is normally inhibitory, so a lesion involving the Purkinje neurons can, hypothetically, increase the excitability of thalamic neurons by disinhibiting this projection.

Few studies have shown a genetic susceptibility to essential tremor. In some patients with familial essential tremor, gly9 susceptibility variant of DRD3 gene was reported (Jeanneteau et al. 2006; Lucotte et al. 2006; Sóvágó et al. 2005). This mutation can lead to increased intracellular levels of cAMP, via excessive inhibition of phosphodiesterase E4, by prolonging the intracellular action of mitogen-activated protein kinase (MAPK) (Hoffmann et al. 1999; Houslay and Milligan 1997; Houslay et al. 1998; Jeanneteau et al. 2006). Increased levels of cAMP can increase I_H and subsequently increase the neuronal membrane excitability (Shaikh and Finlayson 2005).

2.3.4.4 Neuronal Coupling in Inferior Olive

As discussed earlier, inferior olivary neurons can generate low-amplitude subthreshold oscillations. But these can only be sustained for a few seconds and are not enough to generate tremor (Llinás and Yarom 1981, 1986; Leznik and Llinás 2005; Yarom 1991; Placantonakis et al. 2006).

To generate tremor, these oscillations need to be sustained and synchronized across neurons. Connexin gap junctions have been shown to play an important role in synchronizing and sustaining these oscillations (Yarom 1991; Bleasel and Pettigrew 1992; Manor et al. 1997; Condorelli et al. 1998; Long et al. 2002; De Zeeuw et al. 2003; Placantonakis et al. 2006). Studies have shown that each neuron in the inferior olive is coupled with a variable number of neighboring neurons and these "patches" of neurons can have variable coupling strengths across the inferior olive (Hoge et al. 2011). When these patches of neurons are uncoupled, either by genetically knocking out connexin 36 or by blocking it, in vivo, with local administration of carbenoxolone or 18-glycyrrhetinic acid, the ensemble rhythm of the inferior olive gets degraded (Leznik and Llinás 2005; Blenkinsop and Lang 2006; Placantonakis et al. 2006). Because of these studies showing a key role for connexin molecules in neuronal coupling, it has been hypothesized that the electrotonic gap junctions made up of these molecules between adjacent neurons play a major role in facilitating neuronal synchronization in the inferior olive.

In the harmaline model of tremor, the inferior olive is considered as the key central oscillator responsible for producing the tremor (Louis and Lenka 2017). This is based on a multitude of experimental electrophysiological studies showing rhythmic activity in the inferior olive with administration of harmaline. It has

been shown that this rhythmic activity would persist even after cerebellectomy, low decerebration, or spinal cord transection (Llinás and Volkind 1973). But in animal knockout models for connexin 36, the harmaline-induced oscillations are the same as those in wild-type phenotypes (Placantonakis et al. 2006). Hence, it is possible that the harmaline-induced oscillations have a different mechanism for synchronization (Placantonakis et al. 2006).

2.3.4.5 Influence of Cerebellum and Conditional Learning on Synchronized Inferior Olive Discharge and Tremor

The olivocerebellar pathway transmits synchronized activity from the inferior olive to the cerebellar Purkinje cells via two parallel pathways, climbing fibers and parallel fibers, via deep cerebellar nuclei. Studies have proposed that the cerebellar conditional learning may alter the kinematic properties (amplitude and regularity) of the inferior olive discharge (Shaikh et al. 2010). When the olivary input arrives on the cerebellar Purkinje cells directly (via climbing fibers) or indirectly with a delay (via parallel fibers), these cells learn an irrelevant conjunction (classical conditional paradigm). The Purkinje cells then pause with each inferior olive pulse, thus increasing the olivary output, making it smoother and larger. This hypothesis has been tested in patients with oculopalatal tremor (OPT). Ocular oscillations were simulated using computational models of olivocerebellar interaction (Hong and Optican 2008; Shaikh et al. 2010). This model emphasized the significance of neuronal coupling in inferior olive neurons via electrotonic gap junctions, synchronized firing of a population of olivary neurons, and cerebellar motor learning (Hong and Optican 2008; Shaikh et al. 2010). A similar physiology may underlie alterations in the characteristics of essential tremor originating due to olivocerebellar hyperactivity (Louis et al. 2004; Deuschl and Elble 2000; Jenkins and Frackowiak 1993).

It must be emphasized at this point that despite the electrophysiological evidence supporting the central role of inferior olive in the pathogenesis of essential tremor, more recently, multiple studies have questioned this hypothesis (Louis and Lenka 2017). A multitude of functional neuroimaging studies using PET, fMRI, etc., have identified neural correlates of essential tremor and they have mainly revealed abnormal activity in the cortico-bulbo-cerebello-thalamo-cortical network (Louis and Lenka 2017). None of these studies have been able to identify either abnormal activity or alterations in functional connectivity of the inferior olive in patients with essential tremor (Louis and Lenka 2017). In a magnetic resonance spectroscopy (MRS) study of patients with essential tremor and healthy controls, decreased *N*-acetylaspartate (NAA) peak or decreased NAA:Cr ratio (creatine) was mainly observed in the cerebellar cortex (Louis et al. 2002). In addition, numerous post-mortem studies have shown characteristic histopathological changes in patients with essential tremor, especially in the Purkinje cells in the cerebellar cortex, e.g., loss of dendritic spines, increased dendritic pruning, decreased linear cell density, more heterotopic cells, increased axonal branching, and increased number of torpedoes

(Louis and Lenka 2017). All of these studies suggest that the chief pathology in essential tremor lies within the cerebellar cortex, rather than the inferior olive (Louis and Lenka 2017).

2.3.5 *Membrane Electrophysiology and Essential Tremor Frequency*

Tremor frequency is dependent on multiple variables. The biomass and physical property of the part to be moved is one such factor, e.g., tremors involving distal body parts such as fingers typically have a higher frequency compared to tremors involving more proximal heavier body parts such as shoulder (Elble and Koller 1990). However, studies have shown that the tremor frequency involving the same body part varies among individuals (Deuschl et al. 2001).

According to the conductance-based model of essential tremor, variability in the expression of I_T and I_H channels determines the frequency of the tremor in a particular individual (Shaikh et al. 2008a). As per this model, increasing the value of I_H in thalamic neurons increases tremor frequency and decreases tremor amplitude, whereas increasing I_T has the exact opposite effect (Shaikh et al. 2008a). Hence, this model supports the hypothesis of the role played by ion channel profiles and intrinsic membrane properties in generation of tremor and the observed inter-individual variability in tremor characteristics such as frequency and amplitude.

As alluded to earlier, thalamic neurons have two main oscillatory behaviors: a low-frequency oscillation (~6 Hz) and a high-frequency oscillation (9–11 Hz) (Jahnsen and Llinás 1984). Out of these two, only the 6 Hz oscillatory behavior is reflected in essential tremor (Elble 2000). This is, perhaps, a result of selective synchronization of low-frequency oscillations over high-frequency oscillations. For two neurons to be synchronized, a strong enough inhibition to produce an IPSP, followed by subsequent low-threshold spike and PIR, is required. Hence, rebound firing of the inhibit*ory* (presynaptic) neuron could generate an IPSP in the inhibit*ed* (postsynaptic) neuron. This phenomenon has been demonstrated in multiple patch-clamp and computational studies of neuronal coupling (Jahnsen and Llinás 1984; Shaikh et al. 2008a). On the other hand, high-frequency thalamic oscillations are produced by individual neuronal hyperpolarizations, which are typically not strong enough to produce an IPSP sufficient to synchronize with the coupled neuron. Therefore, among the coupled thalamic neurons, only the ones with a low-frequency (6 Hz) oscillatory behavior due to low-threshold spikes and PIR can be synchronized.

2.3.6 Pharmacotherapy of Tremor Supports the Membrane Hypothesis for Essential Tremor

2.3.6.1 Beta-Blockers and Membrane Physiology of Tremor

A nonselective beta-blocker such as propranolol is usually the first choice of treatment for essential tremor (Zesiewicz et al. 2005). As mentioned earlier, a key factor that determines the strength of I_H and I_T currents is the intracellular level of cAMP and a reduction in the level of cAMP decreases the strength of these currents, thus decreasing membrane excitability (Shaikh and Finlayson 2003; Alvarez et al. 1996; Pape and McCormick 1989; Yue and Huguenard 2001; Jahnsen and Llinás 1984). Beta-blockers are known to reduce the intracellular levels of cAMP, thus decreasing membrane excitability (Sozzani et al. 1992; Pascoli et al. 2005; Franzellitti et al. 2011) and decreasing membrane excitability decreases tremor amplitude and frequency (Shaikh et al. 2008a).

2.3.6.2 Anti-Seizure Drugs and Membrane Physiology of Tremor

Primidone, which is an anti-seizure medication, is a very well-established treatment option for essential tremor (Zesiewicz et al. 2005). It is typically not used as the first line because of its side-effect profile. It is a prodrug and has two active metabolites: phenylethylmalonic acid and phenobarbitone (Baumel et al. 1972). Phenobarbitone works by decreasing neural excitability and by increasing postsynaptic GABA-mediated inhibition (Polc and Haefely 1976). As has been discussed previously, increasing external GABAergic inhibition (or decreasing membrane excitability) on a reciprocally inhibited circuit of thalamic neurons, prone to oscillations, could provide stability to the circuit and decrease tremor (Shaikh et al. 2008a).

Other anti-seizure medications that are used clinically in essential tremor include gabapentin and zonisamide. Gabapentin is an antagonist of the alpha-2-delta subunit of calcium channels (Thorpe and Offord 2010). It also blocks NMDA glutamate receptors (Kim et al. 2009). Both of these mechanisms could decrease thalamic membrane excitability and hence contribute to the anti-tremor properties of gabapentin (Shaikh et al. 2008a). Zonisamide blocks I_T currents and can thus decrease neuronal excitability in the thalamus (Morita et al. 2005; Song et al. 2008; Handforth et al. 2009).

2.3.6.3 Membrane Physiology of Tremor and Alcohol

Acute alcohol consumption can have an attenuating effect on tremors and this effect can be explained in multiple ways. First and foremost, ethanol potentiates $GABA_A$-mediated inhibition, thus stabilizing the inherently unstable thalamic circuit oscillations and decreasing neuronal excitability (Jia et al. 2008). In addition,

ethanol also decreases glutamate concentration and NMDA current, which in turn would lead to decreased thalamic membrane excitability and tremor (Manto and Laute 2008; Shaikh et al. 2008a).

2.4 Membrane Physiology and Tremor of Parkinson's Disease

Multiple studies, over the years, have shown that the symptoms of parkinsonism arise as a result of abnormally increased neuronal excitability, pathological oscillations, and synchronization in the basal ganglia neurons, thus affecting their thalamic and cortical connections (Obeso et al. 1997; Bergman et al. 1990, 1998; Herrero et al. 1996; Mitchell et al. 1989; Vila et al. 1996, 1997; Galvan and Wichmann 2008; Gittis et al. 2011). The lack of dopamine appears to play a key role in the increased excitability of the basal ganglia neurons and the increased synchronization leading to sustained oscillatory behavior (Bergman et al. 1998; Gittis et al. 2011).

Single neuron intracellular recordings from dopamine-deprived striatal neurons have shown the presence of spontaneous NMDA and GABA-mediated depolarizing postsynaptic potentials (Calabresi et al. 1993). The two main types of dopamine receptors in the striatum are D1 and D2 and the major source of dopaminergic input to the striatum is the substantia nigra pars reticularis (SNPr). When SNPr is lesioned, it increases the postsynaptic (striatal) sensitivity of D2 receptors, which then enhances the release of glutamate and decreases D1-mediated inhibition. This leads to an overall more excitable striatum, which could then alter its output to other basal nuclei (Vila et al. 1996, 1997; Wichmann et al. 1999; Orieux et al. 2000; Galvan and Wichmann 2008). This state of increased excitability and decreased inhibition could lead to development of pathological oscillatory behavior and tremor.

Neuronal recordings from the subthalamic nucleus of patients with Parkinson's disease show three main patterns: tonic, irregular, and oscillatory (Rodriguez-Oroz et al. 2001). The neurons with tonic and irregular firing properties are common and are equally activated by movement. The neurons with oscillatory behavior in the subthalamic nucleus are of two types: those with long-lasting low-frequency bursts and those with high-frequency bursts. Studies have shown that the dominant oscillation frequency of the neurons with the high-frequency bursts matches the tremor profile and microstimulation or lesion of these neurons significantly attenuates the tremor (Rodriguez-Oroz et al. 2001; Wichmann et al. 1994; Baunez et al. 1995; Guridi et al. 1996; Krack et al. 1997; Limousin et al. 1998). The subthalamic oscillations also propagate into the thalamic and cortical neurons. The neuronal discharges recorded from the thalamus and the globus pallidus are also phase locked with the tremor (Albe-Fessard et al. 1962; Lenz et al. 1994; Guridi et al. 1999; Vitek et al. 1998). The activity recorded from the two distinct cortical–subcortical networks, temporoparietal-brainstem and frontal,

is coherent with the oscillations recorded from the subthalamic nucleus (Litvak et al. 2011). Therefore, it has been proposed that the tremor in Parkinson's disease is a result of pathological oscillations involving a widely distributed network, including subthalamic nucleus, globus pallidus, thalamus, and the cerebral cortex (Alexander et al. 1986; DeLong 1990).

2.5 Membrane Physiology in Drug-Induced Tremor

2.5.1 Valproate-Induced Tremor

Valproate is one of the oldest known anti-seizure medications available and it is used for a variety of neurological conditions such as migraine prophylaxis, epilepsy, mood disorders, and rarely for chronic pain as well. It is also a very common cause of drug-induced tremor (Morgan et al. 2017). The typical tremor profile seen in such patients is mainly that of an action tremor and the tremor can improve with reducing the dose of the medication (Morgan et al. 2017). The electrophysiological profile is quite similar to enhanced physiological tremor and the frequency of the tremor decreases by ~3 Hz with loading, suggesting at least a peripheral mechanical component of the tremor (Morgan et al. 2017).

Valproate has multiple mechanisms of action, including potentiating effects of GABA by decreasing its transamination (Chapman et al. 1982) and by inhibition of I_T (Kelly et al. 1990). Both of these mechanisms should, theoretically, decrease neuronal membrane excitability and have tremor attenuating effect. However, on the contrary, patients on valproate can not only develop a tremor, but also parkinsonism (Zadikoff et al. 2007). One theory to explain this counterintuitive phenomenon is that enhancement of GABA activity decreases dopamine turnover in the nigrostriatal system (Waldmeier and Maitre 1978). Baclofen, a $GABA_B$ agonist, has been shown to decrease dopamine in the striatum (Kabuto et al. 1995). The impact of decreased dopaminergic innervation of the striatum and its relationship to the development of tremor has been discussed previously under Sect. 2.4. Long-term use of valproate can also lead to cerebellar atrophy, which can also produce tremor (Papazian et al. 1995).

2.5.2 Lithium-Induced Tremor

This is one of the most common drug-induced tremors seen in clinical practice (Morgan et al. 2017). Lithium is a very commonly used mood stabilizer and a significant proportion of patients, ranging anywhere from 4% to 65% (depending upon the study), develop tremor as a side effect (Varaflor et al. 1970; Morgan et

al. 2017). Just like valproate-induced tremor, this tremor is also very similar to enhanced physiological tremor with a frequency of 8–12 Hz (Morgan et al. 2017).

Lithium is chemically similar to sodium; hence, lithium ions can replace sodium ions and can cause marked depolarization and alter the configuration of the action potential (Carmeliet 1964). Because of this similarity, lithium ions can be transported inside the cell instead of sodium; however, lithium cannot bind to N-K-ATPase pump (Carmeliet 1964). According to the Goldman-Hodgkin-Katz equation, replacement of sodium by lithium results in a depolarization shift of the resting membrane potential (Thiruvengadam 2001). A reduced neuronal threshold due to the depolarized state of the resting membrane potential can increase the neuronal excitability and a propensity to develop tremor (Shaikh et al. 2008a). Hence, drugs such as propranolol can improve lithium-induced tremor (Kellett et al. 1975). Propranolol nonselectively decreases I_H and I_T currents, thus decreasing neuronal excitability (Pape and McCormick 1989; Shaikh and Finlayson 2003).

2.5.3 Neuroleptic-Induced Tremor

Neuroleptic medications are widely used in psychiatry for patients with psychosis and as adjunctive therapy for mood disorders as well (Morgan et al. 2017). These compounds are lipophilic and strongly block the D2 subtype of dopamine receptors (Susatia and Fernandez 2009). Depletion of dopamine in the presynaptic terminals causes increased activity of the GABAergic system, which in turn decreases dopamine turnover in the nigrostriatal system (Susatia and Fernandez 2009; Waldmeier and Maitre 1978; Kabuto et al. 1995). Hence, the mechanism of tremor generation is similar to that discussed in Sect. 2.4.

2.5.4 Tremor in Hyperthyroidism

Thyroid hormones can have profound effects on the electrical activity of cell membranes. These have been extensively studied for cardiac pacemaker cells but they are less well understood for neurons. Thyroid hormone decreases the duration of monophasic action potential and effective refractory period in cardiac pacemakers, predisposing to cardiac arrhythmias (Yu et al. 2009; Childers 2006). Studies on hippocampal and cortical neurons have shown that thyroid hormone upregulates fast-acting sodium currents and increases the rate of depolarization and the firing rate (Hoffmann and Dietzel 2004). An increased rate of depolarization and reduced refractory period would increase neuronal excitability, thus increasing the likelihood of developing oscillatory behavior and subsequent tremor (Shaikh et al. 2008a).

2.5.5 *Caffeine-Induced Tremor*

Caffeine acts as a stimulant. There are many mechanisms by which caffeine can increase neuronal membrane excitability in the thalamocortical and olivocerebellar circuits and, hence, increase the propensity to generate tremor. At normal doses, caffeine increases cerebral energy metabolism, decreases cerebral blood flow, decreases pH, and activates noradrenaline (Nehlig et al. 1992). Increased noradrenergic tone and decrease in pH favor an increase in I_H and I_T currents, thus reducing the membrane threshold, and increasing membrane excitability (Pape and McCormick 1989; Shaikh and Finlayson 2003, 2005). At high, nonphysiological doses, caffeine mobilizes intracellular calcium and inhibits phosphodiesterases, thus affecting depolarizing currents such as I_H and I_T.

2.5.6 *Tremor Induced by Adrenergic Agonists*

A wide spectrum of medications have adrenergic properties, e.g., epinephrine, norepinephrine, albuterol, salmeterol, terbutaline, amphetamines, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), nicotine, and theophylline. All of these medications are well known to cause or exacerbate tremors (Morgan et al. 2017). The mechanisms are not completely clear but adrenergic agonists can increase I_H and I_T currents and thus increase membrane excitability and hence contribute to tremor (Pape and McCormick 1989; Shaikh et al. 2008a). In addition to their potential effect on central oscillators, beta-adrenergic agonists are also known to have receptors on muscle spindles and their direct effect on muscles can lead to enhanced physiological tremor by sensitizing muscle spindles and enhancing cortico-muscular coherence by synchronizing the afferent signal back from muscle spindles to the central nervous system (Morgan et al. 2017).

2.6 Membrane Mechanisms in Pathogenesis of Acquired Pendular Nystagmus and Saccadic Oscillations

Acquired pendular nystagmus (APN) consists of rhythmic sinusoidal or quasi-sinusoidal ocular oscillations, which can produce significant disabling visual symptoms because of the continuous oscillopsia (Leigh and Zee 2006). APN is considered a tremor equivalent of eyes. It has three main components—horizontal, vertical, and torsional—and the phase relationship between them determines the trajectory of the eyes (Leigh and Zee 2006). Some well-known causes of APN include multiple sclerosis (MS), syndrome of oculopalatal tremor (OPT), and Whipple's disease (Leigh and Zee 2006; Lopez et al. 1996; Deuschl et al. 1994). Another tremor analogue to eyes are saccadic oscillations. These consist of back-to-back

unwanted saccades that interfere with vision. When saccadic oscillations occur purely in horizontal direction, it is called ocular flutter, and when the oscillations are multidirectional, it is known as opsoclonus (Leigh and Zee 2006). Physiologically, these oscillations are present in newborns and some healthy individuals can voluntarily produce these oscillations, known as "voluntary nystagmus" (Shaikh et al. 2007, 2010; Shults et al. 1977). Pathological transient or continuous saccadic oscillations are seen in a variety of conditions, including paraneoplastic syndromes, post-infectious encephalitis, demyelinating disorders, or poisoning (Shaikh et al. 2008a; Leigh and Zee 2006). Experimental and computational studies of APN and saccadic oscillations have shown that the primary disturbances likely occur at the level of neuronal membranes (Das et al. 2000; Shaikh et al. 2007, 2008a, 2010, 2011a, b). In the following subsections, we will discuss the membrane mechanisms for pathogenesis of APN in MS and OPT and the membrane mechanisms for saccadic oscillations.

2.6.1 Membrane Mechanisms for APN in MS

The most widely accepted hypothesis for pathogenesis of APN in MS is an unstable neural integrator, which normally sends premotor signals to hold the eyes in a specific orbital position (Das et al. 2000). This hypothesis is supported by evidence that the ongoing oscillations can be perturbed by velocity signal, e.g., a saccade can reset the oscillation phase (Das et al. 2000).

First, we will discuss the membrane mechanisms responsible for neural integration. Saccadic burst neurons for horizontal and vertical saccades are located within the brainstem and they send velocity signals to the ocular motor neurons in the form of bursts of neural discharge. These bursts are then converted into a steady-state tonic firing in motor neurons by the process of mathematical integration by specialized neurons called the "neural integrator" (Leigh and Zee 2006). The persistent tonic firing rate after the saccade is associated with step-like changes in the inter-spike membrane potential of velocity–position integrator neurons (Aksay et al. 2001). Amplitude of the inter-spike membrane potential and thus neuronal firing rate is directly proportional to the eye position (Aksay et al. 2001). When the membrane is hyperpolarized, brief intracellular pulses (mimicking the saccade) cause step-like change in the inter-spike membrane potential (which could potentially translate into steady change in the gaze position) (Aksay et al. 2001). In contrast, when the membrane is depolarized, there are increasing fluctuations in the inter-spike membrane potential. It is proposed that sustained change in the inter-spike membrane potential is due to persistent synaptic input. There is a mutually excitatory feedback network among ipsilateral neurons and mutually inhibitory feedback network among ipsi- and contralateral neurons. These inhibitory connections serve to yoke the firing rate and inter-spike membrane potential above (ipsilateral) or below (contralateral) the equilibrium (Aksay et al. 2007). Within the network of neurons serving as neural integrator, the persistence of the firing rate

and similarity of the persistence (i.e., evidence of integration) are also determined by the circuit's functional architecture; physically closer neurons have relatively similar persistence of the firing rate (Miri et al. 2011). The latter underscores the importance of strong network connections (as expected in closely placed neurons) in efficiency of integration (Miri et al. 2011).

These considerations allow us to predict that a constant hyperpolarization of the membrane or disruption of the interconnections would prevent changes in inter-spike membrane potential and subsequently impair the ability of the neural integrator to maintain a steady-state change in the firing rate. Indeed, injection of the hyperpolarizing agent, muscimol (a selective $GABA_A$ agonist), at the putative site of the neural integrator in monkeys made the integrator unstable, while depolarization (with glutamate) reversed the effects (Arnold and Robinson 1997; Arnold et al. 1999). Such an unstable neural integrator would then oscillate in the presence of visual feedback (Das et al. 2000).

It has been proposed that the amplitude of the APN is directly proportional to the degree of severity of neural integrator instability and membrane depolarization would reduce the amplitude of the APN. Gabapentin blocks alpha-2-delta subunit of calcium channels and memantine is an NMDA receptor antagonist. Both of these drugs can indirectly depolarize the cells of the horizontal gaze neural integrator located in nucleus prepositus hypoglossi, by their respective actions on cerebellar Purkinje neurons, hence, decreasing the amplitude of APN (Shaikh et al. 2011a; Thurtell et al. 2010).

2.6.2 Membrane Mechanisms for Pathogenesis of APN in OPT

The syndrome of OPT is characterized by low-frequency (1–3 Hz), smooth, and aperiodic ocular and palatal oscillations (Leigh and Zee 2006; Shaikh et al. 2010). It is produced by a lesion affecting the Guillain–Mollaret triangle, which is a circuit connecting the inferior olivary nucleus to the deep cerebellar nuclei and cerebellar cortex via the inferior cerebellar peduncle, the output projection of the deep cerebellar nuclei to the contralateral red nucleus via the superior cerebellar peduncle, and a descending pathway from the red nucleus to the corresponding inferior olive via the central tegmental tract (Guillain and Mollaret 1931) (Fig. 2.4a). Studies have shown that lesions affecting the central tegmental tract, which interrupt the descending pathway originating from the deep cerebellar nuclei (through superior cerebellar peduncle and via the red nucleus) to the inferior olive, lead to the development of OPT (Leigh and Zee 2006; Shaikh et al. 2010) (Fig. 2.4a, b). Patients with OPT develop the syndrome weeks to months after the initial lesion and most patients show imaging evidence of hypertrophic olivary degeneration by that time (Leigh and Zee 2006).

In normal physiological conditions, the inferior olivary neurons show evidence of low-frequency subthreshold oscillations because of their electrotonic coupling via dendro-dendritic gap junctions, formed by pre- and postsynaptic connexions (De

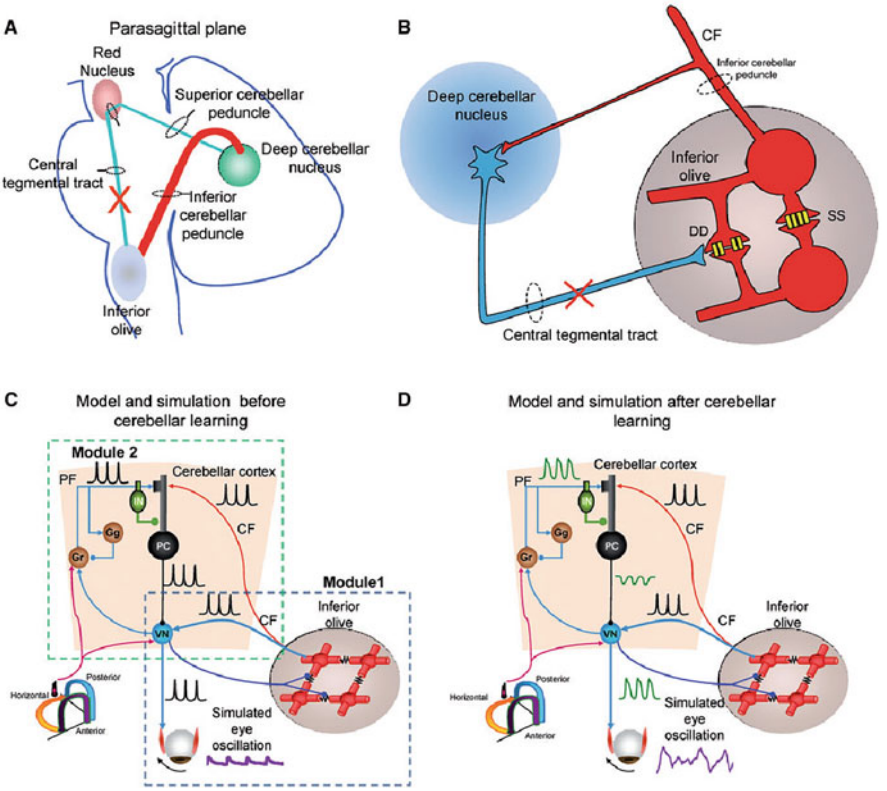

Fig. 2.4 (**a**) Guillain–Mollaret triangle formed by connections between the inferior olive and the cerebellum (via inferior cerebellar peduncle), then output projection via superior cerebellar peduncle to the red nucleus and a descending inhibitory pathway back to the inferior olive via central tegmental tract. (**b**) The conduction strength through the dendro-dendritic gap junctions (schematized with yellow connexon channels; DD) between adjacent inferior olivary neurons are inhibited by projections from the deep cerebellar nuclei (blue projection). Lesions in the Guillain–Mollaret triangle (red X in (**a**) and (**b**)) also result in hypertrophy of inferior olive neurons causing development of abnormal soma-somatic gap junction. (**c**, **d**) Schematic representation of a model for classical delay conditioning. (**c**) Model and traces from simulations after inferior olive hypertrophy but before cerebellar learning. (**d**) Inferior olive and cerebellar modules after hypertrophy and learning. Lower left corner shows icon for semicircular canals (**c** and **d**). Simulated membrane potentials (black), eye oscillations (magenta). *CF* climbing fibers, *DD* dendro-dendritic gap junction, *Gr* granule cell layer, *IN* interneurons; *PC* Purkinje neurons, *PF* parallel fibers, *SS* soma-somatic gap junction. (Adapted from Shaikh et al. (2010))

Zeeuw et al. 1990, 2003; Shaikh et al. 2010). This coupling leads to organization of the olivary neurons into three-dimensional (3D) patches, which project to the cerebellar Purkinje neurons via climbing fibers and produce complex spikes (Shaikh et al. 2010). The descending fibers in the central tegmental tract (originating from the deep cerebellar nuclei), projecting onto the inferior olivary neurons,

are GABAergic and hence provide an inhibitory modulation of the gap junctions (Shaikh et al. 2010) (Fig. 2.4a, b). When this inhibitory feedback modulation is removed, the inferior olive undergoes hypertrophy over time and there occurs an abnormal development of soma-somatic gap junctions between adjacent olivary neurons, thus strengthening the electrotonic coupling of these neurons (De Zeeuw et al. 1990, 1998) (Fig. 2.4b).

A recently proposed dual-mechanism hypothesis suggests that the aperiodic, low-frequency, smooth, ocular oscillations (acquired pendular nystagmus) seen in the syndrome of OPT are a result of the synchronized inferior olivary oscillations (caused by the strengthening of the electrotonic coupling) and a superimposed "smoothing" due to maladaptive slow cerebellar learning (Shaikh et al. 2010). Isolated synchronized inferior olivary oscillations are periodic and jerky (De Zeeuw et al. 1998) (Fig. 2.4c). But the ocular oscillations seen in patients with OPT are smooth and aperiodic (Leigh and Zee 2006; Shaikh et al. 2010). Hence, a role of superimposed cerebellar smoothing was proposed (Shaikh et al. 2010). The patches of electrotonically coupled neurons within the inferior olive act as independent ~2 Hz oscillators. A hypothetical computational model simulating ocular oscillations showed that this synchronized olivary activity, in the absence of superimposed cerebellar smoothing, produces ~2 Hz, low-amplitude, jerky, and regular ocular oscillations, which do not match the ocular oscillations seen in patients with OPT (Shaikh et al. 2010) (Fig. 2.4c). When cerebellar smoothing and amplification is added to this scenario, aperiodic, smooth, ~2 Hz ocular oscillations are produced, which are similar to those seen in patients with OPT (Shaikh et al. 2010) (Fig. 2.4d).

Drugs that can decrease the modulatory effects of the Purkinje cells on the olivary output can decrease the amplitude of the oscillations. This can be achieved by either enhancing GABA-mediated inhibition (e.g., benzodiazepines, primidone, and topiramate) or by decreasing glutamatergic excitation (e.g., memantine, gabapentin, or topiramate). Studies have shown that patients with OPT who took either gabapentin or memantine had decreased amplitude of the oscillations and these drugs also affected the cycle-by-cycle variability of the frequency (Shaikh et al. 2011a; Thurtell et al. 2010).

2.6.3 Membrane Mechanisms for Pathogenesis of Saccadic Oscillations

Saccades are generated by a complex network of reciprocally innervated burst neurons in the brainstem (Leigh and Zee 2006). Analogous to the importance of intrinsic membrane properties of thalamic neurons in generation of tremor, the key determinants in generation of saccadic oscillations are the intrinsic membrane properties of burst neurons and the reciprocal connections between agonist and antagonistic burst neurons (Shaikh et al. 2007; Ramat et al. 2005).

The functional organization of the brainstem circuit for saccade generation consists of two main populations of burst neurons: excitatory burst neurons (EBNs) and inhibitory burst neurons (IBNs). The cortical signals arise in the frontal and parietal eye fields (FEF and PEF) and descend via two parallel pathways (one through superior colliculus and the other through pons and vermis/fastigial oculomotor region [FOR]). Both FOR and superior colliculus project onto the omnipause neurons (OPNs) in the brainstem (Leigh and Zee 2006; Shaikh et al. 2008b). During visual fixation, the OPNs provide tonic inhibition to both EBNs and IBNs to prevent any unwanted saccades (Shaikh et al. 2008b). When a saccade has to be generated, this OPN inhibition is removed, thus leading to post-inhibitory rebound (PIR) in both EBNs and IBNs of the side ipsilateral to the direction of intended saccade. The EBNs project to the motor neurons and the interneurons but the axons of IBNs cross the midline and inhibit the contralateral EBNs, IBNs, and motor neurons. The crossed innervation ensures that only the agonist motor neurons are activated while the antagonist neurons on the contralateral side are inhibited (Sherrington's law of reciprocal innervation) (Ramat et al. 2005).

Because of the reciprocal nature of this circuit and the phenomenon of PIR, this circuit is prone to oscillate. In normal situations, a strong external source of inhibition, like OPNs in this case, prevents the circuit from oscillating. If this inhibition is removed (e.g., due to acquired antagonism or congenital hypofunction of the glycinergic inhibition), saccadic oscillations would result (Shaikh et al. 2007, 2008a). The other proposed mechanism of saccadic oscillations is increased excitability of the burst neurons. This excitability depends upon the amplitude of the PIR, which in turn is determined by the kinetics of I_H and I_T currents, as discussed earlier. A neuromimetic model of saccadic oscillations tested this hypothesis. When the membrane excitability of the burst neurons was increased by increasing I_H and I_T or by decreasing the external inhibition, saccadic oscillations resulted (Shaikh et al. 2008b). This model explains saccadic oscillations generated even in absence of any saccadic command, like during eyeblinks (Ramat et al. 2005).

The burst neurons act like a high-gain amplifier (high gain is likely related to the property of PIR) in a negative position feedback loop. The signal sent to this circuit is that of desired eye displacement and it leads to firing of the burst neurons, which is proportional to the eye velocity generated. As the eye moves, the actual displacement signal is sent back as an efference copy (feedback loop) to be compared to the desired displacement and the difference drives the activity of the burst neurons. Because of the inherent high gain of the amplifier and potential delays in this feedback signal, this system is prone to oscillate even with very small inputs like when generating a small spontaneous saccade (Ramat et al. 2005; Shaikh et al. 2008b). We must emphasize that PIR has not been recorded directly from the burst neurons but these neurons possess the necessary channels to have this membrane property (Shaikh et al. 2008b).

Drugs such as propranolol have been shown to decrease the amplitude of saccadic oscillations in a patient with syndrome of microsaccadic oscillations and limb tremor (Shaikh et al. 2011b).

2.7 Summary and Future Directions

In this chapter, we have discussed several hypothetical mechanisms of intrinsic membrane disturbances that can contribute to the pathophysiology of various tremor disorders. A plethora of studies from multiple different sources, such as animal models of tremor, genetic studies showing association between genetic variants and tremors, and experimental and clinical studies showing pharmacological effects of drugs on specific channels and resultant tremors, have provided strong evidence in support of the membrane hypothesis of tremor disorders. Investigators studying pathological saccadic oscillations and pendular nystagmus have also proposed that the membrane mechanisms responsible for these disorders are quite similar to the ones responsible for other common tremor disorders like essential tremor. Future studies of the neuronal membrane electrophysiology in tremor patients and their potential links with genetic variants will pave the way for more effective personalized and, possibly, gene-based treatment options for tremor patients.

References

Aksay E, Gamkrelidze G, Seung HS, Baker R, Tank DW. In vivo intracellular recording and perturbation of persistent activity in a neural integrator. Nat Neurosci. 2001;4:184–93.

Aksay E, Olasagasti I, Mensh BD, Baker R, Goldman MS, Tank DW. Functional dissection of circuitry in a neural integrator. Nat Neurosci. 2007;10:494–504.

Albe-Fessard D, Arfel G, Guiot G. Activités électriques caractéristiques de quelques structures cérébrales chez l'homme. Ann Chir. 1962;17:1185–214.

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986;9:357–81.

Alvarez JL, Rubio LS, Vassort G. Facilitation of T-type calcium current in bullfrog atrial cells: voltage-dependent relief of a G protein inhibitory tone. J Physiol Lond. 1996;491:321–34.

Apps R, Garwicz M. Anatomical and physiological foundations of cerebellar information processing. Nat Rev Neurosci. 2005;6:297–311.

Arnold DB, Robinson DA. The oculomotor integrator: testing of a neural network model. Exp Brain Res. 1997;113:57–74.

Arnold DB, Robinson DA, Leigh RJ. Nystagmus induced by pharmacological inactivation of the brainstem ocular motor integrator in monkey. Vis Res. 1999;39:4286–95.

Axelrad JE, Louis ED, Honig LS, Flores I, Ross GW, Pahwa R, Lyons KE, Faust PL, Vonsattel JP. Reduced Purkinje cell number in essential tremor: a postmortem study. Arch Neurol. 2008;65:101–7.

Baumel JP, Gallagher BB, Mattson RH. Phenylethylmalonamide. An important metabolite of primidone. Arch Neurol. 1972;27:34–41.

Baunez C, Nieoullon A, Amalric M. In a rat model of parkinsonism, lesions of the subthalamic nucleus reverse increases of reaction time but induce a dramatic premature responding deficit. J Neurosci. 1995;15:6531–41.

Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science. 1990;249:1436–8.

Bergman H, Feingold A, Nini A, Raz A, Slovin H, Abeles M, Vaadia E. Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. Trends Neurosci. 1998;21:32–8.

Bleasel AF, Pettigrew AG. Development and properties of spontaneous oscillations of the membrane potential in inferior olivary neurons in the rat. Brain Res Dev Brain Res. 1992;65:43–50.
Blenkinsop TA, Lang EJ. Block of inferior olive gap junctional coupling decreases Purkinje cell complex spike synchrony and rhythmicity. J Neurosci. 2006;26:1739–48.
Boecker H, Weindl A, Brooks DJ, Ceballos-Baumann AO, Liedtke C, Miederer M, Sprenger T, Wagner KJ, Miederer I. GABAergic dysfunction in essential tremor: an 11C-flumazenil PET study. J Nucl Med. 2010;51:1030–5.
Calabresi P, Mercuri NB, Sancesario G, Bernardi G. Electrophysiology of dopamine-denervated striatal neurons. Implications for Parkinson's disease. Brain. 1993;116:433–52.
Carmeliet EE. Influence of lithium ions on the transmembrane potential and cation content of cardiac cells. J Gen Physiol. 1964;47:501–30.
Chapman A, Keane PE, Meldrum BS, Simiand J, Vernieres JC. Mechanism of anticonvulsant action of valproate. Prog Neurobiol. 1982;19(4):315–59.
Childers R. Electrophysiology of the electrocardiographic changes of atrial fibrillation. J Electrocardiol. 2006;39:S174–9.
Condorelli DF, Parenti R, Spinella F, Trovato Salinaro A, Belluardo N, Cardile V, Cicirata F. Cloning of a new gap junction gene (Cx36) highly expressed in mammalian brain neurons. Eur J Neurosci. 1998;10:1202–8.
Das VE, Oruganti P, Kramer PD, Leigh RJ. Experimental tests of a neural-network model for ocular oscillations caused by disease of central myelin. Exp Brain Res. 2000;133:189–97.
de Montigny C, Lamarre Y. Rhythmic activity induced by harmaline in the olivo-cerebello-bulbar system of the cat. Brain Res. 1973;53:81–95.
De Zeeuw CI, Ruigrok TJ, Schalekamp MP, Boesten AJ, Voogd J. Ultrastructural study of the cat hypertrophic inferior olive following anterograde tracing, immunocytochemistry, and intracellular labeling. Eur J Morphol. 1990;28:240–55.
De Zeeuw CI, Simpson JI, Hoogenraad CC, Galjart N, Koekkoek SK, Ruigrok TJ. Microcircuitry and function of the inferior olive. Trends Neurosci. 1998;21(9):391–400.
De Zeeuw CI, Chorev E, Devor A, Manor Y, Van Der Giessen RS, De Jeu MT, Hoogenraad CC, Bijman J, Ruigrok TJ, French P, Jaarsma D, Kistler WM, Meier C, Petrasch-Parwez E, Dermietzel R, Sohl G, Gueldenagel M, Willecke K, Yarom Y. Deformation of network connectivity in the inferior olive of connexin 36-deficient mice is compensated by morphological and electrophysiological changes at the single neuron level. J Neurosci. 2003;23:4700–11.
DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 1990;13:281–5.
Deng H, Xie WJ, Le WD, Huang MS, Jankovic J. Genetic analysis of the GABRA1 gene in patients with essential tremor. Neurosci Lett. 2006;401:16–9.
Deuschl G, Elble RJ. The pathophysiology of essential tremor. Neurology. 2000;54:S14–20.
Deuschl G, Toro C, Valls-Solo J, Zee DS, Hallett M. Symptomatic and essential palatal tremor. 1. Clinical, physiological and MRI analysis. Brain. 1994;117:775–88.
Deuschl G, Raethjen J, Lindemann M, Krack P. The pathophysiology of tremor. Muscle Nerve. 2001;24:716–35.
Elble RJ. Essential tremor frequency decreases with time. Neurology. 2000;55:1547–51.
Elble RJ, Koller WC. Tremor. Baltimore: John Hopkins; 1990.
Franzellitti S, Buratti S, Valbonesi P, Capuzzo A, Fabbri E. The β-blocker propranolol affects cAMP-dependent signaling and induces the stress response in Mediterranean mussels, Mytilus galloprovincialis. Aquat Toxicol. 2011;101:299–308.
Galvan A, Wichmann T. Pathophysiology of parkinsonism. Clin Neurophysiol. 2008;119:1459–74.
García-Martín E, Martínez C, Alonso-Navarro H, Benito-León J, Lorenzo-Betancor O, Pastor P, Puertas I, Rubio L, López-Alburquerque T, Agúndez JA, Jiménez-Jiménez FJ. Gamma-aminobutyric acid (GABA) receptor rho (GABRR) polymorphisms and risk for essential tremor. J Neurol. 2011;258:203–11.
Gittis AH, Hang GB, Ladow ES, Shoenfeld LR, Atallah BV, Finkbeiner S, Kreitzer AC. Rapid target-specific remodeling of fast-spiking inhibitory circuits after loss of dopamine. Neuron. 2011;71:858–68.

Guillain G, Mollaret P. Deux cas de myoclonies synchrones et rhythmes velopharyngo-laryngo-oculo-diaphragmatiques. Rev Neurol. 1931;2:545–66.
Guillery RW, Harting JK. Structure and connections of the thalamic reticular nucleus: advancing views over half a century. J Comp Neurol. 2003;463:360–71.
Guridi J, Herrero MT, Luquin MR, Guillen J, Ruberg M, Laguna J, et al. Subthalamotomy in parkinsonian monkeys. Behavioural and biochemical analysis. Brain. 1996;119:1717–27.
Guridi J, Gorospe A, Ramos E, Linazasoro G, Rodriguez MC, Obeso JA. Stereotactic targeting of the globus pallidus internus in Parkinson's disease: imaging versus electrophysiological mapping. Neurosurgery. 1999;45:278–87.
Handforth A, Martin FC, Kang GA, Vanek Z. Zonisamide for essential tremor: an evaluator-blinded study. Mov Disord. 2009;24:437–40.
Herrero MT, Levy R, Ruberg M, Luquin MR, Villares J, Guillen J, et al. Consequence of nigrostriatal denervation and L-dopa therapy on the expression of glutamic acid decarboxylase messenger RNA in the pallidum. Neurology. 1996;47:219.
Hoffmann G, Dietzel ID. Thyroid hormone regulates excitability in central neurons from postnatal rats. Neuroscience. 2004;125:369–79.
Hoffmann R, Baillie GS, Mackenzie SJ, Yarwood SJ, Houslay MD. The MAP kinase ERK2 inhibits the cyclic AMP-specific phosphodiesterase, HSPDE4D3 by phosphorylating it at Ser579. EMBO J. 1999;18:893–903.
Hoge GJ, Davidson KG, Yasumura T, Castillo PE, Rash JE, Pereda AE. The extent and strength of electrical coupling between inferior olivary neurons is heterogeneous. J Neurophysiol. 2011;105:1089–101.
Hong S, Optican LM. Interaction between Purkinje cells and inhibitory interneurons may create adjustable output waveforms to generate timed cerebellar output. PLoS One. 2008;3:e2770.
Hotson JR, Prince DA. A calcium-activated hyperpolarization follows repetitive firing in hippocampal neurons. J Neurophysiol. 1980;43:409–19.
Houslay MD, Milligan G. Tailoring cAMP signaling responses through isoform multiplicity. Trends Biochem Sci. 1997;22:217–24.
Houslay MD, Sullivan M, Bolger GB. The multi-enzyme PDE4 cyclic AMP specific phosphodiesterase family: intracellular targeting, regulation and selective inhibition by compounds exerting anti-inflammatory and anti-depressant actions. Adv Pharmacol. 1998;44:225–342.
Hua SE, Lenz FA. Posture-related oscillations in human cerebellar thalamus in essential tremor are enabled by voluntary motor circuits. J Neurophysiol. 2004;93:117–27.
Hua SE, Lenz FA, Zirh TA, Reich SG, Dougherty PM. Thalamic neuronal activity correlated with essential tremor. J Neurol Neurosurg Psychiatry. 1998;64:273–6.
Jahnsen H, Llinás R. Ionic basis for the electro-responsiveness and oscillatory properties of guinea-pig thalamic neurones in vitro. J Physiol. 1984;349:227–47.
Jeanneteau F, Funalot B, Jankovic J, Deng H, Lagarde JP, Lucotte G, et al. A functional variant of the dopamine D3 receptor is associated with risk and age-at-onset of essential tremor. Proc Natl Acad Sci U S A. 2006;103:10753–8.
Jenkins IH, Frackowiak RS. Functional studies of the human cerebellum with positron emission tomography. Rev Neurol (Paris). 1993;149:647–53.
Jia F, Chandra D, Homanics GE, Harrison NL. Ethanol modulates synaptic and extrasynaptic GABAA receptors in the thalamus. J Pharmacol Exp Ther. 2008;326:475–82.
Kabuto H, Yokoi I, Iwaya K, Mori A. Monoamine release in the rat striatum is induced by delta-guanidinovaleric acid and inhibited by GABA agnosts. Life Sci. 1995;56:1741–8.
Kellett JM, Metcalfe M, Bailey J, Coppen AJ. Beta blockade in lithium tremor. J Neurol Neurosurg Psychiatry. 1975;38:719–21.
Kelly KM, Gross RA, Macdonald RL. Valproic acid selectively reduces the low-threshold (T) calcium current in rat nodose neurons. Neurosci Lett. 1990;116:233–8.
Kim YS, Chang HK, Lee JW, Sung YH, Kim SE, Shin MS, Yi JW, Park JH, Kim H, Kim CJ. Protective effect of gabapentin on N-methyl-D-aspartate-induced excitotoxicity in rat hippocampal CA1 neurons. J Pharmacol Sci. 2009;109:144–7.

Koller WC, Pahwa PR, Lyons KE, Wilkinson SB. Deep brain stimulation of the Vim nucleus of the thalamus for the treatment of tremor. Neurology. 2000;55:S29–33.
Krack P, Pollak P, Limousin P, Benazzouz A, Benabid AL. Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease. Lancet. 1997;350:1675.
Kralic JE, Criswell HE, Osterman JL, O'Buckley TK, Wilkie ME, Matthews DB, Hamre K, Breese GR, Homanics GE, Morrow AL. Genetic essential tremor in gamma-aminobutyric acidA receptor alpha1 subunit knockout mice. J Clin Invest. 2005;115:774–9.
Lamarre Y, Mercier LA. Neurophysiological studies of harmaline-induced tremor in the cat. Can J Physiol Pharmacol. 1971;49:1049–58.
Lamarre Y, de Montigny C, Dumont M, Weiss M. Harmaline-induced rhythmic activity of cerebellar and lower brain stem neurons. Brain Res. 1971;32:246–50.
Leigh RJ, Zee DS. The neurology of eye movements. 4th ed. New York: Oxford University Press; 2006. Book/CD-rom.
Lenz FA, Kwan HC, Martin RL, Tasker RR, Dostrovsky JO, Lenz YE. Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. Brain. 1994;117:531–43.
Leznik E, Llinás R. Role of gap junctions in synchronized neuronal oscillations in the inferior olive. J Neurophysiol. 2005;94:2447–56.
Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 1998;339:1105–11.
Litvak V, Jha A, Eusebio A, Oostenveld R, Foltynie T, Limousin P, Zrinzo L, Hariz MI, Friston K, Brown P. Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. Brain. 2011;134:359–74.
Llinás R, Sugimori M. Electrophysiological properties of in vitro Purkinje cell stomata in mammalian cerebellar slices. J Physiol. 1980;305:171–95.
Llinás R, Volkind RA. The olivo-cerebellar system: functional properties as revealed by harmaline-induced tremor. Exp Brain Res. 1973;18:69–87.
Llinás R, Yarom Y. Properties and distribution of ionic conductances generating electroresponsiveness of mammalian inferior olivary neurones in vitro. J Physiol. 1981;315:569–84.
Llinás R, Yarom Y. Oscillatory properties of guinea-pig inferior olivary neurones and their pharmacological modulation: an in vitro study. J Physiol. 1986;376:163–82.
Long MA, Deans MR, Paul DL, Connors BW. Rhythmicity without synchrony in the electrically uncoupled inferior olive. J Neurosci. 2002;22:10898–905.
Lopez LI, Bronstein AM, Gresty MA, DuBoulay EP, Rudge P. Clinical and MRI correlates in 27 patients with acquired pendular nystagmus. Brain. 1996;119:465–72.
Louis ED. Essential tremor: evolving clinicopathological concepts in an era of intensive post-mortem enquiry. Lancet Neurol. 2010;9:613–22.
Louis ED, Lenka A. The olivary hypothesis of essential tremor: time to lay this model to rest? Tremor Other Hyperkinet Mov (N Y). 2017;7:473.
Louis ED, Vonsattel JP. The emerging neuropathology of essential tremor. Mov Disord. 2008;23:174–82.
Louis ED, Shungu DC, Chan S, Mao X, Jurewicz EC, Watner D. Metabolic abnormality in the cerebellum in patients with essential tremor: a proton magnetic resonance spectroscopic imaging study. Neurosci Lett. 2002;333(1):17–20.
Louis ED, Shungu DC, Mao X, Chan S, Jurewicz EC. Cerebellar metabolic symmetry in essential tremor studied with 1H magnetic resonance spectroscopic imaging: implications for disease pathology. Mov Disord. 2004;19:672–7.
Lucotte G, Lagarde JP, Funalot B, Sokoloff P. Linkage with the Ser9Gly DRD3 polymorphism in essential tremor families. Clin Genet. 2006;69:437–40.
Lüthi A, McCormick DA. Modulation of a pacemaker current through Ca(2+)-induced stimulation of cAMP production. Nat Neurosci. 1999;2:634–41.
Manor Y, Rinzel J, Segev I, Yarom Y. Low-amplitude oscillations in the inferior olive: a model based on electrical coupling of neurons with heterogeneous channel densities. J Neurophysiol. 1997;77:2736–52.

Manto M, Laute MA. A possible mechanism for the beneficial effect of ethanol in essential tremor. Eur J Neurol. 2008;15:697–705.
McCormick DA, Pape HC. Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. J Physiol. 1990;431:291–318.
Miri A, Daie K, Arrenberg AB, Baier H, Aksay E, Tank DW. Spatial gradients and multidimensional dynamics in a neural integrator circuit. Nat Neurosci. 2011;14:1150–9.
Mitchell IJ, Clarke CE, Boyce S, Robertson RG, Peggs D, Sambrook MA, et al. Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Neuroscience. 1989;32:213–26.
Morgan JC, Kurek JA, Davis JL, Sethi KD. Insights into pathophysiology from medication-induced tremor. Tremor Other Hyperkinet Mov (N Y). 2017;7:442.
Morita S, Miwa H, Kondo T. Effect of zonisamide on essential tremor: a pilot crossover study in comparison with arotinolol. Parkinsonism Relat Disord. 2005;11:101–3.
Nehlig A, Daval JL, Debry G. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. Brain Res Brain Res Rev. 1992;17:139–70.
O'Suilleabhain P, Dewey RB Jr. Randomized trial comparing primidone initiation schedules for treating essential tremor. Mov Disord. 2002;17:382–6.
Obeso JA, Rodriguez MC, DeLong MR. Basal ganglia pathophysiology: a critical review. Adv Neurol. 1997;74:3–18.
Orieux G, Francois C, Feger J, Yelnik J, Vila M, Ruberg M, et al. Metabolic activity of excitatory parafascicular and pedunculopontine inputs to the subthalamic nucleus in a rat model of Parkinson's disease. Neuroscience. 2000;97:79–88.
Pahwa R, Lyons K, Koller WC. Surgical treatment of essential tremor. Neurology. 2000;54:S39–44.
Papazian O, Cañizales E, Alfonso I, Archila R, Duchowny M, Aicardi J. Reversible dementia and apparent brain atrophy during valproate therapy. Ann Neurol. 1995;38:687–91.
Pape HC, McCormick DA. Noradrenaline and serotonin selectively modulate thalamic burst firing by enhancing a hyperpolarization-activated cation current. Nature. 1989;340:715–8.
Parent A, Hazrati LN. Functional anatomy of the basal ganglia. Part I: The cortico-basal ganglia-thalamo-cortical loop. Brain Res Rev. 1995;20:91–127.
Park YG, Park HY, Lee CJ, Choi S, Jo S, Choi H, Kim YH, Shin HS, Llinas RR, Kim D. Ca(V)3.1 is a tremor rhythm pacemaker in the inferior olive. Proc Natl Acad Sci U S A. 2010;107:10731–6.
Pascoli V, Valjent E, Corbillé AG, Corvol JC, Tassin JP, Girault JA, Hervé D. cAMP and extracellular signal-regulated kinase signaling in response to d-amphetamine and methylphenidate in the prefrontal cortex in vivo: role of beta 1-adrenoceptors. Mol Pharmacol. 2005;68:421–9.
Pinault D. The thalamic reticular nucleus: structure, function and concept. Brain Res Rev. 2004;46:1–31.
Placantonakis DG, Bukovsky AA, Aicher SA, Kiem HP, Welsh JP. Continuous electrical oscillations emerge from a coupled network: a study of the inferior olive using lentiviral knockdown of connexin36. J Neurosci. 2006;26:5008–16.
Polc P, Haefely W. Effects of two benzodiazepines, phenobarbitone, and baclofen on synaptic transmission in the cat cuneate nucleus. Naunyn Schmiedeberg's Arch Pharmacol. 1976;294:121–31.
Quesada A, Bui PH, Homanics GE, Hankinson O, Handforth A. Comparison of mibefradil and derivative NNC 55-0396 effects on behavior, cytochrome P450 activity, and tremor in mouse models of essential tremor. Eur J Pharmacol. 2011;659(1):30–6.
Ramat S, Leigh RJ, Zee DS, Optican LM. Ocular oscillations generated by coupling of brainstem excitatory and inhibitory saccadic burst neurons. Exp Brain Res. 2005;160:89–106.
Rodriguez-Oroz MC, Rodriguez M, Guridi J, Mewes K, Chockkman V, Vitek J, DeLong MR, Obeso JA. The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics. Brain. 2001;124:1777–90.

Shaikh AG, Finlayson PG. Hyperpolarization-activated (I(h)) conductances affect brainstem auditory neuron excitability. Hear Res. 2003;183:126–36.
Shaikh AG, Finlayson PG. Excitability of auditory brainstem neurons, in vivo, is increased by cyclic-AMP. Hear Res. 2005;201:70–80.
Shaikh AG, Miura K, Optican LM, Ramat S, Leigh RJ, Zee DS. A new familial disease of saccadic oscillations and limb tremor provides clues to mechanisms of common tremor disorders. Brain. 2007;130:3020–31.
Shaikh AG, Miura K, Optican LM, Ramat S, Tripp RM, Zee DS. Hypothetical membrane mechanisms in essential tremor. J Transl Med. 2008a;6:68.
Shaikh AG, Ramat S, Optican LM, Miura K, Leigh RJ, Zee DS. Saccadic burst cell membrane dysfunction is responsible for saccadic oscillations. J Neuroophthalmol. 2008b;28(4):329–36.
Shaikh AG, Hong S, Liao K, Tian J, Solomon D, Zee DS, Leigh RJ, Optican LM. Oculopalatal tremor explained by a model of inferior olivary hypertrophy and cerebellar plasticity. Brain. 2010;133:923–40.
Shaikh AG, Thurtell MJ, Optican LM, Leigh RJ. Pharmacological tests of hypotheses for acquired pendular nystagmus. Ann N Y Acad Sci. 2011a;1233:320–6.
Shaikh AG, Zee DS, Optican LM, Miura K, Ramat S, Leigh RJ. The effects of ion-channel blockers validate the conductance based model of saccadic oscillations. Ann N Y Acad Sci. 2011b;1233:58–63.
Sherrington C. On the reciprocal innervation of antagonistic muscles. Thirteenth note. On the antagonism between reflex inhibition and reflex excitation. Proc R Soc Lond B. 1908;80B:565–78.
Shults WT, Stark L, Hoyt WF, Ochs AL. Normal saccadic structure of voluntary nystagmus. Arch Ophthalmol. 1977;95(8):1399–404.
Song IU, Kim JS, Lee SB, Ryu SY, An JY, Kim HT, et al. Effects of zonisamide on isolated head tremor. Eur J Neurol. 2008;15:1212–5.
Sóvágó J, Makkai B, Gulyás B, Hall H. Autoradiographic mapping of dopamine-D2/D3 receptor stimulated [35S]GTPgammaS binding in the human brain. Eur J Neurosci. 2005;22:65–71.
Sozzani S, Agwu DE, McCall CE, O'Flaherty JT, Schmitt JD, Kent JD, McPhail LC. Propranolol, a phosphatidate phosphohydrolase inhibitor, also inhibits protein kinase C. J Biol Chem. 1992;267:20481–8.
Susatia F, Fernandez HH. Drug-induced parkinsonism. Curr Treat Options Neurol. 2009;11:162–9.
Takada M, Hattori T. Glycine: an alternative transmitter candidate of the pallidosubthalamic projection neurons in the rat. J Comp Neurol. 1987;262:465–72.
Thiruvengadam A. Effect of lithium and sodium valproate ions on resting membrane potentials in neurons: a hypothesis. J Affect Disord. 2001;65:95–9.
Thorpe AJ, Offord J. The alpha2-delta protein: an auxiliary subunit of voltage-dependent calcium channels as a recognized drug target. Curr Opin Investig Drugs. 2010;11:761–70.
Thurtell MJ, Joshi AC, Leone AC, Tomsak RL, Kosmorsky GS, Stahl JS, Leigh RJ. Crossover trial of gabapentin and memantine as treatment for acquired nystagmus. Ann Neurol. 2010;67:676–80.
Varaflor L, Lehmann HE, Ban TA. Side effects of lithium carbonate treatment. J Clin Pharmacol J New Drugs. 1970;10:387–9.
Vila M, Herrero MT, Levy R, Faucheux B, Ruberg M, Guillen J, et al. Consequences of nigrostriatal denervation on the gamma-aminobutyric acidic neurons of substantia nigra pars reticulata and superior colliculus in parkinsonian syndromes. Neurology. 1996;46:802–9.
Vila M, Levy R, Herrero MT, Ruberg M, Faucheux B, Obeso JA, et al. Consequences of nigrostriatal denervation on the functioning of the basal ganglia in human and nonhuman primates: an in situ hybridization study of cytochrome oxidase subunit I mRNA. J Neurosci. 1997;17:765–73.
Vitek JL, Bakay RA, Hashimoto T, Kaneoke Y, Mewes K, Zhang JY, et al. Microelectrode-guided pallidotomy: technical approach and its application in medically intractable Parkinson's disease. J Neurosurg. 1998;88:1027–43.

Wainger BJ, DeGennaro M, Santoro B, Siegelbaum SA, Tibbs GR. Molecular mechanism of cAMP modulation of HCN pacemaker channels. Nature. 2001;411:805–10.

Waldmeier PC, Maitre L. Effects of baclofen on dopamine metabolism and interaction with neuroleptic effects. Eur J Pharmacol. 1978;47:191–200.

Wichmann T, Bergman H, DeLong MR. The primate subthalamic nucleus. III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. J Neurophysiol. 1994;72:521–30.

Wichmann T, Bergman H, Starr PA, Subramanian T, Watts RL, DeLong MR. Comparison of MPTP-induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia nigra pars reticulata in primates. Exp Brain Res. 1999;125:397–409.

Wolpert D, Miall R, Kawato M. Internal models in the cerebellum. Trends Cogn Sci. 1998;2:338–47.

Yarom Y. Rhythmogenesis in a hybrid system–interconnecting an olivary neuron to an analog network of coupled oscillators. Neuroscience. 1991;44:263–75.

Yu Z, Huang CX, Wang SY, Wang T, Xu L. Thyroid hormone predisposes rabbits to atrial arrhythmias by shortening monophasic action period and effective refractory period: results from an in vivo study. J Endocrinol Investig. 2009;32:253–7.

Yue BW, Huguenard JR. The role of H-current in regulating strength and frequency of thalamic network oscillations. Thalamus Relat Syst. 2001;1:95–103.

Zadikoff C, Munhoz RP, Asante AN, Politzer N, Wennberg R, Carlen P, Lang A. Movement disorders in patients taking anticonvulsants. J Neurol Neurosurg Psychiatry. 2007;78:147–51.

Zesiewicz TA, Elble R, Louis ED, Hauser RA, Sullivan KL, Dewey RB Jr, Ondo WG, Gronseth GS, Weiner WJ, Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2005;64:2008–20.

Chapter 3
Advances in the Genetics of Human Tremor

Fabio Coppedè

Abstract This chapter aims at describing the recent advances in the genetics of human tremor. Several human disorders are characterized by tremor as one of the possible symptoms, making it almost impossible to fully describe the genetic basis of each of them within the context of a single book chapter. Essential tremor (ET) and Parkinsonian tremor represent the most common forms of human tremor, and their genetics is fully described within the first sections of this chapter. Following the introduction, this chapter starts with a description of the genetics of Parkinson's disease (PD) given the great advances in our understanding during the last two decades. PD is characterized by resting tremor, rigidity, bradykinesia, and postural instability as well as several non-motor symptoms. Studies in PD families identified six well-validated causative genes for autosomal dominant or recessive forms of the disease and several genes for atypical parkinsonism (Blauwendraat et al., Lancet Neurol 19(2):170–178, 2020; Day and Mullin, Genes (Basel) 12(7):1006, 2021). Moreover, more than 90 independent genome-wide significant risk variants have been identified through genome-wide association studies (GWASs) for the sporadic (idiopathic) forms of the disease (Nalls et al., Lancet Neurol 18(12):1091–1102, 2019; Foo et al., JAMA Neurol 77(6):746–754, 2020). However, despite the continuous advance in our understanding of the genetics of Parkinsonian tremor, little is still known concerning essential tremor, the most common pathologic tremor in humans. Whole-genome and exome sequencing studies revealed several candidate genes possibly responsible for ET in a small number of families, but they likely represent private variants. A recent GWAS revealed five genome-wide significant loci associated with ET, and the search of ET genes is still ongoing (Jiménez-Jiménez et al., Pharmaceuticals (Basel) 14(6):516, 2021; Liao et al., JAMA Neurol 79(2):185–193, 2022). Tremor is often observed in other diseases, including ataxias and dystonias, and several examples of monogenic forms of these

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disorders are provided within the text. Moreover, this chapter covers the genetics of familial cortical myoclonic tremor with epilepsy, Roussy–Lévy syndrome, and Wilson disease's tremor.

Keywords Genetics · Tremor · Genome-wide association study (GWAS) · Parkinson's disease (PD) · Essential tremor (ET) · Spinocerebellar ataxia · Dystonia

3.1 Introduction

This chapter aims at describing the recent advances in the genetics of human tremor. Several human disorders are characterized by tremor as one of the possible symptoms, making it almost impossible to fully describe the genetic basis of each of them within the context of a single book chapter. Essential tremor (ET) and Parkinsonian tremor represent the most common forms of human tremor, and their genetics is fully described within the first sections of this chapter. Following the introduction, this chapter starts with a description of the genetics of Parkinson's disease (PD) given the great advances in our understanding during the last two decades. PD is characterized by resting tremor, rigidity, bradykinesia, and postural instability as well as several non-motor symptoms. Studies in PD families identified six well-validated causative genes for autosomal dominant or recessive forms of the disease and several genes for atypical parkinsonism (Blauwendraat et al. 2020; Day and Mullin 2021). Moreover, more than 90 independent genome-wide significant risk variants have been identified through genome-wide association studies (GWASs) for the sporadic (idiopathic) forms of the disease (Nalls et al. 2019; Foo et al. 2020). Despite the continuous advance in our understanding of the genetics of Parkinsonian tremor, little is still known concerning essential tremor, the most common pathologic tremor in humans. Whole-genome and exome sequencing studies revealed several candidate genes possibly responsible for ET in a small number of families, but they likely represent private variants. A recent GWAS revealed five genome-wide significant loci associated with ET, and the search of ET genes is still ongoing (Jiménez-Jiménez et al. 2021; Liao et al. 2022). Tremor is often observed in other diseases, including ataxias and dystonias, and several examples of monogenic forms of these disorders are provided within the text. Moreover, this chapter covers the genetics of familial cortical myoclonic tremor with epilepsy, Roussy–Lévy syndrome, and Wilson's tremor.

3.2 Genetics of Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, and advancing age is the major risk factor for this condition that, in industrialized countries, has a reported prevalence of about 1%

in people aged more than 60 years and of about 3% in those older than 80 years (Balestrino and Schapira 2020). Indeed, recent estimates suggest that over six million individuals are suffering from the disease worldwide, and because the world's population is aging the number of affected individuals is expected to more than double by 2040 (Dorsey and Bloem, 2018). The disease is clinically characterized by resting tremor, rigidity, bradykinesia, and postural instability as well as non-motor symptoms such as autonomic insufficiency, cognitive impairment, and sleep disorders. Some improvement can be achieved with levodopa and dopaminergic therapy, but there is currently no treatment that arrests the progression of the disease. Pathologically, PD is characterized by progressive and profound loss of neuromelanin containing dopaminergic neurons in the substantia nigra with the presence of eosinophilic, intracytoplasmic inclusions termed as Lewy bodies (LBs, containing aggregates of α-synuclein as well as other substances), and Lewy neurites in surviving neurons (Thomas and Beal 2011). The majority of PD cases are sporadic (idiopathic PD), likely arising from a combination of polygenic inheritance, environmental exposures, complex gene–environment interactions, and epigenetic dysregulation superimposed on slow and sustained neuronal dysfunction due to aging (Migliore and Coppedè 2009; Coppedè 2021). Familial PD forms account for only 5–15% of the cases, and to date rare variants in over 20 genes have been suggested to cause monogenic PD forms (Blauwendraat et al. 2020). Loci and genes that have been associated with monogenic PD were originally designated as "*PARK*" loci with a number representing the chronological order of their discovery. However, the relevance of many of these loci is heavily debated and some of them are no longer considered disease-causing ones, so that current recommendations are to use gene names in preference to numbered loci (Blauwendraat et al. 2020; Day and Mullin 2021). Well-established PD genes include autosomal dominant (*SNCA*, *LRRK2*, and *VPS35*) and recessive ones (*PRNK*, *PINK1*, and *DJ1*), as well as other genes leading to atypical parkinsonism (*ATP13A2*, *FBXO7*, *PLA2G6*, and *SYNJ1*). Large-scale sequencing projects and genome-wide association studies (GWASs) are currently helping to define the genetic landscape of PD (Fig. 3.1). While rare and highly penetrant variants in some genes account for monogenic forms of the disease, sporadic PD is likely resulting from interactions among combinations of more common variants with a smaller effect size, environmental risk factors, and aging. Indeed, more than 90 of such common variants have been identified by PD GWASs (Nalls et al. 2019; Foo et al. 2020). In addition, uncommon but not rare variants of certain genes, such as *GBA* and *LRRK2*, exert an intermediate risk for the disease.

3.2.1 Autosomal Dominant PD

3.2.1.1 SNCA

The *a-synuclein* gene (*SNCA*) on 4q21 was the first gene linked to monogenic PD, and alternative gene names are *PARK1* or *PARK4*. A *SNCA* mutation causing a

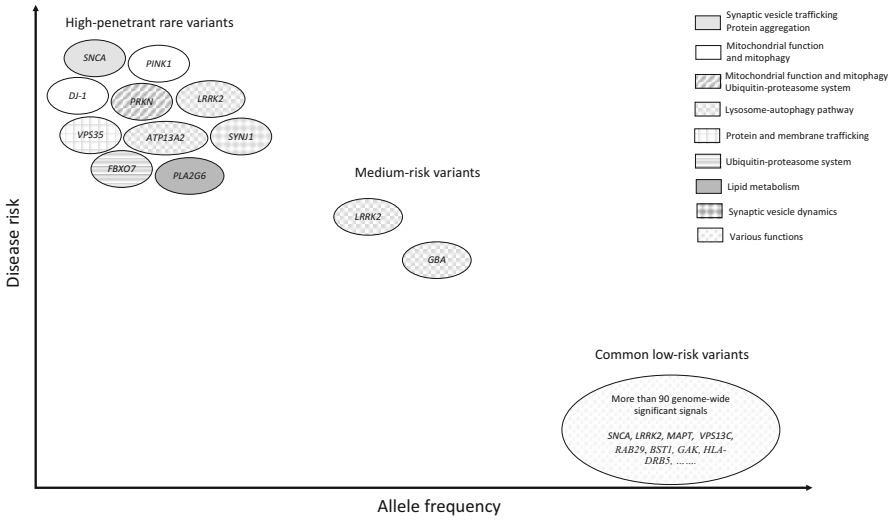

Fig. 3.1 The genetic landscape of Parkinson's disease: The graph shows genes linked to PD, grouped according to the allele frequencies of their variants and the associated risk for the disease. Rare and high-penetrant mutations of *SNCA*, *LRRK2*, *VPS35*, *PARKN*, *PINK1*, and *DJ1* genes account for monogenic autosomal dominant or recessive PD forms, and rare mutations of *ATP13A2*, *FBXO7*, *PLA2G6*, and *SYNJ1* are linked to atypical monogenic parkinsonism. Uncommon but not rare variants in *LRRK2* and *GBA* genes exert an intermediate risk for the disease, and more than 90 common low-risk variants of several genes have been identified through genome-wide association studies

p.A53T substitution was found to segregate with the disease in an Italian kindred and three unrelated families of Greek origin (Polymeropoulos et al. 1997). Another mutation in the *SNCA* gene, leading to a p.A30P substitution, was subsequently described in a small German family with PD (Krüger et al. 1998), and a third mutation resulting in a p.E46K substitution, in a Spanish family (Zarranz et al. 2004). A study in a large family identified a triplication of the *SNCA* gene as causative of PD (Singleton et al. 2003). Individuals from this family had four fully functional copies of *SNCA*. Other PD families have been subsequently described with *SNCA* duplication and a disease course less severe of that observed in carriers of *SNCA* triplication, suggesting the existence of a gene dosage effect (Chartier-Harlin et al. 2004). Particularly, *SNCA* triplications and the p.E46K mutation are more commonly associated with dementia than the p.A30P mutation and gene duplications. The p.A53T mutation has been associated with dementia and the presence of cortical LBs. Although *SNCA* has been the first PD gene identified, *SNCA* missense mutations and multiplications are both extremely rare causes of familial autosomal dominant parkinsonism (Nuytemans et al. 2010). α-Synuclein is expressed throughout the mammalian brain particularly in presynaptic nerve terminals, and mutated α-synuclein has an increased tendency to form aggregates critical to Lewy body formation. These fibrillar aggregates are the major component

of LBs in both familial and idiopathic PD, and aggregation of α-synuclein is thought to be a key event in dopaminergic neuronal cell death. The function of α-synuclein under normal physiological conditions is not yet fully elucidated, although there is evidence that implicates SNCA in neurotransmitter release and vesicle turnover at the presynaptic terminals (Abeliovich et al. 2000; Liu et al. 2004). Genetic polymorphisms in the *SNCA* gene have been consistently associated with PD risk, including a dinucleotide repeat sequence (Rep1) within the promoter region and several single nucleotide polymorphisms (SNPs) at the 3′ end of the gene (Maraganore et al. 2006; Kay et al. 2008; Mata et al. 2011). Moreover, *SNCA* has been among the genes most significantly associated with PD in GWAS (Pankratz et al. 2009; Satake et al. 2009; Simón-Sánchez et al. 2009; Edwards et al. 2010; Nalls et al. 2019; Foo et al. 2020). Meta-analysis of GWAS reveals that *SNCA* is a low-risk locus for idiopathic PD (Nalls et al. 2019), and there is evidence suggesting that *SNCA* alleles associated with increased PD risk are also correlated with higher α-synuclein expression, pointing again to a gene dosage effect (Fuchs et al. 2008). For example, GWASs identified a common *SNCA* variant in European populations (rs356182) that is associated with an increased risk for PD with an odds ratio of about 1.3 (Blauwendraat et al. 2020).

3.2.1.2 LRRK2

The leucine-rich repeat kinase 2 (*LRRK2*) gene maps on the PARK8 locus in 12q12 and was the second causal gene linked to autosomal dominant PD (Paisán-Ruíz et al. 2004; Zimprich et al. 2004). *LRRK2* encodes the protein dardarin which contains several domains including the catalytic domain of a tyrosine kinase, and whose name is derived from *dardara*, the Basque word for tremor. The precise physiological role of dardarin is unknown, but the presence of several domains suggests involvement in a wide variety of functions and, as a kinase, LRRK2 is almost certainly involved in signaling cascades, probably relating to cytoskeletal dynamics (Hardy 2010). Recent evidence suggests that LRRK2 is also involved in clathrin-mediated endocytosis (Heaton et al. 2020). All the identified pathogenic mutations occur in predicted functional domains. The most prevalent *LRRK2* mutation is a p.G2019S missense mutation occurring in 1–2% of PD patients of European origin, 20% of Ashkenazi Jewish patients, and approximately 40% of Arab Berbers with PD. The penetrance of this mutation is incomplete and variable (15–85%) and influenced by age, environment, and genetic background (Iwaki et al. 2020). Another frequent hotspot of *LRRK2* pathogenic mutations is the Arg1441 codon (Nuytemans et al. 2010). A p.G2385R mutation, originally identified as a putative pathogenic mutation in a Taiwanese PD family, was subsequently reported to be a common polymorphism and, probably, one of the most frequent genetic risk factors for PD in Asian populations (Farrer et al. 2007). Large GWASs have confirmed that *LRRK2* polymorphisms are well-validated PD risk factors in European and Asian populations (Nalls et al. 2019; Foo et al. 2020). For example, a common noncoding

variation (rs76904798) upstream of *LRRK2*, leading to increased *LRRK2* expression, is associated with increased PD risk with an odds ratio of 1.15 (Nalls et al. 2019).

3.2.1.3 VPS35

In 2011, a p.D620N mutation in the *VPS35* gene was identified as causative of autosomal dominant late-onset PD in Swiss and Austrian kindreds (Vilariño-Güell et al. 2011; Zimprich et al. 2011). VSP35 is a component of the retromer complex and mediates retrograde transport between endosomes and the trans-Golgi network. Recent studies have demonstrated that VPS35 and the retromer complex influence mitochondrial homeostasis, suggesting that the p.D620N mutation can perturb the maturation of endolysosomes and autophagy as well as membrane receptor recycling, and elicit mitochondrial dysfunction (Sassone et al. 2021).

3.2.2 Autosomal Recessive PD

3.2.2.1 PRKN

Homozygous deletions in *PRKN*, also known as *Parkin* or *PARK2*, were identified in Japanese families as causative of juvenile PD forms (Kitada et al. 1998). Subsequently, several *PARK* mutations, including missense mutations, frameshift mutations and exonic deletions and insertions, have been observed in PD families (Mata et al. 2004), and *PRKN* mutations are nowadays regarded as the most common cause of early-onset PD (EOPD) (Jia et al. 2022). Parkin is an ubiquitin E3 ligase preparing target proteins for their degradation mediated by the ubiquitin–proteasome system (Leroy et al. 1998). Moreover, parkin is involved in mitochondrial maintenance, is required for the repair of mitochondrial oxidative DNA damage, might be involved in mitochondrial cytochrome c release, and induces subsequent autophagy of dysfunctional mitochondria (Deng et al. 2008; Narendra et al. 2008; Poole et al. 2008; Rothfuss et al. 2009).

3.2.2.2 PINK1

Several mutations in the *PTEN-induced putative kinase 1* gene (*PINK-1*) on chromosome 1p35-36 (PARK6), encoding a protein which is mitochondrially located and whose loss of function is supposed to render neurons more vulnerable to cellular stress, have been linked to autosomal recessive EOPD (Valente et al. 2004). *PINK1* mutations, primarily missense mutations, structural variants, and nonsense mutations, cause mitochondrial deficits contributing to PD pathogenesis, and represent the second most common cause of EOPD (Jia et al. 2022). PINK1 is a kinase with an N-terminal mitochondrial targeting sequence, provides protection

against mitochondrial dysfunction and regulates mitochondrial morphology via fission/fusion machinery. PINK1 also acts upstream of parkin in a common pathway. Indeed, studies have described PINK1/parkin function in the maintenance of mitochondrial quality via autophagy (Kawajiri et al. 2011).

3.2.2.3 PARK7

Mutations in *PARK7*, also known as *DJ-1*, including exonic deletions and point mutations, have been associated with EOPD (van Duijn et al. 2001; Lockhart et al. 2004). DJ-1 is a mitochondrial protein involved in the protection against oxidative stress, and it was shown that parkin, PINK1, and DJ-1 form a complex to promote ubiquitination and degradation of parkin substrates, including parkin itself (Xiong et al. 2009). Evidence indicates that DJ-1 works in parallel to the PINK1/parkin pathway to maintain mitochondrial function in the presence of an oxidative environment (Thomas et al. 2011). Collectively, *PRKN*, *PINK1*, and *PARK7* code for proteins required for the ubiquitin-proteasome system and for the maintenance of mitochondria. Their loss of function causes autosomal recessive PD forms that often show early-onset and variable results with respect to Lewy body pathology in the affected brain regions (Jia et al. 2022).

3.2.3 Other Genes Linked to Monogenic PD Forms

Several other genes have been linked to monogenic PD forms but either result in complex or atypical forms of the disease or have less robust evidence for pathogenicity (Blauwendraat et al. 2020). Indeed, the field of PD genetics is in constant flux, with candidates being confirmed, refuted, or newly identified in rapid succession (Wittke et al. 2021). Well-established or high confident PD genes leading to autosomal recessive atypical forms include *ATP13A2*, *FBXO7*, *PLA2G6*, *SYNJ1*, *DNAJC6*, and *VPS13C* (Blauwendraat et al. 2020; Wittke et al. 2021; Jia et al. 2022). Biallelic *ATP13A2* mutations have been linked to an autosomal recessive form of early-onset parkinsonism with pyramidal degeneration (Ramirez et al. 2006). A recent analysis of 19 families with *ATP13A2* mutations revealed a median age at onset of 14 years and atypical parkinsonism in 83% of the carriers, followed by cognitive decline in 75% of them, and other common signs such as vertical gaze palsy, spasticity/pyramidal signs, mini-myoclonus, and psychotic signs and symptoms in almost 50% (Wittke et al. 2021). Functional studies suggest that ATP13A2 deficiency impairs lysosomal polyamine export (van Veen et al. 2020). The *FBXO7* gene encodes for a member of the F-box family of proteins, all of which may have a role in the ubiquitin–proteasome protein-degradation pathway (Shojaee et al. 2008; Di Fonzo et al. 2009) and has been linked to autosomal recessive, juvenile/early-onset parkinsonian-pyramidal syndrome (Di Fonzo et al. 2009). A recent analysis of 26 *FBXO7* mutation carriers originating from ten families showed

that the mean age at onset was 17 years, atypical parkinsonism signs were present in 92% of them and spasticity/pyramidal signs in 73% (Wittke et al. 2021). The *PLA2G6* gene encodes a calcium-independent group VI phospholipase A2 and has been linked to autosomal recessive dystonia-parkinsonism, a disease characterized by levodopa-responsive parkinsonism and dystonia (Paisán-Ruiz et al. 2009, 2010). A recent analysis of 50 patients with *PLA2G6*-dystonia-parkinsonism revealed a mean age of 26 years old at PD diagnosis; moreover, neuropsychiatric symptoms such as depression, anxiety, or personality changes preceded motor symptoms in almost half of the patients (Vela-Desojo et al. 2022). The *SYNJ1* gene codes for polyphosphoinositide phosphatase synaptojanin 1 which has been implicated in synaptic vesicle dynamics, including endocytosis and recycling, and causes autosomal recessive, early-onset parkinsonism (Krebs et al. 2013; Quadri et al. 2013). In addition to parkinsonism, the most commonly reported features in *SYNJ1* mutant carriers were dystonia, gait difficulties, cognitive decline, postural instability, hypomimia, and dysarthria/anarthria (Wittke et al. 2021). *DNAJC6* encodes for auxilin 1, a protein involved in clathrin-mediated synaptic vesicle endocytosis, and *DNAJC6* mutations have been initially described in two families with autosomal recessive juvenile parkinsonism (onset age <11 years), prominent atypical signs, poor or absent response to levodopa, and rapid progression (Edvardson et al. 2012; Koroglu et al. 2013). Subsequently, *DNAJC6* mutations have been found also in early-onset PD cases, characterized by symptoms onset in the third-to-fifth decade of life and slow disease progression (Olgiati et al. 2016). The *VPS13C* gene codes for a member of the VPS13 family of proteins, involved in lipid transport between the endoplasmic reticulum and other organelles, and *VPS13C* gene mutations have been identified in autosomal recessive, early-onset forms of parkinsonism (Lesage et al. 2016; Rudakou et al. 2020). In addition to the above-described genes causing autosomal recessive EOPD forms, mutations in *DCTN1* cause Perry syndrome, a rare autosomal dominant disorder characterized by rapidly progressive early-onset parkinsonism, central hypoventilation, weight loss, insomnia, and depression (Richardson et al. 2020). Several other genes have been linked to typical or atypical parkinsonism, as well as to complex neurological disorders that include parkinsonism as part of their symptoms. For example, *POLG* mutations may cause variable clinical manifestations, including parkinsonism, and *CHCHD2* mutations can cause typical parkinsonism. However, for several of these genes, including *LRP10*, *TMEM230*, *DNAJC13*, *EIF4G1*, *GIGYF2*, *HTRA2*, and *UCHL1*, the pathogenetic role is still debated, some are no longer considered PD genes or further validation is required prior to be considered PD genes (Blauwendraat et al. 2020; Jia et al. 2022).

3.2.4 Susceptibility Genes

Most of PD occurs as apparently sporadic forms and GWASs have revolutionized our efforts to find loci at which common, normal genetic variability contributes to

disease risk. The first GWAS loci for PD were identified in 2009 using data from almost 5000 patients and 9000 controls (Simón-Sánchez et al. 2009). In 2019, a large GWAS including more than 37.000 patients, 18.600 proxy cases (individuals with a first relative with PD) and 1.4 million controls, allowed the identification of 90 independent genome-wide significant risk signals across 78 loci (Nalls et al. 2019). Additional PD loci have been identified in a subsequent GWAS including more than 65.000 cases and almost 1.9 million controls (Foo et al. 2020). Indeed, common variants of small effect size in *SNCA*, *LRRK2*, *VPS13C*, *MAPT*, *RAB29*, *BST1*, *GAK*, *HLA-DRB5*, and many other genes have been associated with increased PD risk (Nalls et al. 2019; Blauwendraat et al. 2020; Jia et al. 2022). Notably, the *GBA* gene is the major genetic risk factor for PD and will be further discussed in the next section.

3.2.4.1 GBA

Mutations in the *GBA* gene encoding glucocerebrosidase, the enzyme deficient in the lysosomal glycolipid storage disorder Gaucher disease (GD: an autosomal recessive disorder with multisystemic manifestations, including involvement of the liver, spleen, bone marrow, lungs, and nervous system), are associated with the development of PD and other Lewy body disorders (Velayati et al. 2010). The observation that a small subset of GD patients develop parkinsonism with brainstem or diffuse Lewy-related pathology (Tayebi et al. 2003), and that relatives of patients with GD have an increased incidence of parkinsonism (Halperin et al. 2006), led researchers to investigate *GBA* mutations as a possible risk factor for PD. Several large-scale genetic studies demonstrated that heterozygote *GBA* variants are the most important genetic risk factor for PD. More than 100 *GBA* variants have been associated with PD, with an overall odds ratio of about 3.5–6 (Sidransky et al. 2009; Gegg et al. 2022). However, while the odds ratio for "mild" risk variants, such as the common p.N370S variant, is lower than 5, certain high-risk variants, such as the p.L444P one, confer a greater risk for PD. Overall, the estimated lifetime risk of developing PD in heterozygous carriers of a *GBA* variant ranges from 7.6% at age 50 years to 30% at age 80, and is influenced by other genetic, environmental, and age-related factors. Indeed, *GBA* variants are the most common genetic risk factor for PD. The accumulation of α-synuclein following loss of glucocerebrosidase activity and subsequent lysosomal dysfunction in neurons is well established. However, the mechanisms by which this occurs warrant further investigation (Gegg et al. 2022).

3.3 Genetics of Essential Tremor

Essential tremor (ET) is one of the most common movement disorders in adults and the most common pathologic tremor in humans. The median disease prevalence

is estimated to be 0.4% across all ages, and the mean prevalence 0.67% (Louis and McCreary 2021). However, ET prevalence increases markedly with age, with recent estimates suggesting a 74% increase for every decade increase in age, reaching more than 20% in nonagenarians (Louis and Ferreira 2010; Louis and McCreary 2021). ET shows a bimodal age of onset, with a smaller peak in the second decade of life and a larger peak in the sixth decade (Brin and Koller 1998). Childhood-onset ET is usually hereditary and three times more frequent in males than in females (Ferrara and Jankovic 2009). The disease is characterized by an action tremor with mixed postural and kinetic elements. The postural tremor is commonly seen in the hands and the kinetic tremor is brought out by action, such as writing, eating, or pouring a cup of water (Dalvi and Mercury 2011). ET is a heterogeneous condition with variable clinical expression in affected patients. While the hands are most commonly affected, many patients have a head tremor as well. Approximately 90–95% of the patients have tremor in their upper extremities, 30–34% have a head tremor, 12–20% a voice tremor, and 5–10% a face or trunk tremor. Almost 10% of the patients have a lower limb tremor (Whaley et al. 2007; Dalvi and Mercury 2011). Non-motor symptoms including mild cognitive changes, changes in personality, anxiety, and depression are more frequent in ET patients than in normal age-matched controls (Zesiewicz et al. 2010). According to recent classification criteria, ET is defined as an isolated tremor syndrome manifesting as an action tremor of bilateral upper extremities for a minimum of 3 years duration, in the absence of any other neurological signs such as parkinsonism, ataxia, or dystonia. Tremor involving the voice, head, and lower extremities may or may not be present. ET patients with additional neurological signs (dystonia, rest tremor, impaired tandem gait) are now categorized as "ET plus" (Lenka and Jankovic 2021). The analysis of postmortem ET brains revealed that 75% of them are characterized by cerebellar changes, including loss of Purkinje cells and increase in the number of axonal swellings, termed "torpedoes." Lewy bodies were observed in the locus coeruleus of the remaining 25% of the brains (Louis et al. 2007). Overall, ET can be considered a cerebellar disorder with pathologic changes affecting either the cerebellum itself or neurons that synapse with Purkinje cells (Dalvi and Mercury 2011). Studies in twins revealed elevated concordance among monozygotic twins, suggesting that the disease has a high heritability (Lorenz et al. 2004). Most of the studies indicate that ET is a familial disorder in 40–50% of the cases, and the disease is often inherited in a manner suggesting an autosomal dominant genetic pattern with incomplete penetrance. A family history of ET appears to correlate with younger age at onset, and first-degree relatives of ET patients have a fivefold increased risk to develop the disease than normal controls. Non-familial "sporadic" ET cases are known and might result from either low-penetrant autosomal dominant loci or from multifactorial inheritance (Deng et al. 2007). Linkage analyses revealed at least four loci for familial ET in Iceland and North American families located at chromosomes 3q13, 2p22-p25, 6p23, and 5q35. However, the causative gene has yet to be identified (Dalvi and Mercury 2011; Jiménez-Jiménez et al. 2021). Whole-genome/exome sequencing approaches have revealed several additional putative genes for ET, but lack of replication in other families suggests that they are

likely private variants (Jiménez-Jiménez et al. 2021). GWASs have also identified putative ET loci, but only a recent GWAS including 7.177 ET patients and 475.877 controls revealed five independent genome-wide significant loci that explained approximately 18% of ET heritability (Liao et al. 2022). The results of this GWAS suggest that a portion of ET heritability can be explained by common genetic variants (Liao et al. 2022). Moreover, genetic factors alone do not explain all cases of ET, and several environmental factors including exposure to neurotoxic compounds such as β-carboline alkaloids and ethanol, as well as pesticide and lead exposure, are potential ET risk factors, while smoking and antioxidant intake may be protective (Ong et al. 2019).

3.3.1 Linkage Studies

In 1997, the first ET locus (ETM1) was mapped to chromosome 3q13 in 75 members of 16 Icelandic families (Gulcher et al. 1997). A Ser9Gly variant in the dopamine D3 receptor (*DRD3*) gene, located in the ETM1 locus, was subsequently associated with disease risk and age at onset (Jeanneteau et al. 2006). Subsequent studies failed to find a significant association of the *DRD3* variant with ET, suggesting that it is unlikely to be a causal factor for ET (Lorenz et al. 2009). The ETM2 locus was mapped to a 9.1 cM region on chromosome 2p22-p25 (Higgins et al. 1997) in a large American family of Czech descent. Subsequent studies suggested an association between ET and an A265G substitution in the HS1-binding protein 3 gene (*HS1BP3*) mapping within the ETM2 locus (Higgins et al. 2005). However, the association with the *HS1BP3* gene was not replicated by other investigators (Deng et al. 2005; Shatunov et al. 2005). Linkage to ETM1 and ETM2 loci was not evident in several ET families suggesting genetic heterogeneity in ET. A third ET locus was mapped to chromosome 6p23. Several genes within this locus have been investigated as candidates, but none of them was found to bear pathogenic mutations (Shatunov et al. 2006). No linkage of these three loci with familial ET was found in other studies (Aridon et al. 2008; Novelletto et al. 2011; Zahorakova et al. 2010), suggesting genetic heterogeneity for ET. The analysis of 48 essential tremor patients from five pedigrees revealed another locus on chromosome 5q35 linked to essential tremor, but exome sequencing did not identify a potential causative variant in this region (Hicks et al. 2016).

3.3.2 Whole-Genome and Exome Sequencing Studies

Whole-genome and exome sequencing studies revealed several candidate genes possibly responsible for ET in a small number of families, including *FUS* (designated as *ETM4*), *HTRA2*, *TENM4* (designated as *ETM5*), *SORT1*, *SCN11A*, *NOTCH2NLC* (designated as *ETM6*), *NOS3*, *KCNS2*, *HAPLN4*, *USP46*, *CACNA1G*, *SLIT3*,

CCDC183, *MMP10*, and *GPR151*. However, mutations of these genes were found only in singular families, suggesting that they could probably represent private variants (reviewed in Jiménez-Jiménez et al. 2021).

3.3.3 GWASs

The first GWAS in ET identified a sequence variant (rs9652490) of the *LINGO1* gene to be a risk factor in European and American populations (Stefansson et al. 2009). Subsequent GWASs identified variants of *SLC1A2*, *STK32B*, *PPARGC1A*, and *CTNNA3*, as possible ET risk factors, but further GWASs failed to replicate these findings (Thier et al. 2012; Müller et al. 2016; Houle et al. 2017). Recently, a GWAS including 7.177 ET patients and 475.877 control individuals revealed five independent genome-wide significant loci that explained approximately 18% of ET heritability. Functional analyses found significant enrichment in the cerebellar hemisphere, cerebellum, and axonogenesis pathways (Liao et al. 2022). Overall, the genetic etiology of ET remains still largely elusive, and the search of ET genes is still ongoing.

3.4 Tremor in Ataxias

The ataxias are a heterogeneous group of progressive neurodegenerative disorders with ataxia as the leading symptom. Cerebellar ataxias can be divided into acquired, sporadic and hereditary forms (Krygier and Mazurkiewicz-Bełdzińska 2021). Inherited ataxias include autosomal dominant spinocerebellar ataxias (SCAs), autosomal recessive cerebellar ataxias, episodic ataxias (EA), and X-linked ataxias (Manto and Marmolino 2009; Krygier and Mazurkiewicz-Bełdzińska 2021). Tremor is often observed in ataxias (Magrinelli et al. 2020). The aim of this section of this chapter is the discussion of several of the best-known examples of cerebellar ataxias characterized by tremor as one of the symptoms (Table 3.1).

3.4.1 SCA2 and SCA3

Parkinsonism, dystonia, and postural tremor are particularly prevalent in SCAs types 2 (SCA2) and 3 (SCA3), caused by abnormal CAG trinucleotide repeat expansion of *ATXN2* and *ATXN3* genes, respectively. SCA2 is characterized by a broad group of progressive features, including gait ataxia, postural instability, cerebellar dysarthria, dysmetria, and dysdiachokinesia, as well as non-cerebellar manifestations including slow saccadic eye movements, peripheral neuropathy, cognitive decline, dopamine-responsive parkinsonism, dystonia, and chorea (Kry-

Table 3.1 Some examples of loci and genes associated with inherited ataxias

Designation	Locus	Gene	Inheritance	Function or probable function
SCA2	12q24	*ATXN2*	AD	Ataxin-2, RNA processing
SCA3	14q21	*ATXN3*	AD	Ataxin-3, deubiquitinating enzyme, ubiquitin–proteasome system
SCA7	3p14.1	*ATXN7*	AD	Ataxin-7, transcription factor that appears to be critically important for chromatin remodeling at the level of histone acetylation and deubiquitination
SCA12	5q32	*PPP2R2B*	AD	Regulatory subunit of protein phosphatase 2A
SCA15/SCA16	3p26.1	*ITPR1*	AD	Inositol 1,4,5-triphosphate receptor 1, mediates calcium release from endoplasmic reticulum
SCA20	11q12	Unknown	AD	Unknown
SCA27	13q34	*FGF14*	AD	Fibroblast growth factor 14, involved in regulation of voltage-gated calcium channel activity, synaptic plasticity, and neurogenesis
FXTAS	Xq27.3	*FMR1*	X-linked	Fragile X mental retardation 1 gene, development of synapses
CA	19p13.3	*ATCAY*	AR	Caytaxin, glutamate synthesis
AOA1	9p13.3	*APTX*	AR	DNA repair
AOA2	9q34.13	*SETX*	AR	DNA/RNA helicase
AT	11q22-q23	*ATM*	AR	DNA repair

gier and Mazurkiewicz-Bełdzińska 2021). The disease is caused by a CAG repeat expansion of *ATNX2*, which can expand in families over successive generations resulting in earlier onset age and faster progression. Affected individuals have alleles with 32 or more CAG trinucleotide repeats, resulting in polyglutamine tract expansion in the protein (Lastres-Becker et al. 2008). Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3), is the most common form of spinocerebellar ataxia worldwide, caused by CAG trinucleotide repeat expansion in *ataxin-3* (*ATXN3*), coding a conserved and ubiquitous protein known to bind polyubiquitin chains and to function as a deubiquitinating enzyme. Affected individuals have alleles with 52 or more trinucleotide repeats (Matos et al. 2011). The parkinsonian phenotype of SCA2 and SCA3 is often observed in Asians (Lu et al. 2004; Kim et al. 2007).

3.4.2 SCA7

Spinocerebellar ataxia type 7 (SCA7) results from CAG repeat expansion in the *ATXN7* gene on chromosome 3p14.1 and is characterized by progressive ataxia and variable age at onset, degree of severity, and rate of progression among and

within families. Associated symptoms can include palatal tremor, cone-rod retinal dystrophy, and vision loss (Magrinelli et al. 2020; Krygier and Mazurkiewicz-Bełdzińska 2021).

3.4.3 SCA12

Spinocerebellar ataxia type 12 (SCA12) is a late-onset, autosomal dominant, slowly progressive disorder. Action tremor is the usual presenting sign, often starting in the fourth decade. At disease onset, SCA12 manifests characteristic action tremors in the upper limbs. Disease progression is slow, and patients display varied clinical manifestations, including gait ataxia, abnormal eye movements, parkinsonism, dystonia, hyperreflexia, and psychiatric and cognitive manifestations (Manto 2010; Srivastava et al. 2017; Magrinelli et al. 2020). The disease is caused by a CAG repeat expansion in *PPP2R2B*, a gene that encodes Bβ, a regulatory subunit of protein phosphatase 2A (PP2A). Alleles with 43 or more CAG repeats are observed in SCA12 patients (Srivastava et al. 2017). The CAG expansion in *PPP2R2B* correlates with increased Bβ expression and does not result in polyglutamine production. SCA12 may be considered in patients who present with action tremor and later develop signs of cerebellar and cortical dysfunction (O'Hearn et al. 2011).

3.4.4 SCA15 and SCA16

Spinocerebellar ataxia type 15 (SCA15), formerly known as SCA15/SCA16, is rare and slowly progressive dominantly inherited ataxia. Its main distinguishing characteristic is tremor, often affecting the head, which is seen in about half of the affected individuals, and which may be the presenting feature (Storey and Gardner 2012). The disease is due to various deletions of the inositol 1,4,5-triphosphate receptor 1 gene (*ITPR1*) on chromosome 3. "SCA16" has been shown to be due to an *ITPR1* mutation and has now been subsumed into SCA15 (Iwaki et al. 2008).

3.4.5 SCA20

Spinocerebellar ataxia type 20 (SCA20) is a very rare slowly progressive dominantly inherited disorder reported in individuals from a large Anglo-Celtic family from Australia. Its distinguishing clinical features, each present in most affected persons, are palatal tremor, and a form of dysphonia resembling spasmodic dysphonia. The responsible locus was mapped in the pericentric region of chromosome 11 (Knight et al. 2004), but the specific gene(s) underlying SCA20 have not yet been identified (Müller 2021).

3.4.6 SCA27

Spinocerebellar ataxia type 27 (SCA27) is characterized by disease onset in late childhood/early adulthood, and symptoms including slowly progressive cerebellar ataxia, early-onset tremor, orofacial dyskinesia frequently in association with ocular problems, psychiatric symptoms, and cognitive deficits (Müller 2021). The disease results from dominant mutations of the *FGF14* gene, on chromosome 13q34 (van Swieten et al. 2003). FGF14 controls channel gating, axonal targeting and phosphorylation in neurons effecting excitability. It is also required for synaptic transmission, plasticity, and neurogenesis (Müller 2021).

3.4.7 Fragile X-Associated Tremor/Ataxia Syndrome

The fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder affecting mainly men over the age of 50 years. The disease is caused by a CGG repeat expansion in the premutation range (55–200) in the fragile X mental retardation 1 (*FMR1*) gene whose full mutation causes the fragile X syndrome (FXS), the most common cause of inherited mental retardation. Major signs are cerebellar gait ataxia, intention tremor, frontal executive dysfunction, and global brain atrophy. Other frequent findings are parkinsonism, peripheral neuropathy, psychiatric symptoms, and autonomic dysfunction. Affected females have a less severe disease, and some symptoms different from that of men, for example, muscle pain (Leehey 2009).

3.4.8 Others

As discussed in the Introduction of this section tremor is often observed in several ataxias, including other SCAs and recessive ataxias, and not limited to the above detailed examples. Early-onset hypotonia and nonprogressive axial cerebellar ataxia, associated with nystagmus, intention tremor, and dysarthria characterize Cayman ataxia (CA). The name derives from the fact that the disease has been initially found in the Grand Cayman Island. CA is an autosomal recessive disease caused by mutation of *ATCAY*, which codes for caytaxin, a protein involved in glutamate synthesis and in synaptogenesis of cerebellar granular neurons and Purkinje cells (Hayakawa et al. 2007). More recently, CA resulting from *ATCAY* mutation has been reported also outside of the Grand Cayman Island, in a Pakistani family (Manzoor et al. 2018). Tremor is also observed in other autosomal recessive ataxias, such as those caused by defects of DNA repair genes (Gueven et al. 2007; Embiruçu et al. 2009). Ataxia with oculomotor apraxia type 1 (AOA1) is a condition characterized by involuntary movements (chorea and dystonia) and/or

progressive global ataxia, with dysarthria associated with hands and head tremor. The disease is caused by mutation in the *APTX* gene which encodes aprataxin, a nuclear protein involved in single-strand DNA repair. Ataxia with oculomotor apraxia type 2 (AOA2) is characterized by global progressive ataxia with onset usually between 8 and 25 years of age. Dystonia, head and postural tremor, chorea, dysphagia, pes cavus, and scoliosis are occasionally seen. The disease is caused by autosomal recessive mutations of *SETX* encoding senataxin, a DNA/RNA helicase involved in RNA processing and DNA repair. Peripheral neuropathy and movement disorder, as tremor or choreoathetosis, are seen after 5 years of age in ataxia–telangiectasia (AT), a recessive disorder caused by mutations of the *ATM* gene that encodes for a serine/threonine kinase responsible for DNA repair during the cell cycle (Gueven et al. 2007).

3.5 Familial Cortical Myoclonic Tremor with Epilepsy

Familial cortical myoclonic tremor with epilepsy (FCMTE), also referred to as familial adult myoclonic epilepsy (FAME), benign adult familial myoclonic epilepsy (BAFME) or autosomal dominant cortical myoclonus and epilepsy (ADCME), refers to a clinical entity first described in Japan and subsequently in more than 100 families worldwide and characterized by postural myoclonic tremor of the distal limbs, familial history of epilepsy, a rather benign outcome, and autosomal dominant inheritance (Regragui et al. 2006; van den Ende et al. 2018). Seven loci for FCMTE have been reported (Table 3.2), but the genetic variants underlying the disorder have remained elusive for several years and identified only recently. Intronic pentanucleotide repeat expansions composed of mixed TTTCA/TTTTA repeats in the *SAMD12* gene have been identified as the cause of FCMTE1 in Japanese and Chinese populations. *SAMD12* codes for the sterile alpha motif domain-containing protein 12, a protein predicted to be involved in transmembrane receptor protein tyrosine kinase signaling pathway (Ishiura et al. 2018; Cen et al. 2018; Zeng et al. 2019; Lei et al. 2019). Subsequently, ATTTC repeat expansions in the first intron of *STARD7* was identified as the cause of FCMTE2. *STARD7* codes for the protein StAR-related lipid transfer domain containing 7, a phosphatidylcholine-specific lipid transfer protein essential for the maintenance of mitochondrial membrane composition and dynamics (Corbett et al. 2019). Unstable TTTTA/TTTCA expansions in *MARCH6* have been associated with FCMTE3; *MARCH6* codes for membrane-associated ring-CH-type finger 6, a member of a family of membrane-associated E3 ubiquitin ligases (Florian et al. 2019). FCMTE4 was linked to chromosome 3q26.32-3q28 in a large FCMT family from Thailand, and insertions of the intronic TTTCA repeats in *YEATS2*, coding a protein involved in histone acetylation, were subsequently identified as the causative mechanism (Yeetong et al. 2019). Pentanucleotide repeat expansions have been also linked to FCMTE6 and FCMTE7, and particularly a TTTCA repeat expansion in the upstream noncoding region of exon 1 of the *TNRC6A* gene on

Table 3.2 Loci linked to familial cortical myoclonic tremor with epilepsy

Designation	Locus	Gene	Inheritance	Function or probable function
FCMTE1	8q23.3-q24.11	*SAMD12*	AD	Involved in transmembrane receptor protein tyrosine kinase signaling pathway
FCMTE2	2p11.1-q12.2	*STARD7*	AD	Phosphatidylcholine-specific lipid transfer protein essential for the maintenance of mitochondrial membrane composition and dynamics
FCMTE3	5p15.31-p15	*MARCH6*	AD	Membrane-associated E3 ubiquitin ligase
FCMTE4	3q26.32-3q28	*YEATS2*	AD	Member of a complex involved in acetylation of histones H3 and H4
FCMTE5	1q32.1	*CNTN2*	AR	Proliferation, migration, and axon guidance of neurons in the developing cerebellum
FCMTE6	16p12.1	*TNRC6A*	AD	Plays a role in RNA-mediated gene silencing by both micro-RNAs and short interfering RNAs
FCMTE7	4q32.1	*RAPGEF2*	AD	Guanine nucleotide exchange factor that links cell surface receptors and Rap/Ras GTPases in intracellular signaling cascades

chromosome 16p12.1 (FCMTE6), and a TTTCA repeat expansion in the *RAPGEF2* on chromosome 4q32.1 (FCMTE7) were observed in Japanese families, overall suggesting that pentanucleotide repeat expansions are a common causal mechanism for autosomal dominant cortical myoclonic tremor with epilepsy (Ishiura et al. 2018). One exception is FCMTE5 that was reported in a consanguineous Egyptian family and characterized by onset of seizures in adolescence, followed by the development of cortical myoclonic tremor later in life. The disease showed an autosomal recessive inheritance pattern, patients in this family conformed to the core criteria of FCMTE but some unusual features were also present, and the disease was caused by a homozygous frameshift mutation in the *CNTN2* gene (Stogmann et al. 2013).

3.6 Dystonic Tremor

Dystonia is a hyperkinetic movement disorder characterized by sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. According to a consensus statement of the Movement Disorder Society (MDS) expert members, dystonia is defined as “a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal and often repet-

itive movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation" (Albanese et al. 2013). It also further classifies dystonia into two main axes: axis 1, clinical characteristics, and axis 2, etiology. Axis 1 takes into consideration age at onset, body distribution, the temporal pattern of the hyperkinetic movement, and associated features, that is, if the dystonia is isolated, combined, or complex. In isolated dystonia, dystonia is the only motor feature except for tremor, in combined dystonia, the dystonia is combined with other movement disorders such as myoclonus, parkinsonism, and others, while complex dystonia is accompanied by neurologic or systemic manifestations beyond movement disorders. Axis 2 defines whether dystonia is inherited, acquired, or idiopathic (di Biase et al. 2022). Inherited dystonias show genetic heterogeneity, including autosomal dominant, autosomal recessive, X-linked, and mitochondrial forms (Müller 2009; di Biase et al. 2022). According to the Human Genome Organization (HUGO) nomenclature, genetic loci for dystonia are named using a DYT prefix followed by a number representing the chronological order of their discovery, that is, DYT1-DYTn. However, the MDS task force has recently proposed a novel nomenclature plan in which pure dystonia is designated with a DYT prefix followed by the gene name (e.g., DYT1 becomes DYT-*TOR1A*), while dystonia combined with parkinsonism or ataxia would be designated as DYT/PARK or DYT/SCA, respectively, each followed by the gene name (e.g., DYT5a becomes DYT/PARK-*GCH1*) (Mencacci and Jinnah, 2019). Tremor has been reported as a general manifestation in dystonias. Dystonic tremor manifests as a rhythmic, intermittent, patterned movement in body regions which are primarily affected or not by dystonia (Magrinelli et al. 2020). Recently, Pandey et al. (2021) reviewed the literature to assess the prevalence and clinical characteristics of tremor in different types of primary monogenic dystonia, observing that tremor has been reported in at least 15 different monogenic dystonias and ranges in prevalence according to the different monogenic subtype (Pandey et al. 2021). Table 3.3 shows some of the best-known genes associated with primary monogenic dystonias in which tremor is a common feature.

3.6.1 Dominant Dystonias

Tremor has been observed in several autosomal dominant dystonias. For example, tremor has been reported in 66% of patients with dystonia 24 (DYT24 or DYT-*ANO3*) an autosomal dominant cranio-cervical dystonia resulting from mutations in the *ANO3* gene, coding for anoctamin-3, a transmembrane protein that belongs to a family of calcium-activated chloride channels (Charlesworth et al. 2012; Pandey et al. 2021). Dystonia 6 (DYT6 or DYT-*THAP1*) is caused by mutations of the transcription factor THAP1, and tremors ranging from mild, asymmetrical, rest, and postural bilateral upper limb to occasional head and lower limb tremors have been reported 18% of the patients (Fuchs et al. 2009; Pandey et al. 2021).

Table 3.3 Some examples of loci and genes associated with inherited dystonias

Designation	Locus	Gene	Inheritance	Function or probable function
DYT1	9q34	*TOR1A*	AD	ATPase with chaperone functions
DYT2	1p35.1	*HPCA*	AR	Neuron-specific Ca (2+)-binding protein
DYT3	Xq13.1	*TAF1*	X-linked R	Tata binding protein associated factor
DYT5a	14q22.1-q22.2	*GCH1*	AD	Dopamine synthesis
DYT5b	11p15.5	*TH*	AR	Dopamine synthesis
DYT6	8p11.21	*THAP1*	AD	Transcription factor that regulates the expression of *TOR1A*
DYT16	2q31.2	*PRKRA*	AR	Protein kinase
DYT24	11p14.3-p14.2	*ANO3*	AD	Calcium-activated chloride channels
DYT25	18p11.21	*GNAL*	AD	Stimulatory alpha-subunit of G proteins

Dystonia 25 (DYT 25 or DYT-*GNAL*) is an autosomal dominant neurologic disorder characterized by adult onset of focal dystonia, usually involving the neck. Tremor is reported to occur in the head and upper limbs and has been reported in 12% of the patients. The disease is caused by mutations of the *GNAL* gene that encodes a stimulatory alpha-subunit of G proteins with high expression in the basal ganglia (Fuchs et al. 2013; Pandey et al. 2021). Tremor has been also observed in 11% of the patients with dystonia 1 (DYT1 or DYT-*TOR1A*), an early-onset primary dystonia caused by mutations in the *TOR1A* gene encoding the protein torsin A, a member of a superfamily of ATPases with chaperone functions (Ozelius et al. 1997; Pandey et al. 2021). Concerning dystonias combined with parkinsonism, postural tremor was observed in 18% of the patients with dystonia 5a (DYT5a or DYT/PARK-*GCH1*), a rare autosomal dominant dystonia-parkinsonism caused by mutations of *GCH1*, a gene that codes for GTP-cyclohydrolase I, essential for the synthesis of dopamine (Ichinose et al. 1994; Pandey et al. 2021).

3.6.2 Recessive Dystonias

Bilateral upper limb tremors and occasionally head tremor have been reported in 100% of patients with dystonia 2 (DYT2 or DYT-*HPCA*), an autosomal recessive dystonia due to mutations in the *HPCA* gene on 1p35.1 coding for hippocalcin, a member of a family of neuron-specific Ca (2+)-binding proteins found in the retina and brain. However, the analysis included only three patients, so that the complete presence of tremor should be taken with caution (Charlesworth et al. 2015; Pandey et al. 2021). Among combined dystonias, tremor has been reported in 44% of the patients with dystonia 5b (DYT5b or DYT/PARK-*TH*), caused by mutations of the tyrosine hydroxylase (*TH*) gene on the short arm of chromosome 11, resulting in lack of the tyrosine hydroxylase enzyme leading to impaired conversion of tyrosine

into L-dopa (Verbeek et al. 2007). Tyrosine hydroxylase is a rate-limiting enzyme in dopamine biosynthesis and missense mutations in both alleles of the *TH* gene cause dopamine-related phenotypes, including dystonia and infantile Parkinsonism. Dystonia 16 (DYT16 or DYT-*PRKRA*) was observed in seven Brazilian patients and linked to mutations of the gene *PRKRA*, encoding a protein kinase, interferon-inducible double-stranded RNA-dependent activator. Parkinsonism was observed in four of the seven patients (Camargos et al. 2008), and tremor has been reported in 17% of DYT16 patients. X-linked recessive dystonia or dystonia 3 (DYT3 or DYT-*TAF1*) is an adult-onset dystonia often accompanied by parkinsonism, resulting from recessive mutations of *TAF1* on chromosome Xq13.1 (Makino et al. 2007). Tremor has been reported in 4% of DYT3 patients (Pandey et al. 2021). In addition to the examples described in this chapter, tremor has been observed in other pure or combined dystonias, such as in 64% of the cases of dystonia-parkinsonism resulting from mutations in the *SLC6A3* gene, as well as in myoclonus-dystonia resulting from mutations in *KCTD17*, and other dystonia-parkinsonisms resulting from mutations in *SPR* and *PTS* genes, albeit in a limited number of patients (Pandey et al. 2021).

3.7 Roussy–Lévy Syndrome

Charcot–Marie–Tooth (CMT) disease encompasses a genetically heterogeneous group of inherited neuropathies, also known as hereditary motor and sensory neuropathies (HSMN). CMT results from mutations in more than 30 genes expressed in Schwann cells and neurons causing overlapping phenotypes. The classic CMT phenotype reflects length-dependent axonal degeneration characterized by distal sensory loss and weakness, deep tendon reflex abnormalities, and skeletal deformities (Patzkó and Shy 2011). The first cases of CMT associated with ET have been reported more than 30 years ago (Salisachs 1975, 1976). Subsequently, others provided evidence that CMT disease with tremor coincides with the Roussy–Lévy syndrome (Barbieri et al. 1984). The Roussy–Lévy syndrome was first described in 1926 by Roussy and Lévy as a disorder beginning in infancy or childhood and presenting with pes cavus and tendon areflexia, distal limb weakness, tremor in the upper limbs, gait ataxia, and distal sensory loss. In 1998 Auer-Grumbach et al. reported a family with affected members in four generations, showing the clinical signs of Roussy–Lévy syndrome and a partial duplication at chromosome 17p11.2, a genetic defect commonly found in CMT1A patients (the duplication of the *PMP22* gene), suggesting a close relation with the CMT syndrome. The *PMP22* gene encodes a 22-kDa protein that comprises 2–5% of peripheral nervous system myelin. It is produced primarily by Schwann cells and expressed in the compact portion of essentially all myelinated fibers in the peripheral nervous system (Auer-Grumbach et al. 1998). In members of the original family studied by Roussy and Lévy, Plante-Bordeneuve et al. (1999) identified a heterozygous mutation in the myelin protein zero (*MPZ*) gene, encoding the major structural protein of peripheral

myelin; mutations in this gene are also associated with CMT1B (Plante-Bordeneuve et al. 1999).

3.8 Wilson's Disease

Wilson's disease is an inherited autosomal recessive disorder of copper balance leading to hepatic damage and neurological disturbance of variable degree. The hepatic and the neurological form can be distinguished, but many patients present with a mixture of both. An estimate for the disease frequency in most populations is about 17 per million, suggesting a carrier frequency ranging from 1 in 90 to 1 in 122 (Huster 2010; Lorincz 2010). The disease is caused by mutations of the *ATP7B* gene on chromosome 13q14.3, encoding a copper transporting P-type transmembrane ATPase. Mutations in *ATP7B* result in abnormal copper metabolism and subsequent toxic accumulation of copper (Thomas et al. 1995). Overall, over 700 *ATP7B* mutations have been so far identified with only a few of them functionally characterized (Chanpong and Dhawan, 2022). The patient is usually presymptomatic during early life, but the accumulation of copper causes subclinical liver disease. Disease symptoms are highly variable and can manifest between early childhood and the fifth or sixth decade of life, with a peak incidence of around 17 years. Hepatic, neurological, and psychiatric manifestations are observed. Neurological features include dysarthria, dystonia, tremor, parkinsonism, choreoathetosis, ataxia, and subtle cognitive impairment. Tremor is reported in 22–55% of the cases, occurring at rest, upon assumption of a posture, or with action. Clinical signs include asymmetric distal accentuated tremor of the hands, "wing beating" tremor, intention tremor, and sometimes tremor of the trunk and head. Parkinsonism has been reported in 19–62% of the cases. Psychiatric symptoms, including attention deficit, depression, and mood swings, are observed in up to one-third of the patients (Huster 2010; Lorincz 2010; Chanpong and Dhawan, 2022).

3.9 Conclusions

Advances have been obtained in recent years in our understanding of the genetics of PD, both in monogenic and idiopathic forms (Blauwendraat et al. 2020; Jia et al. 2022). Studies in autosomal dominant and recessive forms of the disease, as well as in monogenic atypical forms, have highlighted central roles for protein aggregation and turnover, lysosomal pathways, mitochondrial damage and turnover, endocytosis, and synaptic vesicle trafficking in the pathophysiology of the disease (Jia et al. 2022). In parallel, genome sequencing approaches and large-scale GWASs are increasingly helping to clarify the genetic landscape of the disease that is continuously updated (Blauwendraat et al. 2020; Jia et al. 2022). Less is known concerning the genetics of ET for which some putative gene variants identified

in families are likely private ones, and only a recent GWAS provided significant genome-wide signals associated with disease risk (Liao et al. 2022). Genetic heterogeneity, incomplete penetrance, and the fact that some tremor disorders are erroneously referred to as ET because they resemble it at both onset and for many years thereafter are among the most probable reasons explaining why the search of ET genes is still ongoing (Magrinelli et al. 2020). Tremor occurs in several other neurological disorders, such as ataxias, dystonias, and peripheral neuropathies. This chapter provides several examples of hereditary forms of these disorders. Overall, the compromising of several pathways can result in neuronal dysfunction and tremor, and the heterogeneity of the diseases characterized by tremor as one of the possible symptoms is reflected by the heterogeneity of genes and pathways causing such diseases. Mutations in the same gene can cause different diseases, depending on the nature of the mutation itself, making the picture even more complex. Some examples are the *MAPT* gene, that can cause frontotemporal dementia with parkinsonism or increase the risk for idiopathic PD, or mutations of *FRM1* that can lead to either fragile X syndrome or fragile X-associated/tremor ataxia syndrome, depending on the length of the repeated tract. Similarly, as in the case of *SNCA* and *LRRK* genes, rare high-penetrant variants are observed in families with monogenic PD, while more common variants confer a slight increase in the risk for idiopathic forms. Overall, this chapter gives a broad overview of human disorders characterized by tremor and of the genetics beyond them.

References

Abeliovich A, Schmitz Y, Fariñas I, Choi-Lundberg D, Ho WH, Castillo PE, Shinsky N, Verdugo JM, Armanini M, Ryan A, Hynes M, Phillips H, Sulzer D, Rosenthal A. Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. Neuron. 2000;25(1):239–52.

Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863–73.

Aridon P, Ragonese P, De Fusco M, Salemi G, Casari G, Savettieri G. Further evidence of genetic heterogeneity in familial essential tremor. Parkinsonism Relat Disord. 2008;14(1):15–8.

Auer-Grumbach M, Strasser-Fuchs S, Wagner K, Körner E, Fazekas F. Roussy–Lévy syndrome is a phenotypic variant of Charcot-Marie-Tooth syndrome IA associated with a duplication on chromosome 17p11.2. J Neurol Sci. 1998;154(1):72–5.

Balestrino R, Schapira AHV. Parkinson disease. Eur J Neurol. 2020;27(1):27–42.

Barbieri F, Filla A, Ragno M, Crisci C, Santoro L, Corona M, Campanella G. Evidence that Charcot-Marie-Tooth disease with tremor coincides with the Roussy-Levy syndrome. Can J Neurol Sci. 1984;11(4 Suppl):534–40.

Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. Lancet Neurol. 2020;19(2):170–8.

Brin MF, Koller W. Epidemiology and genetics of essential tremor. Mov Disord. 1998;13(Suppl 3):55–63.

Camargos S, Scholz S, Simón-Sánchez J, Paisán-Ruiz C, Lewis P, Hernandez D, Ding J, Gibbs JR, Cookson MR, Bras J, Guerreiro R, Oliveira CR, Lees A, Hardy J, Cardoso F, Singleton AB.

DYT16, a novel young-onset dystonia-parkinsonism disorder: identification of a segregating mutation in the stress-response protein PRKRA. Lancet Neurol. 2008;7(3):207–15.

Cen Z, Jiang Z, Chen Y, Zheng X, Xie F, Yang X, Lu X, Ouyang Z, Wu H, Chen S, Yin H, Qiu X, Wang S, Ding M, Tang Y, Yu F, Li C, Wang T, Ishiura H, Tsuji S, Jiao C, Liu C, Xiao J, Luo W. Intronic pentanucleotide TTTCA repeat insertion in the SAMD12 gene causes familial cortical myoclonic tremor with epilepsy type 1. Brain. 2018;141(8):2280–8.

Chanpong A, Dhawan A. Wilson disease in children and young adults – state of the art. Saudi J Gastroenterol. 2022;28(1):21–31.

Charlesworth G, Plagnol V, Holmström KM, Bras J, Sheerin UM, Preza E, Rubio-Agusti I, Ryten M, Schneider SA, Stamelou M, Trabzuni D, Abramov AY, Bhatia KP, Wood NW. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. Am J Hum Genet. 2012;91(6):1041–50.

Charlesworth G, Angelova PR, Bartolomé-Robledo F, Ryten M, Trabzuni D, Stamelou M, Abramov AY, Bhatia KP, Wood NW. Mutations in HPCA cause autosomal-recessive primary isolated dystonia. Am J Hum Genet. 2015;96(4):657–65.

Chartier-Harlin MC, Kachergus J, Roumier C, Mouroux V, Douay X, Lincoln S, Levecque C, Larvor L, Andrieux J, Hulihan M, Waucquier N, Defebvre L, Amouyel P, Farrer M, Destée A. Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. Lancet. 2004;364(9440):1167–9.

Coppedè F. One-carbon epigenetics and redox biology of neurodegeneration. Free Radic Biol Med. 2021;170:19–33.

Corbett MA, Kroes T, Veneziano L, Bennett MF, Florian R, Schneider AL, Coppola A, Licchetta L, Franceschetti S, Suppa A, Wenger A, Mei D, Pendziwiat M, Kaya S, Delledonne M, Straussberg R, Xumerle L, Regan B, Crompton D, van Rootselaar AF, Correll A, Catford R, Bisulli F, Chakraborty S, Baldassari S, Tinuper P, Barton K, Carswell S, Smith M, Berardelli A, Carroll R, Gardner A, Friend KL, Blatt I, Iacomino M, Di Bonaventura C, Striano S, Buratti J, Keren B, Nava C, Forlani S, Rudolf G, Hirsch E, Leguern E, Labauge P, Balestrini S, Sander JW, Afawi Z, Helbig I, Ishiura H, Tsuji S, Sisodiya SM, Casari G, Sadleir LG, van Coller R, Tijssen MAJ, Klein KM, van den Maagdenberg AMJM, Zara F, Guerrini R, Berkovic SF, Pippucci T, Canafoglia L, Bahlo M, Striano P, Scheffer IE, Brancati F, Depienne C, Gecz J. Intronic ATTTC repeat expansions in STARD7 in familial adult myoclonic epilepsy linked to chromosome 2. Nat Commun. 2019;10(1):4920.

Dalvi A, Mercury MG. Essential tremor–not just a shake. Dis Mon. 2011;57(3):127–34.

Day JO, Mullin S. The genetics of Parkinson's disease and implications for clinical practice. Genes (Basel). 2021;12(7):1006.

Deng H, Le WD, Guo Y, Huang MS, Xie WJ, Jankovic J. Extended study of A265G variant of HS1BP3 in essential tremor and Parkinson disease. Neurology. 2005;65(4):651–2.

Deng H, Le W, Jankovic J. Genetics of essential tremor. Brain. 2007;130(Pt 6):1456–64.

Deng H, Dodson MW, Huang H, Guo M. The Parkinson's disease genes pink1 and parkin promote mitochondrial fission and/or inhibit fusion in Drosophila. Proc Natl Acad Sci U S A. 2008;105(38):14503–8.

di Biase L, Di Santo A, Caminiti ML, Pecoraro PM, Di Lazzaro V. Classification of dystonia. Life (Basel). 2022;12(2):206.

Di Fonzo A, Dekker MC, Montagna P, Baruzzi A, Yonova EH, Correia Guedes L, Szczerbinska A, Zhao T, Dubbel-Hulsman LO, Wouters CH, de Graaff E, Oyen WJ, Simons EJ, Breedveld GJ, Oostra BA, Horstink MW, Bonifati V. FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. Neurology. 2009;72(3):240–5.

Dorsey ER, Bloem BR. The Parkinson pandemic-a call to action. JAMA Neurol. 2018;75(1):9–10.

Edvardson S, Cinnamon Y, Ta-Shma A, Shaag A, Yim YI, Zenvirt S, Jalas C, Lesage S, Brice A, Taraboulos A, Kaestner KH, Greene LE, Elpeleg O. A deleterious mutation in DNAJC6 encoding the neuronal-specific clathrin-uncoating co-chaperone auxilin, is associated with juvenile parkinsonism. PLoS One. 2012;7(5):e36458.

Edwards TL, Scott WK, Almonte C, Burt A, Powell EH, Beecham GW, Wang L, Züchner S, Konidari I, Wang G, Singer C, Nahab F, Scott B, Stajich JM, Pericak-Vance M, Haines J, Vance

JM, Martin ER. Genome-wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for Parkinson disease. Ann Hum Genet. 2010;74(2):97–109.

Embiruçu EK, Martyn ML, Schlesinger D, Kok F. Autosomal recessive ataxias: 20 types, and counting. Arq Neuropsiquiatr. 2009;67(4):1143–56.

Farrer MJ, Stone JT, Lin CH, Dächsel JC, Hulihan MM, Haugarvoll K, Ross OA, Wu RM. Lrrk2 G2385R is an ancestral risk factor for Parkinson's disease in Asia. Parkinsonism Relat Disord. 2007;13(2):89–92.

Ferrara J, Jankovic J. Epidemiology and management of essential tremor in children. Paediatr Drugs. 2009;11(5):293–307.

Florian RT, Kraft F, Leitão E, Kaya S, Klebe S, Magnin E, van Rootselaar AF, Buratti J, Kühnel T, Schröder C, Giesselmann S, Tschernoster N, Altmueller J, Lamiral A, Keren B, Nava C, Bouteiller D, Forlani S, Jornea L, Kubica R, Ye T, Plassard D, Jost B, Meyer V, Deleuze JF, Delpu Y, Avarello MDM, Vijfhuizen LS, Rudolf G, Hirsch E, Kroes T, Reif PS, Rosenow F, Ganos C, Vidailhet M, Thivard L, Mathieu A, Bourgeron T, Kurth I, Rafehi H, Steenpass L, Horsthemke B, FAME Consortium, LeGuern E, Klein KM, Labauge P, Bennett MF, Bahlo M, Gecz J, Corbett MA, Tijssen MAJ, van den Maagdenberg AMJM, Depienne C. Unstable TTTTA/TTTCA expansions in MARCH6 are associated with familial adult myoclonic epilepsy type 3. Nat Commun. 2019;10(1):4919.

Foo JN, Chew EGY, Chung SJ, Peng R, Blauwendraat C, Nalls MA, Mok KY, Satake W, Toda T, Chao Y, Tan LCS, Tandiono M, Lian MM, Ng EY, Prakash KM, Au WL, Meah WY, Mok SQ, Annuar AA, Chan AYY, Chen L, Chen Y, Jeon BS, Jiang L, Lim JL, Lin JJ, Liu C, Mao C, Mok V, Pei Z, Shang HF, Shi CH, Song K, Tan AH, Wu YR, Xu YM, Xu R, Yan Y, Yang J, Zhang B, Koh WP, Lim SY, Khor CC, Liu J, Tan EK. Identification of risk loci for Parkinson disease in Asians and comparison of risk between Asians and Europeans: a genome-wide association study. JAMA Neurol. 2020;77(6):746–54.

Fuchs J, Tichopad A, Golub Y, Munz M, Schweitzer KJ, Wolf B, Berg D, Mueller JC, Gasser T. Genetic variability in the SNCA gene influences alpha-synuclein levels in the blood and brain. FASEB J. 2008;22(5):1327–34.

Fuchs T, Gavarini S, Saunders-Pullman R, Raymond D, Ehrlich ME, Bressman SB, Ozelius LJ. Mutations in the THAP1 gene are responsible for DYT6 primary torsion dystonia. Nat Genet. 2009;41(3):286–8.

Fuchs T, Saunders-Pullman R, Masuho I, Luciano MS, Raymond D, Factor S, Lang AE, Liang TW, Trosch RM, White S, Ainehsazan E, Hervé D, Sharma N, Ehrlich ME, Martemyanov KA, Bressman SB, Ozelius LJ. Mutations in GNAL cause primary torsion dystonia. Nat Genet. 2013;45(1):88–92.

Gegg ME, Menozzi E, Schapira AHV. Glucocerebrosidase-associated Parkinson disease: Pathogenic mechanisms and potential drug treatments. Neurobiol Dis. 2022;166:105663.

Gueven N, Chen P, Nakamura J, Becherel OJ, Kijas AW, Grattan-Smith P, Lavin MF. A subgroup of spinocerebellar ataxias defective in DNA damage responses. Neuroscience. 2007;145:1418–25.

Gulcher JR, Jónsson P, Kong A, Kristjánsson K, Frigge ML, Kárason A, Einarsdóttir IE, Stefánsson H, Einarsdóttir AS, Sigurthoardóttir S, Baldursson S, Björnsdóttir S, Hrafnkelsdóttir SM, Jakobsson F, Benedickz J, Stefánsson K. Mapping of a familial essential tremor gene, FET1, to chromosome 3q13. Nat Genet. 1997;17(1):84–7.

Halperin A, Elstein D, Zimran A. Increased incidence of Parkinson disease among relatives of patients with Gaucher disease. Blood Cells Mol Dis. 2006;36(3):426–8.

Hardy J. Genetic analysis of pathways to Parkinson disease. Neuron. 2010;68(2):201–6.

Hayakawa Y, Itoh M, Yamada A, Mitsuda T, Nakagawa T. Expression and localization of Cayman ataxia-related protein, Caytaxin, is regulated in a developmental- and spatial-dependent manner. Brain Res. 2007;1129:100–9.

Heaton GR, Landeck N, Mamais A, Nalls MA, Nixon-Abell J, Kumaran R, Beilina A, Pellegrini L, Li Y, International Parkinson Disease Genomics Consortium (IPDGC), Harvey K, Cookson MR. Sequential screening nominates the Parkinson's disease associated kinase LRRK2 as a regulator of Clathrin-mediated endocytosis. Neurobiol Dis. 2020;141:104948.

Hicks JE, Konidari I, Scott BL, Stajich JM, Ashley-Koch AE, Gilbert JR, Scott WK. Linkage of familial essential tremor to chromosome 5q35. Mov Disord. 2016;31(7):1059–62.

Higgins JJ, Pho LT, Nee LE. A gene (ETM) for essential tremor maps to chromosome 2p22-p25. Mov Disord. 1997;12(6):859–64.

Higgins JJ, Lombardi RQ, Pucilowska J, Jankovic J, Tan EK, Rooney JP. A variant in the HS1-BP3 gene is associated with familial essential tremor. Neurology. 2005;64(3):417–21.

Houle G, Ambalavanan A, Schmouth JF, Leblond CS, Spiegelman D, Laurent SB, Bourassa CV, Grayson C, Panisset M, Chouinard S, Dupré N, Vilariño-Güell C, Rajput A, Girard SL, Dion PA, Rouleau GA. No rare deleterious variants from STK32B, PPARGC1A, and CTNNA3 are associated with essential tremor. Neurol Genet. 2017;3(5):e195.

Huster D. Wilson disease. Best Pract Res Clin Gastroenterol. 2010;24(5):531–9.

Ichinose H, Ohye T, Takahashi E, Seki N, Hori T, Segawa M, Nomura Y, Endo K, Tanaka H, Tsuji S, et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nat Genet. 1994;8(3):236–42.

Ishiura H, Doi K, Mitsui J, Yoshimura J, Matsukawa MK, Fujiyama A, Toyoshima Y, Kakita A, Takahashi H, Suzuki Y, Sugano S, Qu W, Ichikawa K, Yurino H, Higasa K, Shibata S, Mitsue A, Tanaka M, Ichikawa Y, Takahashi Y, Date H, Matsukawa T, Kanda J, Nakamoto FK, Higashihara M, Abe K, Koike R, Sasagawa M, Kuroha Y, Hasegawa N, Kanesawa N, Kondo T, Hitomi T, Tada M, Takano H, Saito Y, Sanpei K, Onodera O, Nishizawa M, Nakamura M, Yasuda T, Sakiyama Y, Otsuka M, Ueki A, Kaida KI, Shimizu J, Hanajima R, Hayashi T, Terao Y, Inomata-Terada S, Hamada M, Shirota Y, Kubota A, Ugawa Y, Koh K, Takiyama Y, Ohsawa-Yoshida N, Ishiura S, Yamasaki R, Tamaoka A, Akiyama H, Otsuki T, Sano A, Ikeda A, Goto J, Morishita S, Tsuji S. Expansions of intronic TTTCA and TTTTA repeats in benign adult familial myoclonic epilepsy. Nat Genet. 2018;50(4):581–90.

Iwaki A, Kawano Y, Miura S, Shibata H, Matsuse D, Li W, Furuya H, Ohyagi Y, Taniwaki T, Kira J, Fukumaki Y. Heterozygous deletion of ITPR1, but not SUMF1, in spinocerebellar ataxia type 16. J Med Genet. 2008;45(1):32–5.

Iwaki H, Blauwendraat C, Makarious MB, Bandrés-Ciga S, Leonard HL, Gibbs JR, Hernandez DG, Scholz SW, Faghri F, International Parkinson's Disease Genomics Consortium (IPDGC), Nalls MA, Singleton AB. Penetrance of Parkinson's disease in LRRK2 p.G2019S carriers is modified by a polygenic risk score. Mov Disord. 2020;35(5):774–80.

Jeanneteau F, Funalot B, Jankovic J, Deng H, Lagarde JP, Lucotte G, Sokoloff P. A functional variant of the dopamine D3 receptor is associated with risk and age-at-onset of essential tremor. Proc Natl Acad Sci U S A. 2006;103(28):10753–8.

Jia F, Fellner A, Kumar KR. Monogenic Parkinson's disease: genotype, phenotype, pathophysiology, and genetic testing. Genes (Basel). 2022;13(3):471.

Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Álvarez I, Pastor P, Agúndez JAG. Genomic markers for essential tremor. Pharmaceuticals (Basel). 2021;14(6):516.

Kawajiri S, Saiki S, Sato S, Hattori N. Genetic mutations and functions of PINK1. Trends Pharmacol Sci. 2011;32(10):573–80.

Kay DM, Factor SA, Samii A, Higgins DS, Griffith A, Roberts JW, Leis BC, Nutt JG, Montimurro JS, Keefe RG, Atkins AJ, Yearout D, Zabetian CP, Payami H. Genetic association between alpha-synuclein and idiopathic Parkinson's disease. Am J Med Genet B Neuropsychiatr Genet. 2008;147B(7):1222–30.

Kim JM, Hong S, Kim GP, Choi YJ, Kim YK, Park SS, Kim SE, Jeon BS. Importance of low-range CAG expansion and CAA interruption in SCA2 parkinsonism. Arch Neurol. 2007;64(10):1510–8.

Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature. 1998;392(6676):605–8.

Knight MA, Gardner RJ, Bahlo M, Matsuura T, Dixon JA, Forrest SM, Storey E. Dominantly inherited ataxia and dysphonia with dentate calcification: spinocerebellar ataxia type 20. Brain. 2004;127(Pt 5):1172–81.

Köroğlu Ç, Baysal L, Cetinkaya M, Karasoy H, Tolun A. DNAJC6 is responsible for juvenile parkinsonism with phenotypic variability. Parkinsonism Relat Disord. 2013;19(3):320–4.

Krebs CE, Karkheiran S, Powell JC, Cao M, Makarov V, Darvish H, Di Paolo G, Walker RH, Shahidi GA, Buxbaum JD, De Camilli P, Yue Z, Paisán-Ruiz C. The Sac1 domain of SYNJ1 identified mutated in a family with early-onset progressive Parkinsonism with generalized seizures. Hum Mutat. 2013;34(9):1200–7.

Krüger R, Kuhn W, Müller T, Woitalla D, Graeber M, Kösel S, Przuntek H, Epplen JT, Schöls L, Riess O. Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nat Genet. 1998;18(2):106–8.

Krygier M, Mazurkiewicz-Bełdzińska M. Milestones in genetics of cerebellar ataxias. Neurogenetics. 2021;22(4):225–34.

Lastres-Becker I, Rüb U, Auburger G. Spinocerebellar ataxia 2 (SCA2). Cerebellum. 2008;7(2):115–24.

Leehey MA. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. J Investig Med. 2009;57(8):830–6.

Lei XX, Liu Q, Lu Q, Huang Y, Zhou XQ, Sun HY, Wu LW, Cui LY, Zhang X. TTTCA repeat expansion causes familial cortical myoclonic tremor with epilepsy. Eur J Neurol. 2019;26(3):513–8.

Lenka A, Jankovic J. Tremor syndromes: an updated review. Front Neurol. 2021;12:684835.

Leroy E, Boyer R, Auburger G, Leube B, Ulm G, Mezey E, Harta G, Brownstein MJ, Jonnalagada S, Chernova T, Dehejia A, Lavedan C, Gasser T, Steinbach PJ, Wilkinson KD, Polymeropoulos MH. The ubiquitin pathway in Parkinson's disease. Nature. 1998;395(6701):451–2.

Lesage S, Drouet V, Majounie E, Deramecourt V, Jacoupy M, Nicolas A, Cormier-Dequaire F, Hassoun SM, Pujol C, Ciura S, Erpapazoglou Z, Usenko T, Maurage CA, Sahbatou M, Liebau S, Ding J, Bilgic B, Emre M, Erginel-Unaltuna N, Guven G, Tison F, Tranchant C, Vidailhet M, Corvol JC, Krack P, Leutenegger AL, Nalls MA, Hernandez DG, Heutink P, Gibbs JR, Hardy J, Wood NW, Gasser T, Durr A, Deleuze JF, Tazir M, Destée A, Lohmann E, Kabashi E, Singleton A, Corti O, Brice A, French Parkinson's Disease Genetics Study (PDG); International Parkinson's Disease Genomics Consortium (IPDGC). Loss of VPS13C function in autosomal-recessive parkinsonism causes mitochondrial dysfunction and increases PINK1/Parkin-dependent mitophagy. Am J Hum Genet. 2016;98(3):500–13.

Liao C, Castonguay CE, Heilbron K, Vuokila V, Medeiros M, Houle G, Akçimen F, Ross JP, Catoire H, Diez-Fairen M, Kang J, Mueller SH, Girard SL, Hopfner F, Lorenz D, Clark LN, Soto-Beasley AI, Klebe S, Hallett M, Wszolek ZK, Pendziwiat M, Lorenzo-Betancor O, Seppi K, Berg D, Vilariño-Güell C, Postuma RB, Bernard G, Dupré N, Jankovic J, Testa CM, Ross OA, Arzberger T, Chouinard S, Louis ED, Mandich P, Vitale C, Barone P, García-Martín E, Alonso-Navarro H, JAG A, Jiménez-Jiménez FJ, Pastor P, Rajput A, Deuschl G, Kuhlenbaümer G, Meijer IA, Dion PA, Rouleau GA, 23andMe Research Team. Association of essential tremor with novel risk loci: a genome-wide association study and meta-analysis. JAMA Neurol. 2022;79(2):185–93.

Liu S, Ninan I, Antonova I, Battaglia F, Trinchese F, Narasanna A, Kolodilov N, Dauer W, Hawkins RD, Arancio O. Alpha-synuclein produces a long-lasting increase in neurotransmitter release. EMBO J. 2004;23(22):4506–16.

Lockhart PJ, Lincoln S, Hulihan M, Kachergus J, Wilkes K, Bisceglio G, Mash DC, Farrer MJ. DJ-1 mutations are a rare cause of recessively inherited early onset parkinsonism mediated by loss of protein function. J Med Genet. 2004;41(3):e22.

Lorenz D, Frederiksen H, Moises H, Kopper F, Deuschl G, Christensen K. High concordance for essential tremor in monozygotic twins of old age. Neurology. 2004;62(2):208–11.

Lorenz D, Klebe S, Stevanin G, Thier S, Nebel A, Feingold J, Frederiksen H, Denis E, Christensen K, Schreiber S, Brice A, Deuschl G, Dürr A. Dopamine receptor D3 gene and essential tremor in large series of German, Danish and French patients. Eur J Hum Genet. 2009;17(6):766–73.

Lorincz MT. Neurologic Wilson's disease. Ann N Y Acad Sci. 2010;1184:173–87.
Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010;25(5):534–41.
Louis ED, McCreary M. How common is essential tremor? Update on the worldwide prevalence of essential tremor. Tremor Other Hyperkinet Mov (N Y). 2021;11:28.
Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA, Rajput A, Pahwa R, Lyons KE, Ross GW, Borden S, Moskowitz CB, Lawton A, Hernandez N. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain. 2007;130(Pt 12):3297–307.
Lu CS, Chang HC, Kuo PC, Liu YL, Wu WS, Weng YH, Yen TC, Chou YH. The parkinsonian phenotype of spinocerebellar ataxia type 3 in a Taiwanese family. Parkinsonism Relat Disord. 2004;10(6):369–73.
Magrinelli F, Latorre A, Balint B, Mackenzie M, Mulroy E, Stamelou M, Tinazzi M, Bhatia KP. Isolated and combined genetic tremor syndromes: a critical appraisal based on the 2018 MDS criteria. Parkinsonism Relat Disord. 2020;77:121–40.
Makino S, Kaji R, Ando S, Tomizawa M, Yasuno K, Goto S, Matsumoto S, Tabuena MD, Maranon E, Dantes M, Lee LV, Ogasawara K, Tooyama I, Akatsu H, Nishimura M, Tamiya G. Reduced neuron-specific expression of the TAF1 gene is associated with X-linked dystonia-parkinsonism. Am J Hum Genet. 2007;80(3):393–406.
Manto M. Cerebellar disorders. A practical approach to diagnosis and management. Cambridge: Cambridge University Press; 2010.
Manto M, Marmolino D. Cerebellar ataxias. Curr Opin Neurol. 2009;22(4):419–29.
Manzoor H, Brüggemann N, Hussain HMJ, Bäumer T, Hinrichs F, Wajid M, Münchau A, Naz S, Lohmann K. Novel homozygous variants in ATCAY, MCOLN1, and SACS in complex neurological disorders. Parkinsonism Relat Disord. 2018;51:91–5.
Maraganore DM, de Andrade M, Elbaz A, Farrer MJ, Ioannidis JP, Krüger R, Rocca WA, Schneider NK, Lesnick TG, Lincoln SJ, Hulihan MM, Aasly JO, Ashizawa T, Chartier-Harlin MC, Checkoway H, Ferrarese C, Hadjigeorgiou G, Hattori N, Kawakami H, Lambert JC, Lynch T, Mellick GD, Papapetropoulos S, Parsian A, Quattrone A, Riess O, Tan EK, Van Broeckhoven C, Genetic Epidemiology of Parkinson's Disease (GEO-PD) Consortium. Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease. JAMA. 2006;296(6):661–70.
Mata IF, Lockhart PJ, Farrer MJ. Parkin genetics: one model for Parkinson's disease. Hum Mol Genet. 2004;13 Spec No 1:R127–33.
Mata IF, Yearout D, Alvarez V, Coto E, de Mena L, Ribacoba R, Lorenzo-Betancor O, Samaranch L, Pastor P, Cervantes S, Infante J, Garcia-Gorostiaga I, Sierra M, Combarros O, Snapinn KW, Edwards KL, Zabetian CP. Replication of MAPT and SNCA, but not PARK16-18, as susceptibility genes for Parkinson's disease. Mov Disord. 2011;26(5):819–23.
Matos CA, de Macedo-Ribeiro S, Carvalho AL. Polyglutamine diseases: the special case of ataxin-3 and Machado-Joseph disease. Prog Neurobiol. 2011;95(1):26–48.
Mencacci NE, Jinnah HA. Naming genes for dystonia: DYT-z or ditzy? Tremor Other Hyperkinet Mov (N Y). 2019:9. https://doi.org/10.7916/tohm.v0.710.eCollection2019
Migliore L, Coppedè F. Genetics, environmental factors and the emerging role of epigenetics in neurodegenerative diseases. Mutat Res. 2009;667(1–2):82–97.
Müller U. The monogenic primary dystonias. Brain. 2009;132(Pt 8):2005–25.
Müller U. Spinocerebellar ataxias (SCAs) caused by common mutations. Neurogenetics. 2021;22(4):235–50.
Müller SH, Girard SL, Hopfner F, Merner ND, Bourassa CV, Lorenz D, Clark LN, Tittmann L, Soto-Ortolaza AI, Klebe S, Hallett M, Schneider SA, Hodgkinson CA, Lieb W, Wszolek ZK, Pendziwiat M, Lorenzo-Betancor O, Poewe W, Ortega-Cubero S, Seppi K, Rajput A, Hussl A, Rajput AH, Berg D, Dion PA, Wurster I, Shulman JM, Srulijes K, Haubenberger D, Pastor P, Vilariño-Güell C, Postuma RB, Bernard G, Ladwig KH, Dupré N, Jankovic J, Strauch K, Panisset M, Winkelmann J, Testa CM, Reischl E, Zeuner KE, Ross OA, Arzberger T, Chouinard S, Deuschl G, Louis ED, Kuhlenbäumer G, Rouleau GA. Genome-wide association study in essential tremor identifies three new loci. Brain. 2016;139(Pt 12):3163–9.

Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, Tan M, Kia DA, Noyce AJ, Xue A, Bras J, Young E, von Coelln R, Simón-Sánchez J, Schulte C, Sharma M, Krohn L, Pihlstrøm L, Siitonen A, Iwaki H, Leonard H, Faghri F, Gibbs JR, Hernandez DG, Scholz SW, Botia JA, Martinez M, Corvol JC, Lesage S, Jankovic J, Shulman LM, Sutherland M, Tienari P, Majamaa K, Toft M, Andreassen OA, Bangale T, Brice A, Yang J, Gan-Or Z, Gasser T, Heutink P, Shulman JM, Wood NW, Hinds DA, Hardy JA, Morris HR, Gratten J, Visscher PM, Graham RR, Singleton AB, 23andMe Research Team; System Genomics of Parkinson's Disease Consortium; International Parkinson's Disease Genomics Consortium. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol. 2019;18(12):1091–102.

Narendra D, Tanaka A, Suen DF, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J Cell Biol. 2008;183(5):795–803.

Novelletto A, Gulli R, Ciotti P, Vitale C, Malaspina P, Blasi P, Pippucci T, Seri M, Cozzolino A, Bilo L, Abbruzzese G, Martinelli P, Bellone E, Barone P, Mandich P. Linkage exclusion in Italian families with hereditary essential tremor. Eur J Neurol. 2011;18(9):e118–20.

Nuytemans K, Theuns J, Cruts M, Van Broeckhoven C. Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update. Hum Mutat. 2010;31(7):763–80.

O'Hearn E, Holmes SE, Margolis RL. Spinocerebellar ataxia type 12. Handb Clin Neurol. 2011;103:535–47.

Olgiati S, Quadri M, Fang M, Rood JP, Saute JA, Chien HF, Bouwkamp CG, Graafland J, Minneboo M, Breedveld GJ, Zhang J, International Parkinsonism Genetics Network, Verheijen FW, Boon AJ, Kievit AJ, Jardim LB, Mandemakers W, Barbosa ER, Rieder CR, Leenders KL, Wang J, Bonifati V. DNAJC6 mutations associated with early-onset Parkinson's disease. Ann Neurol. 2016;79(2):244–56.

Ong YL, Deng X, Tan EK. Etiologic links between environmental and lifestyle factors and essential tremor. Ann Clin Transl Neurol. 2019;6(5):979–89.

Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, Shalish C, de Leon D, Brin MF, Raymond D, Corey DP, Fahn S, Risch NJ, Buckler AJ, Gusella JF, Breakefield XO. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet. 1997;17(1):40–8.

Paisán-Ruíz C, Jain S, Evans EW, Gilks WP, Simón J, van der Brug M, López de Munain A, Aparicio S, Gil AM, Khan N, Johnson J, Martinez JR, Nicholl D, Carrera IM, Pena AS, de Silva R, Lees A, Martí-Massó JF, Pérez-Tur J, Wood NW, Singleton AB. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron. 2004;44(4):595–600.

Paisán-Ruiz C, Bhatia KP, Li A, Hernandez D, Davis M, Wood NW, Hardy J, Houlden H, Singleton A, Schneider SA. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann Neurol. 2009;65(1):19–23.

Paisán-Ruiz C, Guevara R, Federoff M, Hanagasi H, Sina F, Elahi E, Schneider SA, Schwingenschuh P, Bajaj N, Emre M, Singleton AB, Hardy J, Bhatia KP, Brandner S, Lees AJ, Houlden H. Early-onset L-dopa-responsive parkinsonism with pyramidal signs due to ATP13A2, PLA2G6, FBXO7 and spatacsin mutations. Mov Disord. 2010;25(12):1791–800.

Pandey S, Bhattad S, Dinesh S. Tremor in primary monogenic dystonia. Curr Neurol Neurosci Rep. 2021;21(9):48.

Pankratz N, Wilk JB, Latourelle JC, DeStefano AL, Halter C, Pugh EW, Doheny KF, Gusella JF, Nichols WC, Foroud T, Myers RH, PSG-PROGENI and GenePD Investigators, Coordinators and Molecular Genetic Laboratories. Genomewide association study for susceptibility genes contributing to familial Parkinson disease. Hum Genet. 2009;124(6):593–605.

Patzkó A, Shy ME. Update on Charcot-Marie-Tooth disease. Curr Neurol Neurosci Rep. 2011;11(1):78–88.

Plante-Bordeneuve V, Guiochon-Mantel A, Lacroix C, Lapresle J, Said G. The Roussy-Levy family: from the original description to the gene. Ann Neurol. 1999;46:770–3.

Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997;276(5321):2045–7.

Poole AC, Thomas RE, Andrews LA, McBride HM, Whitworth AJ, Pallanck LJ. The PINK1/Parkin pathway regulates mitochondrial morphology. Proc Natl Acad Sci U S A. 2008;105(5):1638–43.

Quadri M, Fang M, Picillo M, Olgiati S, Breedveld GJ, Graafland J, Wu B, Xu F, Erro R, Amboni M, Pappatà S, Quarantelli M, Annesi G, Quattrone A, Chien HF, Barbosa ER, International Parkinsonism Genetics Network, Oostra BA, Barone P, Wang J, Bonifati V. Mutation in the SYNJ1 gene associated with autosomal recessive, early-onset Parkinsonism. Hum Mutat. 2013;34(9):1208–15.

Ramirez A, Heimbach A, Gründemann J, Stiller B, Hampshire D, Cid LP, Goebel I, Mubaidin AF, Wriekat AL, Roeper J, Al-Din A, Hillmer AM, Karsak M, Liss B, Woods CG, Behrens MI, Kubisch C. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat Genet. 2006;38(10):1184–91.

Regragui W, Gerdelat-Mas A, Simonetta-Moreau M. Cortical tremor (FCMTE: familial cortical myoclonic tremor with epilepsy). Neurophysiol Clin. 2006;36(5–6):345–9.

Richardson D, McEntagart MM, Isaacs JD. DCTN1-related Parkinson-plus disorder (Perry syndrome). Pract Neurol. 2020;20(4):317–9.

Rothfuss O, Fischer H, Hasegawa T, Maisel M, Leitner P, Miesel F, Sharma M, Bornemann A, Berg D, Gasser T, Patenge N. Parkin protects mitochondrial genome integrity and supports mitochondrial DNA repair. Hum Mol Genet. 2009;18(20):3832–50.

Rudakou U, Ruskey JA, Krohn L, Laurent SB, Spiegelman D, Greenbaum L, Yahalom G, Desautels A, Montplaisir JY, Fahn S, Waters CH, Levy O, Kehoe CM, Narayan S, Dauvilliers Y, Dupré N, Hassin-Baer S, Alcalay RN, Rouleau GA, Fon EA, Gan-Or Z. Analysis of common and rare VPS13C variants in late-onset Parkinson disease. Neurol Genet. 2020;6(1):385.

Salisachs P. Unusual motor conduction velocity values in Charcot-Marie-Tooth disease associated with essential tremor: report of a kinship. Eur Neurol. 1975;13(4):377–82.

Salisachs P. Charcot-Marie-Tooth disease associated with "essential tremor": report of 7 cases and a review of the literature. J Neurol Sci. 1976;28(1):17–40.

Sassone J, Reale C, Dati G, Regoni M, Pellecchia MT, Garavaglia B. The role of VPS35 in the pathobiology of Parkinson's disease. Cell Mol Neurobiol. 2021;41(2):199–227.

Satake W, Nakabayashi Y, Mizuta I, Hirota Y, Ito C, Kubo M, Kawaguchi T, Tsunoda T, Watanabe M, Takeda A, Tomiyama H, Nakashima K, Hasegawa K, Obata F, Yoshikawa T, Kawakami H, Sakoda S, Yamamoto M, Hattori N, Murata M, Nakamura Y, Toda T. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. Nat Genet. 2009;41(12):1303–7.

Shatunov A, Jankovic J, Elble R, Sambuughin N, Singleton A, Hallett M, Goldfarb L. A variant in the HS1-BP3 gene is associated with familial essential tremor. Neurology. 2005;65(12):1995.

Shatunov A, Sambuughin N, Jankovic J, Elble R, Lee HS, Singleton AB, Dagvadorj A, Ji J, Zhang Y, Kimonis VE, Hardy J, Hallett M, Goldfarb LG. Genomewide scans in North American families reveal genetic linkage of essential tremor to a region on chromosome 6p23. Brain. 2006;129(Pt 9):2318–31.

Shojaee S, Sina F, Banihosseini SS, Kazemi MH, Kalhor R, Shahidi GA, Fakhrai-Rad H, Ronaghi M, Elahi E. Genome-wide linkage analysis of a Parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays. Am J Hum Genet. 2008;82(6):1375–84.

Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, Bar-Shira A, Berg D, Bras J, Brice A, Chen CM, Clark LN, Condroyer C, De Marco EV, Dürr A, Eblan MJ, Fahn S, Farrer MJ, Fung HC, Gan-Or Z, Gasser T, Gershoni-Baruch R, Giladi N, Griffith A, Gurevich T, Januario C, Kropp P, Lang AE, Lee-Chen GJ, Lesage S, Marder K, Mata IF, Mirelman A, Mitsui J, Mizuta I, Nicoletti G, Oliveira C, Ottman R, Orr-Urtreger A, Pereira LV, Quattrone A, Rogaeva E, Rolfs A, Rosenbaum H, Rozenberg R, Samii A, Samaddar T, Schulte C, Sharma M,

Singleton A, Spitz M, Tan EK, Tayebi N, Toda T, Troiano AR, Tsuji S, Wittstock M, Wolfsberg TG, Wu YR, Zabetian CP, Zhao Y, Ziegler SG. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. 2009;361(17):1651–61.

Simón-Sánchez J, Schulte C, Bras JM, Sharma M, Gibbs JR, Berg D, Paisán-Ruiz C, Lichtner P, Scholz SW, Hernandez DG, Krüger R, Federoff M, Klein C, Goate A, Perlmutter J, Bonin M, Nalls MA, Illig T, Gieger C, Houlden H, Steffens M, Okun MS, Racette BA, Cookson MR, Foote KD, Fernandez HH, Traynor BJ, Schreiber S, Arepalli S, Zonozi R, Gwinn K, van der Brug M, Lopez G, Chanock SJ, Schatzkin A, Park Y, Hollenbeck A, Gao J, Huang X, Wood NW, Lorenz D, Deuschl G, Chen H, Riess O, Hardy JA, Singleton AB, Gasser T. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet. 2009;41(12):1308–12.

Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K. Alpha-synuclein locus triplication causes Parkinson's disease. Science. 2003;302(5646):841.

Srivastava AK, Takkar A, Garg A, Faruq M. Clinical behaviour of spinocerebellar ataxia type 12 and intermediate length abnormal CAG repeats in PPP2R2B. Brain. 2017;140(1):27–36.

Stefansson H, Steinberg S, Petursson H, Gustafsson O, Gudjonsdottir IH, Jonsdottir GA, Palsson ST, Jonsson T, Saemundsdottir J, Bjornsdottir G, Böttcher Y, Thorlacius T, Haubenberger D, Zimprich A, Auff E, Hotzy C, Testa CM, Miyatake LA, Rosen AR, Kristleifsson K, Rye D, Asmus F, Schöls L, Dichgans M, Jakobsson F, Benedikz J, Thorsteinsdottir U, Gulcher J, Kong A, Stefansson K. Variant in the sequence of the LINGO1 gene confers risk of essential tremor. Nat Genet. 2009;41(3):277–9.

Stogmann E, Reinthaler E, Eltawil S, El Etribi MA, Hemeda M, El Nahhas N, Gaber AM, Fouad A, Edris S, Benet-Pages A, Eck SH, Pataraia E, Mei D, Brice A, Lesage S, Guerrini R, Zimprich F, Strom TM, Zimprich A. Autosomal recessive cortical myoclonic tremor and epilepsy: association with a mutation in the potassium channel associated gene CNTN2. Brain. 2013;136(Pt 4):1155–60.

Storey E, Gardner RJ. Spinocerebellar ataxia type 15. Handb Clin Neurol. 2012;103:561–5.

Tayebi N, Walker J, Stubblefield B, Orvisky E, LaMarca ME, Wong K, Rosenbaum H, Schiffmann R, Bembi B, Sidransky E. Gaucher disease with parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? Mol Genet Metab. 2003;79(2):104–9.

Thier S, Lorenz D, Nothnagel M, Poremba C, Papengut F, Appenzeller S, Paschen S, Hofschulte F, Hussl AC, Hering S, Poewe W, Asmus F, Gasser T, Schöls L, Christensen K, Nebel A, Schreiber S, Klebe S, Deuschl G, Kuhlenbäumer G. Polymorphisms in the glial glutamate transporter SLC1A2 are associated with essential tremor. Neurology. 2012;79(3):243–8.

Thomas B, Beal MF. Molecular insights into Parkinson's disease. F1000 Med Rep. 2011;3:7.

Thomas GR, Forbes JR, Roberts EA, Walshe JM, Cox DW. The Wilson disease gene: spectrum of mutations and their consequences. Nat Genet. 1995;9(2):210–7.

Thomas KJ, McCoy MK, Blackinton J, Beilina A, van der Brug M, Sandebring A, Miller D, Maric D, Cedazo-Minguez A, Cookson MR. DJ-1 acts in parallel to the PINK1/parkin pathway to control mitochondrial function and autophagy. Hum Mol Genet. 2011;20(1):40–50.

Valente EM, Abou-Sleiman PM, Caputo V, Muqit MM, Harvey K, Gispert S, Ali Z, Del Turco D, Bentivoglio AR, Healy DG, Albanese A, Nussbaum R, González-Maldonado R, Deller T, Salvi S, Cortelli P, Gilks WP, Latchman DS, Harvey RJ, Dallapiccola B, Auburger G, Wood NW. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science. 2004;304(5674):1158–60.

van den Ende T, Sharifi S, van der Salm SMA, van Rootselaar AF. Familial cortical myoclonic tremor and epilepsy, an enigmatic disorder: from phenotypes to pathophysiology and genetics. A systematic review. Tremor Other Hyperkinet Mov (N Y). 2018;8:503.

van Duijn CM, Dekker MC, Bonifati V, Galjaard RJ, Houwing-Duistermaat JJ, Snijders PJ, Testers L, Breedveld GJ, Horstink M, Sandkuijl LA, van Swieten JC, Oostra BA, Heutink P. Park7, a

novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. Am J Hum Genet. 2001;69(3):629–34.

van Swieten JC, Brusse E, de Graaf BM, Krieger E, van de Graaf R, de Koning I, Maat-Kievit A, Leegwater P, Dooijes D, Oostra BA, Heutink P. A mutation in the fibroblast growth factor 14 gene is associated with autosomal dominant cerebellar ataxia [corrected]. Am J Hum Genet. 2003;72(1):191–9.

van Veen S, Martin S, Van den Haute C, Benoy V, Lyons J, Vanhoutte R, Kahler JP, Decuypere JP, Gelders G, Lambie E, Zielich J, Swinnen JV, Annaert W, Agostinis P, Ghesquière B, Verhelst S, Baekelandt V, Eggermont J, Vangheluwe P. ATP13A2 deficiency disrupts lysosomal polyamine export. Nature. 2020;578(7795):419–24.

Vela-Desojo L, Urso D, Osuna-López M, Hoenicka J. Non-motor symptoms in PLA2G6-associated dystonia-parkinsonism: a case report and literature review. J Clin Med. 2022;11(6):1590.

Velayati A, Yu WH, Sidransky E. The role of glucocerebrosidase mutations in Parkinson disease and Lewy body disorders. Curr Neurol Neurosci Rep. 2010;10(3):190–8.

Verbeek MM, Steenbergen-Spanjers GC, Willemsen MA, Hol FA, Smeitink J, Seeger J, Grattan-Smith P, Ryan MM, Hoffmann GF, Donati MA, Blau N, Wevers RA. Mutations in the cyclic adenosine monophosphate response element of the tyrosine hydroxylase gene. Ann Neurol. 2007;62(4):422–6.

Vilariño-Güell C, Wider C, Ross OA, Dachsel JC, Kachergus JM, Lincoln SJ, Soto-Ortolaza AI, Cobb SA, Wilhoite GJ, Bacon JA, Behrouz B, Melrose HL, Hentati E, Puschmann A, Evans DM, Conibear E, Wasserman WW, Aasly JO, Burkhard PR, Djaldetti R, Ghika J, Hentati F, Krygowska-Wajs A, Lynch T, Melamed E, Rajput A, Rajput AH, Solida A, Wu RM, Uitti RJ, Wszolek ZK, Vingerhoets F, Farrer MJ. VPS35 mutations in Parkinson disease. Am J Hum Genet. 2011;89(1):162–7.

Whaley NR, Putzke JD, Baba Y, Wszolek ZK, Uitti RJ. Essential tremor: phenotypic expression in a clinical cohort. Parkinsonism Relat Disord. 2007;13(6):333–9.

Wittke C, Petkovic S, Dobricic V, Schaake S, MDS-endorsed PSP Study Group, Respondek G, Weissbach A, Madoev H, Trinh J, Vollstedt EJ, Kuhnke N, Lohmann K, Dulovic Mahlow M, Marras C, König IR, Stamelou M, Bonifati V, Lill CM, Kasten M, Huppertz HJ, Höglinger G, Klein C. Genotype-phenotype relations for the atypical parkinsonism genes: MDSGene systematic review. Mov Disord. 2021;36(7):1499–510.

Xiong H, Wang D, Chen L, Choo YS, Ma H, Tang C, Xia K, Jiang W, Ronai Z, Zhuang X, Zhang Z. Parkin, PINK1, and DJ-1 form a ubiquitin E3 ligase complex promoting unfolded protein degradation. J Clin Invest. 2009;119(3):650–60.

Yeetong P, Pongpanich M, Srichomthong C, Assawapitaksakul A, Shotelersuk V, Tantirukdham N, Chunharas C, Suphapeetiporn K, Shotelersuk V. TTTCA repeat insertions in an intron of YEATS2 in benign adult familial myoclonic epilepsy type 4. Brain. 2019;142(11):3360–6.

Zahorakova D, Ulmanova O, Kemlink D, Kofrankova M, Roth J, Martasek P, Ruzicka E. No association with the ETM2 locus in Czech patients with familial essential tremor. Neuro Endocrinol Lett. 2010;31(4):549–52.

Zarranz JJ, Alegre J, Gómez-Esteban JC, Lezcano E, Ros R, Ampuero I, Vidal L, Hoenicka J, Rodriguez O, Atarés B, Llorens V, Gomez Tortosa E, del Ser T, Muñoz DG, de Yebenes JG. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol. 2004;55(2):164–73.

Zeng S, Zhang MY, Wang XJ, Hu ZM, Li JC, Li N, Wang JL, Liang F, Yang Q, Liu Q, Fang L, Hao JW, Shi FD, Ding XB, Teng JF, Yin XM, Jiang H, Liao WP, Liu JY, Wang K, Xia K, Tang BS. Long-read sequencing identified intronic repeat expansions in SAMD12 from Chinese pedigrees affected with familial cortical myoclonic tremor with epilepsy. J Med Genet. 2019;56(4):265–70.

Zesiewicz TA, Chari A, Jahan I, Miller AM, Sullivan KL. Overview of essential tremor. Neuropsychiatr Dis Treat. 2010;6:401–8.

Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, Kachergus J, Hulihan M, Uitti RJ, Calne DB, Stoessl AJ, Pfeiffer RF, Patenge N, Carbajal IC, Vieregge P, Asmus F, Müller-Myhsok B, Dickson DW, Meitinger T, Strom TM, Wszolek ZK, Gasser T. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron. 2004;44(4):601–7.

Zimprich A, Benet-Pagès A, Struhal W, Graf E, Eck SH, Offman MN, Haubenberger D, Spielberger S, Schulte EC, Lichtner P, Rossle SC, Klopp N, Wolf E, Seppi K, Pirker W, Presslauer S, Mollenhauer B, Katzenschlager R, Foki T, Hotzy C, Reinthaler E, Harutyunyan A, Kralovics R, Peters A, Zimprich F, Brücke T, Poewe W, Auff E, Trenkwalder C, Rost B, Ransmayr G, Winkelmann J, Meitinger T, Strom TM. A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. Am J Hum Genet. 2011;89(1):168–75.

Chapter 4
Two Origins of Tremors Related to the Guillain-Mollaret Triangle: The Forward Model-Related Tremor and the Inferior Olive Oscillation-Related Tremor

Shinji Kakei, Mario Manto, Hirokazu Tanaka, and Hiroshi Mitoma

Abstract Lesions in the Guillain-Mollaret (G-M) triangle frequently cause various types of tremors. Nevertheless, we know relatively little about their mechanisms. The deep cerebellar nuclei, representing a primary node of the triangle, have two distinct output paths: the primary glutamatergic *excitatory* path to the thalamus, the red nucleus, and other brain stem nuclei, and the secondary GABAergic *inhibitory* path to the inferior olive (IO). The excitatory path contributes to the cerebrocerebellar loop (*the long loop*), while the inhibitory path contributes to the cerebello-olivo-cerebellar loop (*the short loop*). We propose a novel hypothesis: each loop contributes to a pathophysiologically distinct type of tremors. A lesion in the cerebrocerebellar loop causes an irregular tremor. A lesion in this loop affects the cerebellar forward model. It deteriorates its accuracy of prediction and compensation of the sensory feedback delay, resulting in *irregular instability* of *voluntary* motor control. Therefore, this type of tremors, such as intention tremor or kinetic tremor, is usually associated with other symptoms of cerebellar ataxia,

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such as dysmetria. We call this type of tremor *forward-model-related* tremor. The second type of *regular* tremor appears to originate from the synchronized oscillation of IO cells due, at least in animal models, to reduced degrees of freedom in IO activities. The regular burst activity of IO cells is precisely transmitted along the olivo-cerebello-cerebral path to the motor cortex before inducing bursts of activities of agonist and antagonist muscles. We call this type of tremor *IO-oscillation-related* tremor. Although these types of regular tremors, such as essential tremor or rest tremor, do not necessarily accompany ataxia, the aberrant IO activities (i.e., aberrant complex spike, CS, activities) may induce *moderate* maladaptation of cerebellar forward models by reducing degrees of freedom in fundamental mechanisms of plasticity such as long-term depression (LTD) and long-term potentiation (LTP) of the cerebellar circuitry. Our hypothesis explains how lesions in or around the G-M triangle result in *mixtures* of two types of tremors, resulting in a complex phenotypic presentation.

Keywords Tremor · Cerebellum · Pathogenesis · Guillain-Mollaret triangle · Predictions · Loops

4.1 Introduction

Tremor represents one of the commonest movement disorders (see this Volume). The structures of the posterior fossa (cerebellum and brainstem nuclei) play a key role in the mechanisms leading to body oscillations. In particular, the deep cerebellar nuclei (DCN) represent a primary node of the so-called Guillain-Mollaret (G-M) triangle, an anatomical circuit known to play a major role in tremor genesis both in animal models and in human disorders affecting the posterior fossa (Elble 1998). DCN have two main output paths: the primary *excitatory* path to the thalamus, the red nucleus (RN), and other brain stem nuclei, and the secondary *inhibitory* path to the inferior olive (IO). The excitatory path contributes to the cerebrocerebellar loop (*the long loop*), while the inhibitory path contributes to the cerebello-olivo-cerebellar loop (*the short loop*).

In our previous report (Kakei et al. 2021a), we proposed a hypothesis that each loop contributes to a physiologically distinct type of tremors (Table 4.1). A lesion in the cerebrocerebellar loop causes one type of irregular tremor. This type of tremor includes “intention tremor” (Charcot 1868), “tremor during target-directed

Table 4.1 Two types of tremors

Type of tremor	Responsible loop	Voluntariness	Regularity
Forward model-related tremor	The cerebrocerebellar loop (long loop)	Voluntary	Irregular
Inferior olive oscillation-related tremor	The cerebello-olivo-cerebellar loop (short loop)	Involuntary	Regular

movements," or "cerebellar outflow tremor" (Solomon et al. 1994; Bastian and Thach 1995; Krauss et al. 1995; Mitoma 1996; Deuschl et al. 1998; Lehéricy et al. 2001; Choi 2016; Boonstra et al. 2017; Bhatia et al. 2018), "kinetic tremor" (e.g., terminal tremor) (Holmes 1922a,b; Haines and Manto 2007), "irregular static tremor" (Holmes 1922a,b; Haines and Manto 2007), and "disturbed continuity of movement" (Garcin 1969). These tremors or tremor-like movements are evident during *voluntary* movements or voluntary maintenance of a posture against gravity, most notable for goal-directed movements.

The synchronized oscillation of IO cells causes the second type of regular tremor due to reduced degrees of freedom in IO activities. This type of tremors includes essential tremor (ET, a disorder for which the cerebellar cortex shows pathological changes), palatal tremor, and rest tremor, which are *involuntary*.

Nevertheless, it is notable that the two types of tremors may coexist in a patient. For instance, "Holmes' tremor (HT)," as a modern term (Deuschl et al. 1998; Kipfer and Frigerio 2013; Choi 2016), is a rare tremor characterized by a concomitant expression of intention tremor and rest tremor.

Overall, cerebellar tremors contain various phenotypes (Table 4.2). From physiological and control engineering points of view, the difference in *regularity* and *voluntariness* strongly suggests a contribution of distinct mechanisms in tremor generation. Namely, regularity and voluntariness appear to provide critical clues for understanding the pathophysiology of diverse phenotypes of tremors. We will address these issues in the following section.

4.2 Physiological Backgrounds of Two Types of Tremors

In the previous section, we proposed a hypothesis that complex phenotypes of "tremors" are explicable as a sum of two distinct conditions: involuntary regular tremors and voluntary irregular tremors (or, more precisely, tremor-like movements), and each condition is related to distinct pathophysiology of distinct cell circuitries. Next, we will address the two tremor generation mechanisms based on recent physiological, morphological, and clinical findings.

4.2.1 Two Loop Circuitries in the Dentato-rubro-olivary (Guillain-Mollaret (G-M)) Triangle and Their Functions

It has long been established that patients with lesions in or in the vicinity of the G-M triangle (Fig. 4.1) frequently show various types of tremors (Choi 2016). In addition, previous studies established that the G-M triangle contains two distinct loop circuitries: (1) the cerebrocerebellar loop (*the long loop*, Figs. 4.1 and 4.2) the cerebello-olivo-cerebellar loop (*the short loop*, Fig. 4.1).

Table 4.2 Phenotypes in tremors

Type of tremor	Clinical phenomenology	Responsible region
Kinetic tremor in Holmes' classic study	*Irregular* and discontinuous sways Sometimes marked at the beginning of the movement	The cerebellum (probably destruction of the cerebellar cortex and/or the white matter)
Static tremor in Holmes' classic study	Subtype I: *irregular* oscillation in the extension of upper limbs during the maintenance of the limb against gravity Subtype II: *regular* oscillations of a limb or some of its segments during maintenance of the limb accurately in certain positions	The cerebellum (probably destruction of the cerebellar cortex and/or the white matter)
Intention tremor	Amplitude increase (i.e., *irregularity*) during visually guided movements toward a target at the movement termination	The dentato-rubro-thalamic tract
"Holmes' tremor" (midbrain tremor)	Concomitant expression of *regular* rest tremor[a] and *irregular* intention tremor with/without postural tremor[a] Slow frequency, usually less than 4.5 Hz Late-onset of pathologies	Superior peduncle, midbrain tegmentum, and posterior thalamus
Palatal tremor	Rhythmic *regular* movements of the soft palate Late-onset of pathologies	The brainstem and the cerebellum
Essential tremor	Bilateral, largely symmetric, and *regular* postural tremor or kinetic tremor[a] Involving hands and forearm, with or without head tremor and tremor in other locations	Cerebellar cortex (Purkinjopathy)
Rest tremor	Tremor that occurs in a body part that is not voluntarily activated and is completely supported against gravity	Basal ganglia[b]

[a]Definition by Consensus Statement of the Movement Disorder Society on Tremor (1998)
[b]It is now established that basal ganglia and cerebellum communicate via disynaptic loops
Kinetic tremor: Tremor occurring during any voluntary movement
Postural tremor: Tremor present while voluntarily maintaining a position against gravity
Rest tremor: Tremor that occurs in a body part that is not voluntarily activated and is entirely supported against gravity. Adapted from Kakei et al. (2021a) under CC-BY license

4.2.1.1 Physiology of the Short Loop

Smaller inhibitory DN cells project to the contralateral IO after passing through SCP (Fig. 4.1, *scp*) and crossing the midline. The IO cells, in turn, project to the contralateral cerebellar cortex to terminate on Purkinje cells (PCs) (Fig. 4.1, *pc*) as climbing fibers (Fig. 4.1, *c*). It is important to note that activities of IO cells (equivalently, complex spike (CS) activities of PCs) are exceptionally low (~1 Hz) and rarely exceed 2–3 Hz under physiological conditions (Ishikawa et al.

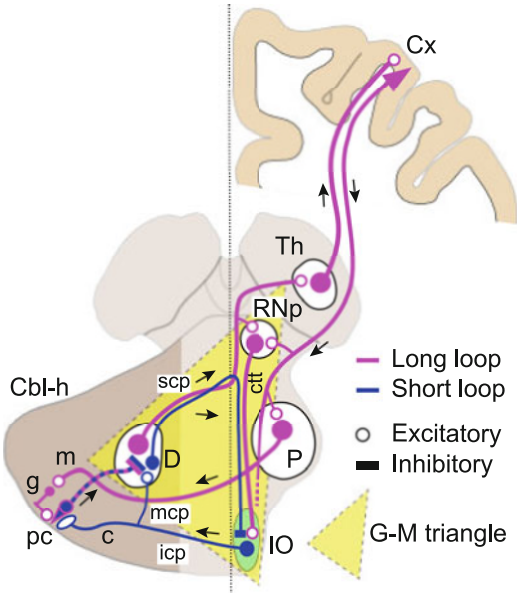

Fig. 4.1 Anatomy of the short loop (*blue*) and the long loop (*magenta*) in the Guillain-Mollaret (G-M) triangle (Bazzigaluppi et al. 2012; De Zeeuw et al. 1990; De Zeeuw et al. 1998; Garifoli et al. 2001; Kelly and Strick 2003; Tsukahara et al. 1975; Ruigrok and Voogd 1995). *c* climbing fiber, *Cbl-h* cerebellar hemisphere, *ctt* central tegmental tract, *Cx* cerebral cortex, *D* dentate nucleus, *g* granule cell, *icp* inferior cerebellar peduncle, *m* mossy fiber, *mcp* middle cerebellar peduncle, *IO* inferior olive, *P* pontine nuclei, *pc* Purkinje cell, *Rp* parvocellular red nucleus, *scp* superior cerebellar peduncle, *Th* thalamus. Note that in Fig. 4.1, we omitted collateral of the pontocerebellar projection (***P***) to the dentate nucleus (***D***) due to its extreme scarcity (Na et al. 2019). The virtual lack of the collateral is critically important to model the hemispheric part of the cerebellum as a Kalman filter (Tanaka et al. 2019, 2020; Kakei et al. 2021b). (Modified from Kakei et al. (2021a) under CC-BY license)

2014). In contrast, MFs of the long loop demonstrate much higher activities and modulations (~100 Hz) for the same conditions (Ishikawa et al. 2014). Therefore, the short loop can transmit much less information than the long loop at a single cell level. Nevertheless, it does not necessarily mean the short loop is ineffective. Indeed, synchronous activation of IO cells is effective enough to induce strong rebound excitation of DCN cells through synchronous CS activities of PC ensembles (Hoebeek et al. 2010).

4.2.1.2 Physiology of the Long Loop

The long loop is almost identical to the cerebrocerebellar loop (Kelly and Strick 2003; Strick et al. 2009; Bostan et al. 2013). Axons from larger excitatory DN cells, after passing through the superior cerebellar peduncle (SCP) (Fig. 4.1, *scp*) and crossing the midline, project to the contralateral parvocellular RN (Fig. 4.1, RN_p)

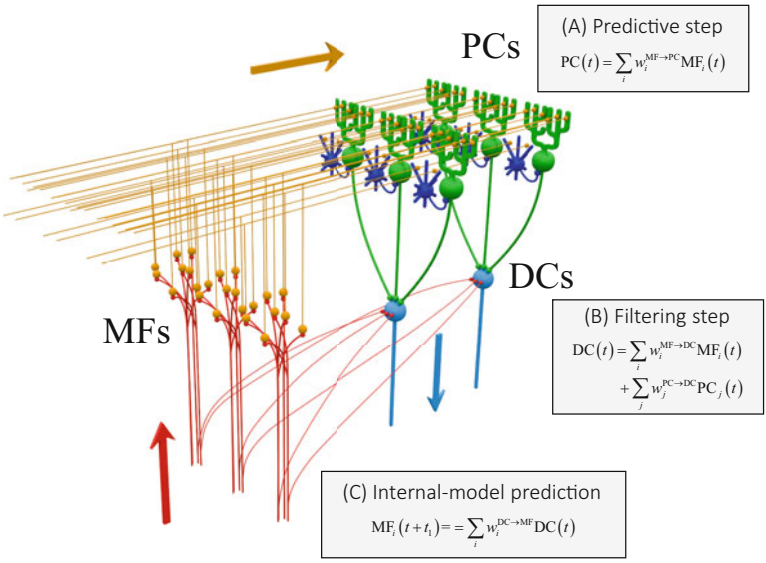

Fig. 4.2 Equivalence of the cerebrocerebellar circuitry to a Kalman filter. Schematic of the Kalman filter model of the cerebrocerebellum overlaid on the cerebellar circuit. MF mossy fiber (red), PC Purkinje cell (green), DC dentate cell (light blue). Granule cells (orange) and inhibitory interneurons (blue) that are not analyzed in this work are included to show the basic structure of the cerebellar neuron circuitry. Three stages of linear computation obtained in our analysis correspond to the three types of computation of the Kalman filter. MF inputs that contribute to the predictive step (A) and MF inputs that contribute to the filtering step (B) have different sources, as demonstrated and discussed in Tanaka et al. (2019, 2020) and Kakei et al. (2021b). MF inputs that contribute to the predictive step (A) and MF inputs that contribute to the filtering step (B) have different sources, as demonstrated and discussed in Tanaka et al. (2019, 2020) and Kakei et al. (2021b). (Reproduced from Tanaka et al. (2019) under CC-BY license)

and the thalamus (Fig. 4.1, *Th*) with collaterals. Next, thalamocortical cells relay the cerebellar inputs to various cortical areas (Fig. 4.1, *Cx*). The return path to the cerebellum is the cortico-pontocerebellar tract, which originates from various parts of cortical regions (Kelly and Strick 2003; Strick et al. 2009; Bostan et al. 2013). Next, the corticofugal axons project directly to the pontine nuclei (PN, Fig. 4.1, *P*). Finally, PN cells relay the input to the contralateral cerebellar hemisphere (Fig. 4.1, *Cbl-h*) as mossy fibers (MFs, Fig. 4.1, *m*) via the middle cerebellar peduncle (Fig. 4.1, *mcp*) to close the long loop (Kelly and Strick 2003; Strick et al. 2009).

4.2.2 *Physiological Operation of the Short Loop*

The DN (more generally the deep cerebellar nuclei (DCN)) also contains smaller GABAergic cells that project to the inferior olive (IO) to inhibit IO cells (Garifoli et al. 2001). The GABAergic terminals in IO are concentrated around gap junctions between IO cells (De Zeeuw et al. 1998) and reduce their conductance, thereby suppressing synchronous activities of IO cells (Bazzigaluppi et al. 2012). In addition, IO cells also receive massive excitatory inputs from RNp, that is, rubro-olivary projection (De Zeeuw et al. 1990; Ruigrok and Voogd 1995; Bazzigaluppi et al. 2012), which pass through the central tegmental tract (Fig. 4.1, *ctt*). The excitatory terminals of the rubro-olivary projection are concentrated around the gap junctions, thereby facilitating synchronous activities of IO cells (De Zeeuw et al. 1998; Bazzigaluppi et al. 2012). Note that the rubro-olivary cells receive collaterals of cerebello-thalamic projection (Fig. 4.1). In summary, IO cells receive inhibitory and excitatory inputs, the former suppresses, and the latter facilitates synchronous activities of IO cells.

4.2.2.1 A Putative Servo-Like Mechanism to Limit the Synchrony of IO Cells

In physiological conditions, the inhibitory input from DN and the excitatory input from RNp appear to balance in IO cells. For instance, when DN cells get more active, the direct inhibition from DN increases, while the disynaptic excitatory input via RNp (i.e., DN-RNp-IO input) also increases concomitantly. In contrast, when DN cells get inhibited, the direct inhibition from DN to IO decreases (i.e., disinhibition), while the disynaptic excitation via RNp decreases concomitantly. In this way, regardless of output alteration from DN, modulations of inhibitory and excitatory inputs to IO appear to balance each other. Overall, the synchrony between IO cells seems limited within a specific range in physiological conditions with this servo-like mechanism.

4.2.3 *Physiological Operation of the Long Loop: The Cerebrocerebellum as Loci of Forward Models*

One critical problem in biological motor control is that afferent sensory signals have inevitable temporal delays reaching the central nervous system. Therefore, the brain always observes "the past" of its own body and environment. A visual signal, for instance, arrives at the primary visual cortex about 30 ms later and at the parietal cortex about 80 ms later than the onset of the stimulus (Schmolesky et al. 1998). Among factors contributing to the feedback delay, such as a synaptic delay or an electromechanical delay, the dominant factor is the nerve conduction delay,

ranging from 10 ms for a shrew to about 100 ms for an elephant. Sensory delays are comparable to typical time scales of rapid movements and hence *not* negligible.

The delay in sensory feedback is problematic in sensing the body and environment and controlling the body. In control engineering, feedback control based on a past state causes *oscillatory and unstable* (i.e., *irregular*) movements if the delay in feedback control is of the order of or larger than the time constant of a controlled plant (Wolpert and Miall 1996). For example, the delays in visual feedback are comparable to the movement time of rapid reaching movement of the upper limb (about a few hundred milliseconds) and saccadic eye movements (typically less than 50 ms). Therefore, in biological motor control, feedback control based on delayed sensory signals would result in unstable and irregular movements. Nevertheless, animals can perform fast movement without losing their stability. It is evidence that biological motor control is equipped with a mechanism to compensate for the sensory delay for a fast and stable movement.

One mechanism proposed to cope with the delay in sensory feedback is to compute a future state of the body based on a current estimate of the body and an efferent signal of motor control. This *predictive* computation internally emulates or models an actual movement of the body by essentially solving an equation of motion of the body forward in time, thereby known as an internal forward model (Wolpert et al. 1998; McNamee and Wolpert 2019). An internal forward model predicts the state of the body time by time that is then used by a feedback controller, thereby allowing fast and stable movements. The feedback control based on the prediction of the internal forward model is called *internal feedback*. There are lines of evidence supporting the hypothesis of the predictive forward model and internal feedback from neuroimaging studies (Heinks-Maldonado et al. 2006; Bäss et al. 2008), noninvasive stimulation studies (Miall et al. 2007; Lesage et al. 2012), and psychophysical studies (Lang and Bastian 1999; Nowak et al. 2004, 2007) in human.

Previous studies repeatedly suggested the cerebrocerebellum as a potential site of the forward model based on neuroanatomical data and clinical observations (e.g., Miall et al. 1993; Haggard and Wing 1995; Wolpert and Miall 1996; Bastian 2006; Ebner and Pasalar 2008). A forward model requires two distinct inputs: (a) the copy of descending motor commands and (b) a set of sensory feedback signals, which are necessary to update the forward model. The two inputs are integrated within the forward model to generate the state estimate. The cerebellum receives both of these inputs. It receives inputs from cortical motor areas via the pontine nuclei (PN) (i.e., cerebrocerebellar inputs) (Brodal and Bijaalie 1992; Schmahmann 2004. These inputs represent the efference copy of descending motor commands (Ishikawa et al. 2014, 2016; Tomatsu et al. 2016). The cerebellum also receives somatosensory inputs directly from the ascending spinocerebellar tracts and indirectly via brain stem nuclei, such as the cuneate nucleus or the lateral reticular nucleus. These sensory inputs may provide an update on the state to be estimated. The above argument may appear to support the cerebellar forward model hypothesis. But in reality, it is on insufficient grounds because the two lines of inputs are primarily separate in the cerebellar cortex. The MF inputs from the cortical motor areas (via PN) distribute mainly in the hemispheric (i.e., lateral) part (Na et al. 2019), while

the sensory MF inputs from the spinal cord or the brain stem nuclei distribute in more rostral and medial part (the anterior lobe and the intermediate zone) (e.g., Wu et al. 1999) of the cerebellar cortex. Therefore, one may expect a convergence of the two MF inputs only in a minor part of the intermediate zone. Moreover, the simple summation of the two MF inputs contradicts their *asymmetric* roles in the forward model. The efference copy input plays an essential role in a state prediction, while the sensory input plays a critical role in updating the prediction, as will be discussed later.

As for the output from a forward model, we expect it to correlate with the future state of the motor apparatus (Wolpert and Miall 1996). In principle, we should examine the output from the cerebrocerebellum in DN because it is the sole output node from the cerebrocerebellum. Nevertheless, previous studies tried to address this issue by analyzing the Purkinje cell (PC) activities, probably due to easiness of access. Note that PCs' activity represents an intermediate representation of the cerebellar circuitry and is *not suitable* for identifying the output of a forward model. In this regard, few studies are eligible to address the nature of the output of the cerebellum (Thach 1975, 1978; Thier and Markanday 2019).

4.2.3.1 System Identification of the Transformation in the Cerebrocerebellum: Its Similarity to the Kalman Filter

If the cerebrocerebellum functions as a forward model, it is expected that the current output from DN should contain predictive information about the future MF input. Therefore, in our previous study (Tanaka et al. 2019, 2020), we examined the relationship between the activities of MFs (cerebellar inputs), PCs (intermediate representation), and DN cells (DCs) (cerebellar outputs) (Fig. 4.3). Briefly, we demonstrated that the activities of individual PCs were reconstructed precisely as a weighted sum of those of MFs. Similarly, the activities of individual DCs were reconstructed strictly as a weighted sum of those of PCs and MFs. We further proved that the activities of DCs contained predictive information about future MF inputs (Tanaka et al. 2019, 2020). Namely, the output from the cerebrocerebellum can predict 200 ms into the future to compensate for the delay of sensory feedback. We finally note that the linear relationship between MF, PC, and DC activities resembles an optimal linear estimator known as the Kalman filter (Kalman and Bucy 1961; Tanaka et al. 2019, 2020; Kakei et al. 2021b).

The functional similarity of the cerebellum to the Kalman filter has been hypothesized in some previous studies. Paulin (1989, 1997) indicated that the cerebellum could be a neural analog of a Kalman filter. Droulez and Cornílleau-Pérèz (1993) drew attention to the relevance of multisensory integration in the moving organism to the Kalman filter. Nevertheless, the suggested similarity was only at the superficial level and lacked correspondence to the cerebellar network. In our previous study, we demonstrated the three computational steps in the cerebellar circuit that are compatible with the Kalman filter (Tanaka et al. 2019, 2020) (Fig. 4.2): (1) the PCs compute a predictive state from a current estimate conveyed by

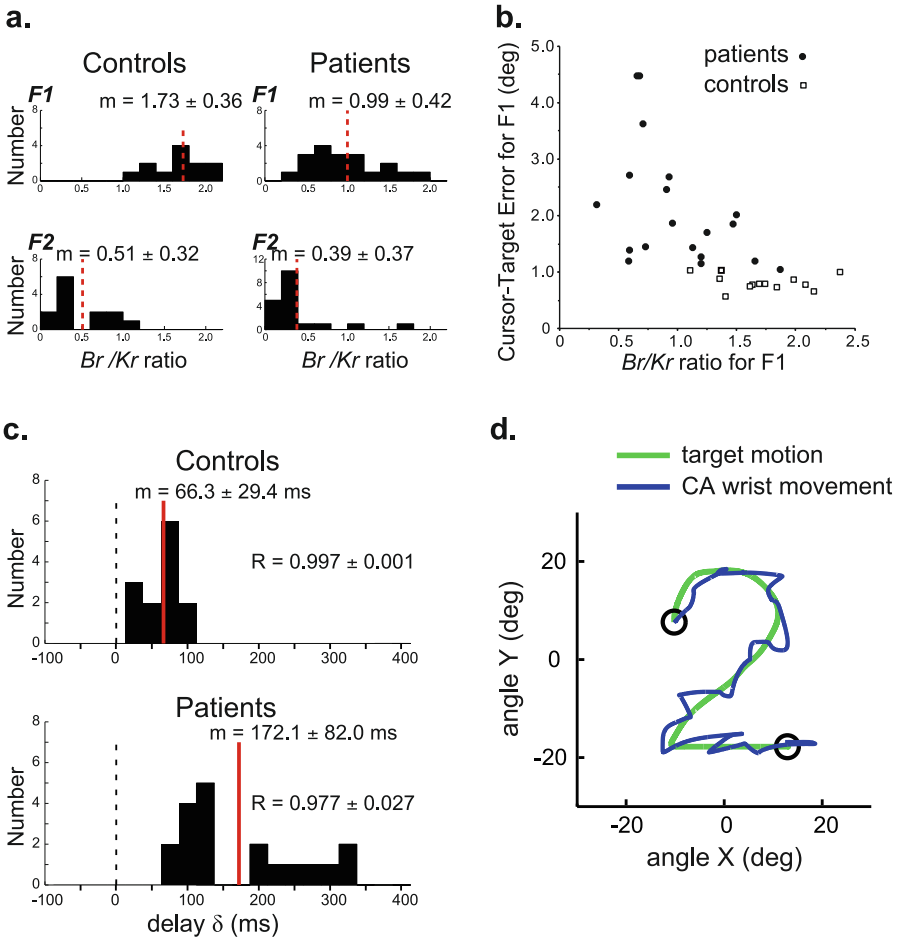

Fig. 4.3 Deficits of forward models in patients with cerebellar ataxia (CA) (**a**) Comparison of the B_r/K_r ratios that represent the recipe of the motor commands for the F1 and F2 components between the controls and the CA patients. *Controls*: B_r/K_r ratios of the control subjects for the F1 component (top) and the F2 component (bottom) ($n = 13$). Note the highly significant difference between the two components. *Patients*: B_r/K_r ratios of the patients for the F1 (top) and the F2 (bottom) components ($n = 19$). Note the selective decrease of B_r/K_r ratios for the F1 component in the patients. (**b**) Correlation between the B_r/K_r ratios for F1 component and Cursor-Target error for F1 (F1 error, in short). We defined the F1 error as an average error between the target motion and the F1 component of the movement. Note the negative correlation. (**c**) We calculated the delay of the predictive (F1) component of the movement relative to the target motion with a cross-correlation analysis for Controls ($n = 13$) and Patients ($n = 19$). (**d**) A highly ataxic wrist movement of a CA patient. Note the irregular tremor-like movement trajectory. (Adapted from Kakei et al. (2021a) under CC-BY license)

the MFs (Prediction step); (2) the DCs combine the predicted state from the PCs and sensory feedback from the MFs (Filtering step); (3) the DCs represent future activities of MFs (Cerebellar prediction).

In this way, the cerebellum appears to perform not only *an internal-forward-model prediction* but also *an optimal integration of a predicted state and sensory feedback signals* in a way that is equivalent to the Kalman filter (Tanaka et al. 2019, 2020; Kakei et al. 2021b) (Fig. 4.2).

4.2.4 Interaction Between the Two Loops

It is important to note that the two loops (the long loop and the short loop) are not independent, as depicted in Fig. 4.1. First, they share the same PCs in the cerebellar cortex. Second, the long loop has a side path to modulate the activities of IO cells through RNp. The excitatory side path (i.e., rubro-olivary) input counterbalances with the inhibitory dentato-olivary (i.e., cerebello-olivary) input. Therefore, the two loops are *interactive and dependent* on each other. The instability of one loop may consequently impact the other loop. Namely, abnormal discharges of PCs spread through the two loops (see the example of *essential tremor*).

4.3 Generation of Two Types of Tremors

We underline that both loops are designed to avoid tremor or instability, as described above. Indeed, the short loop appears to have a neural mechanism to avoid synchronous discharges of IO cells. In contrast, the long loop has evolved to function as a forward model to prevent control instability. Nevertheless, in pathological conditions, each safety mechanism may fail, resulting in a distinct type of tremor.

4.3.1 Failure of the Short Loop Results in Regular Oscillatory Tremors

As described in the Introduction, the modern definition of the term "tremor" is "the involuntary, rhythmic, oscillatory movement of a body part" (Deuschl et al. 1998; Bhatia et al. 2018). Naturally, several previous studies, both basic and clinical, addressed the location of the oscillator. A consensus is that IO plays an essential role in generating regular tremors (Baumel et al. 2009; Hoebeek et al. 2010; Bazzigaluppi et al. 2012). For instance, harmaline-induced tremor in rodents has been repeatedly used as an animal model for ET. Cheng et al. (2013) made a subcutaneous injection of harmaline hydrochloride (20 mg/kg) in mice

and then videotaped the responses. Regular *action* and *postural tremors* began no more than 5 min after harmaline injection and peaked at approximately 30 min. The forelimb tremor was *a postural* or *action tremor*, similar to that observed in ET or the so-called "Holmes' tremor (HT)" (see Sect. 4.4.1). In these model animals, a large population of IO cells discharge in synchrony and rhythmically (Handforth 2016; Zhang and Santaniello 2019; Handforth and Lang 2021), thereby inducing synchronized CSs of Purkinje cells. Then, the synchronized CSs ignite the synchronized rebound excitation of DN cells (Hoebeek et al. 2010; Witter et al. 2013). The cerebellar output finally induces, through the thalamocortical pathway, rhythmical and reciprocal discharges of agonists and antagonists muscles, that is, tremor. As described already, there is a mechanism to avoid synchronous discharges of IO cells in physiological conditions.

Nevertheless, IO cells are somehow switched into a synchronization mode in pathological conditions and for specific posture and/or movement to induce rhythmical discharges, resulting in regular tremors. Therefore, we infer that involuntary and regular tremors, such as static tremor described by Holmes (1922a,b), rest tremor, and postural tremor of HT and ET are likely to depend on the same mechanism. Furthermore, we also infer that HT and palatal tremor depend on the same mechanism, although they may not share the same efferent pathway. Namely, the palatal tremor appears to spare the Vim nucleus of the thalamus because Vim thalamotomy is ineffective for palatal tremor. In contrast, the HT depends on the Vim nucleus because it is effective to HT (Maki et al. 2015).

4.3.2 Generation of Irregular Tremor-Like Movement and Its Relevance to the Forward Model Hypothesis of the Cerebellum

Not all tremors or tremor-like movements are regular or oscillatory (see the Introduction), as noted by Holmes himself (1922a, b). Nevertheless, the irregularity in cycle and amplitude is crucial because it strongly suggests different generation mechanisms from the regular tremors described above. Moreover, it is noteworthy that the irregularity appears during *voluntary* movement, as exemplified in their names "kinetic" or "intention." Here we explain the irregularity (i.e., kinetic tremor in Holmes' classic study and intention tremor) as a malfunction of the cerebellar forward model.

Our previous study (Kakei et al. 2019) demonstrated clinical evidence that supported the cerebellar forward model hypothesis (e.g., Miall et al. 2007; Bastian 2006). A series of studies from our group confirmed the impaired predictive control in movements of patients with degenerative cerebellar ataxia (CA). We first decomposed the muscle activities for the wrist movement into a low-frequency ($\leq$0.5 Hz) component (F1) and a high-frequency (>0.5 Hz) component (F2). The F1 and F2 components represented the predictive control and the feedback

correction, respectively (Kakei et al. 2019). Then for each component, with the use of a canonical correlation analysis, we identified a recipe of muscle activities by determining a relationship between the muscle tension and movement kinematics (the wrist angle $\theta(t)$, and the wrist angular velocity $\dot{\theta}(t)$) weighted by the coefficients of K_r (the elastic term) and B_r (the viscous term) (Lee et al. 2012, 2015; Mitoma et al. 2016; Kakei et al. 2019). Importantly, the ratio of B_r/K_r characterized the recipe of muscle activities for each component. In control subjects, the B_r/K_r ratio for the predictive (F1) component showed a higher B_r/K_r ratio (Fig. 4.3a), suggesting the velocity control dominance. On the other hand, the corrective (F2) component showed a much smaller B_r/K_r ratio (Fig. 4.3a), suggesting the role of F2 component in feedback correction of positional errors (Kakei et al. 2019). In contrast, CA patients showed a selective decrease in the B_r/K_r ratio for the predictive (F1) component (Fig. 4.3a), suggesting poor recruitment of the continuous predictive velocity control and compensatory dependence on the position-dependent intermittent pursuit (Kakei et al. 2019). The loss of component-specific differences in the B_r/K_r ratio suggests *impairment of predictive control in* CA. Indeed, the *decrease* in the B_r/K_r ratio in CA correlated with the *increase* in motor errors in the predictive (F1) movement (Fig. 4.3b) (Kakei et al. 2019). Another critical difference between the control and CA was the *increased delay* of CA's predictive (F1) component (Fig. 4.3c). In the control subjects, the predictive (F1) movement lagged the target motion only by 66 ms, which was too small to be a visual feedback delay. In other words, this value provides proof of predictive motor control (Kakei et al. 2019). In contrast, in patients with CA, the delay increased by more than 100 ms, as much as 172 ms. The increased delay is comparable to a visual feedback delay, demonstrating a *lack* of compensation for feedback delay in CA patients. In summary, ataxic movements are consistent with an impairment of a forward model in terms of both accuracy and delay compensation. As mentioned already, the delay in prediction alone provides instability in control of goal-directed movement. Moreover, the increase in prediction error makes the oscillatory movement irregular because it makes each corrective (i.e., feedback) movement unreliable due to increased uncertainty of the current state and future state. The residual errors further trigger a chain of irregular corrective movements around the target trajectory (Fig. 4.3d, *CA wrist movement*). Note that the chain of corrective movements (i.e., the tremor-like movement in Fig. 4.3d) is *voluntary*, although it must be far from the CA patient's intended movement.

The long loop (Fig. 4.1) could be disrupted at any point along the loop. In addition, the disruption may vary from a partial one to a complete one. In case of complete disruption, malfunction of the forward model may be irreversible, and the resultant irregular tremor must be severe and persisting because the cerebellar reserve (Mitoma et al. 2019) is unavailable. In contrast, in the case of a partial disruption, the initial irregular tremor may recover partially or entirely depending on the level of compensation with the cerebellar reserve. For instance, Sasaki and his colleagues made cerebellar hemispherectomy in monkeys trained for skilled hand movements and observed recovery from cerebellar ataxia for many months (Sasaki and Gemba 1981; Sasaki et al. 1982). When the lesion involved both the

DN and interpositus nuclei (IN), the monkeys revealed typical cerebellar symptoms, such as hypotonia, asthenia, awkwardness, dysmetria, and *kinetic and/or static tremors*. These symptoms lasted for several months until they sacrificed the animals. However, in the cases in which the lesion involved DN but spared IN, the symptoms disappeared in a few weeks.

These studies suggest that cerebellar reserve remains much less in a lesion in the SCP than in a lesion in the cerebellar hemisphere. Thus, tremors in the former lesion (e.g., *intention tremor*) develop more irregular and abrupt natures than tremors in the latter lesion (e.g., *kinetic tremor in Holmes' classic study*). This type of irregular tremor may disappear in a short period when the cerebellar reserve is available, as typically seen in patients with a localized cerebellar stroke.

4.4 Impairments in the G-M Triangle

4.4.1 Disruptions of the Two Loops in the G-M Triangle

The G-M triangle includes vital parts of the long and short loops. In particular, both loops belong to the same bundle in SCP (Fig. 4.1, *sp*). On the other hand, SCP is divided into the ascending and descending branches after crossing the midline (Ruigrok and Voogd 1990). The ascending branch mainly contains thicker excitatory fibers, while the descending branch mainly contains finer inhibitory fibers (De Zeeuw et al. 1998). Therefore, a focal lesion of SCP or a large lesion in the G-M triangle may disrupt both loops. On the other hand, a localized lesion of the ascending or descending branches may disrupt the long or short loops separately.

For instance, selective disruption of the long loop disorganizes the online operation of the cerebellar forward model. It leads to the manifestation of irregular tremors, including kinetic tremors in Holmes' classic study and intention tremors, when the dysfunction exceeds a threshold. We also hypothesize that the disruption of the short loop (i.e., removal of inhibition on the gap junctions between IO cells) shifts IO activities toward the synchronous mode like a local injection of bicuculine into IO (Hoang et al. 2020) to induce regular tremors such as regular *postural tremor* in Holmes' classic study.

It has been a focus of debate why HT exhibits diverse tremors (i.e., rest, postural, and intention tremors) after a period of time. HT (Deuschl et al. 1998; Kipfer and Frigerio 2013; Choi 2016) was previously called cerebellar outflow tremor (Solomon et al. 1994), whose causal lesions include SCP, midbrain tegmentum, or posterior thalamus (see typical examples in Fig. 4.4). These foci are aligned on the dentato-thalamic (DN-Th) tract, dentato-olivary tract, or rubro-olivary tract and are in or close to the G-M triangle (Figs. 4.1 and 4.4). A lesion in the G-M triangle may well disrupt the two loops in a complicated manner, as exemplified in Fig. 4.4, causing the diverse types of HTs.

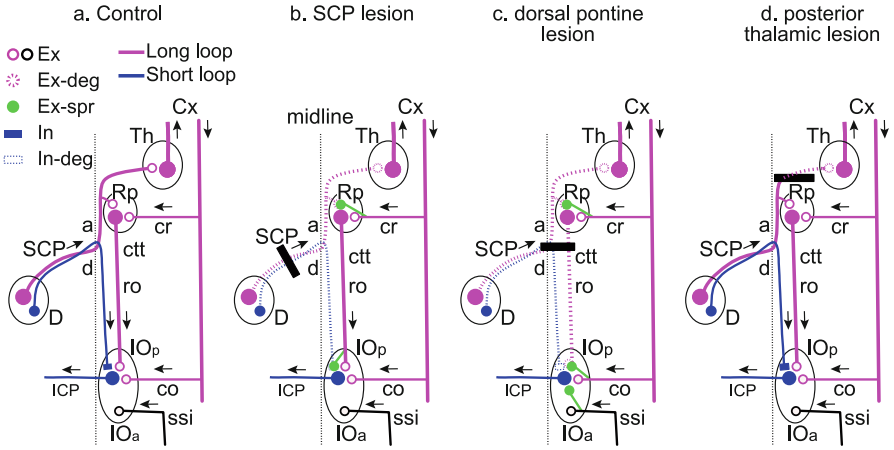

Fig. 4.4 Representative possible lesion sites in the G-M triangle for Holmes' tremor and hypothetical synaptic reorganizations in IO. We used the same color convention for the long loop (*magenta*) and the short loop (*blue*) as in Fig. 4.1. (**a**) *Control*: normal control. (**b**) *SCP lesion*: this lesion (*thick bar*) disrupts the ascending limb (***a***) and the descending limb (***d***) of SCP. The former induces synaptic reorganization in Rp, while the latter induces synaptic reorganization in the principal olive (IOp) due to degeneration of inputs. (**c**) *Dorsal pontine lesion*: this lesion disrupts the central tegmental tract (*ctt*) in addition to the two limbs of SCP. Synaptic reorganization in IOp may be more fundamental than in **b** due to the severer (***Ex*** + ***In***) loss of inputs to IOp. (**d**) *Posterior thalamic lesion*: this lesion disrupts the cerebellar input to Th and nearby pathways such as the medial lemniscus or lenticular fascicule (not depicted). Note that IOp receives input from D, while the accessory olive (IOa) receives input from the interpositus nucleus (I, not shown) and receives spinal somatosensory inputs (*ssi*). D and I have distinct projection areas in the red nucleus: D projects to Rp, while I projects to the magnocellular red nucleus (Rm, not depicted). ***co***: cortico-olivary input, *cr* cortico-rubral input, *Ex* excitatory synapses, *Ex-deg* degeneration of excitatory synapses, *Ex-spr* sprouting of excitatory synapses, *In* inhibitory synapses, *In-deg* degeneration of inhibitory synapses

For instance, an *SCP lesion* (Fig. 4.4b) disrupts both the long and short loops. As explained before, the former disruption may induce the irregular tremor, while the latter may induce the regular tremor. In IO, degenerated inhibitory terminals (Fig. 4.4b, In-deg) may be eventually replaced with sprouting of terminals from other excitatory inputs to IOp (Fig. 4.4b, Ex-spr). The increase in excitatory input further worsens the unbalance between the inhibitory and excitatory inputs and intensifies the synchrony of IOp cells.

A *dorsal pontine lesion* (Fig. 4.4c) may also induce simultaneous disruptions of the two loops near the bifurcation point of the descending limb (***d***) and the ascending limb (***a***) of SCP, resulting in coexistence of the regular and irregular tremors. In addition, this lesion may also disrupt neighboring ctt (Fig. 4.4c) and may cause even more fundamental reorganization in IOp due to the severer loss of inputs to IOp. For instance, the degeneration of inhibitory terminals from the dentate (D)(Fig. 4.4c, In-deg) and the excitatory terminals from the red nucleus (Rp) (Fig. 4.4c, Ex-deg) may

provide even more ample space for sprouting from other excitatory inputs (Fig. 4.4c, Ex-spr, e.g., co and ssi).

A *posterior thalamic lesion* (Fig. 4.4d) may provide selective disruption of the cerebello-thalamic projection (i.e., a part of the long loop (***a***)) while sparing the short loop (***d***). In other words, synaptic reorganization in IO is unlikely for this lesion. Therefore, it is most likely to observe irregular tremors, while it is relatively unlikely to observe regular tremors. In addition, this lesion may also disrupt neighboring pathways such as the medial lemniscus or lenticular fascicule (not depicted in Fig. 4.4).

Recent clinical observations by Nsengiyumva (2021) appear, at least partly, to support these inferences. They examined 17 patients with HT. Eleven patients representing the midbrain type of HT had a similar clinical pattern. They all had a myorythmic tremor at rest, which increased the amplitude on posture and goal-directed movements. The myorythmic tremor at rest appears to correspond to the regular tremor, while the increase in amplitude on goal-directed movement seems to conform to the irregular tremor. Furthermore, they had no other abnormal movements in the affected limb. The symptoms of these patients appear compatible with the presumed symptoms for the SCP lesion (Fig. 4.4b) or the dorsal pontine lesion (Fig. 4.4c) as described above.

The other six patients, representing the posterior thalamic type of HT, had slow, irregular, and large proximal tremors and distal choreathetoid movements. These patients also had significant proximal/distal dystonic posturing associated with proprioceptive sensory deficits. These symptoms appear compatible with the presumed symptoms for the posterior thalamic lesion (Fig. 4.4d).

4.4.2 Disinhibition of IO as a Pathophysiological Mechanism for Regular Tremors and Its Implication for ET

In the SCP lesion (Fig. 4.4b) and the dorsal pontine lesion (Fig. 4.4c), the primary degeneration of the inhibitory synapses and the secondary sprouting of the excitatory synapses may result in hyperactivity of IO cells and eventually result in regular tremors with hypertrophic olivary degeneration (Gatlin et al. 2011; Wang et al. 2019). On the other hand, there are no known morphologic changes in the inputs to IO in ET patients. Recently, Choe et al. (2016) reported a significant decrease in PCs in ET patients compared to age-matched controls. The reduced PC inhibition may result in hyperactivity of DCN cells due to reduced PC inhibition (i.e., disinhibition). Nevertheless, the hyperactivity of DCN cells alone is not enough to induce the synchronous activity of IO cells and regular tremors as long as there remains a balance between the inhibitory and excitatory inputs in IO (see Sect. 4.2.2). It is necessary to identify the missing piece that breaks the balance to understand the pathophysiology of ET.

4.4.3 *Reorganization and Maladaptation in the G-M Triangle*

4.4.3.1 Reorganization in the Short Loop

The emergence of regular rest or postural tremors in HT needs several weeks or longer (usually 4 weeks to 2 years) after disruption of the short loop. The longer latent period may correspond to the time required for synaptic reorganization around the gap junctions of IO cells, that is, reduction of inhibitory terminals and concomitant sprouting of excitatory terminals (Fig. 4.4b and c) (Tsukahara et al. 1975; Katsumaru et al. 1986). However, this hypothesis does not necessarily exclude the possibility of regular tremors during acute phases (Choi 2016). For instance, the above-mentioned harmaline-induced tremor model suggests the existence of a *switch* to ignite regular tremors without chronic reorganizations of neuron circuitries.

4.4.3.2 Induction of Maladaptation Caused by Regular Tremors

There is a causal relationship between abnormal synchronization of IO activities and the regular tremor. The aberrant IO activities, through aberrant CS activities, may induce *secondary* maladaptation of cerebellar forward models through aberrant patterns of LTD and/or LTP of the cerebellar circuitry (Fig. 4.5, *dashed arrow*). The problem may be twofold. First, during a regular tremor, average CS activities (>4 Hz) are much higher than normal CS activities (~1 Hz). Therefore, CS activities

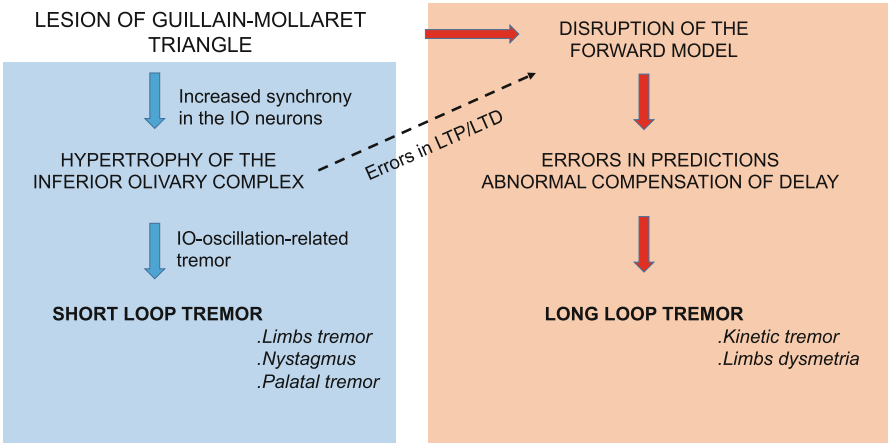

Fig. 4.5 Summary diagram. A lesion in the G-M triangle may well disrupt the short loop (left panel) and the long loop (right panel) to cause diverse types of tremors. In addition, the aberrant activities in the short loop (i.e., aberrant complex spike activities) may induce *secondary* maladaptation of cerebellar forward models through aberrant patterns of LTD and/or LTP of the cerebellar circuitry (*dashed arrow*). (Adapted from Kakei et al. (2021a) under CC-BY license)

are corrupted by increased noise (i.e., low S/N ratio) during regular tremors. Second, Hoang et al. (2020) recently found that high coupling strengths of IO cells induce their synchronous firing and decrease the amount of information encoded by the firing dynamics of IO cells. Therefore, the two mechanisms may gradually deteriorate the forward model and increase its prediction error in the long term, resulting in moderately awkward motor control and/or *irregular* tremors. In this regard, it may be possible with this mechanism to explain moderately awkward and unskilled (if not severely ataxic) movements of ET or Parkinson's disease patients with rest tremor and even the intention tremor of HT.

In conclusion, it is important to note that in HT, or more generally tremors induced by lesions in the G-M triangle, disruptions of the two loops may coexist and cause various combinations of the regular and irregular types of tremors depending on location, size, and incubation period of the lesion. In addition, the complex pathological condition is further prone to secondary changes such as synaptic reorganization and maladaptation in the long term. Finally, since the two loops are *interactive and dependent* on each other, *pathological crosstalk* occurs in these loops.

4.5 Consideration of Neuroimaging Studies

Our proposal of dual pathogenesis will now require an in-depth multimodal assessment to establish how it can be translated into direct clinical practice. This ambitious goal will likely remain a highly challenging task. For the time being, let us conclude this manuscript with a brief consideration of neuroimaging studies because it allows us to assess the morphological and functional aspects of tremor patients. Structural imaging by MRI provides insights into focal or diffuse anatomical lesions, complemented in particular by diffusion imaging (DTI), fMRI, and assessment of metabolic brain networks (Klein 2013; Pourfar et al. 2013). Diffusion tractography shows the neuronal connections in the brain. It allows to draw conclusions in terms of deafferentation following a focal lesion such as a stroke and infer the remote effects of this connection.

One typical example was provided by Seidel et al. (2009), who reported the case of a 20-year-old patient with right-sided HT 9 months after a midbrain/pontine hemorrhage. Tractography demonstrated reduced fiber connectivity of the superior and middle cerebellar peduncles on the lesioned side. The hemorrhage affected the red nucleus directly and impacted nigro-striatal projections and the cortico-rubro-cerebellar loop, underlining that the tremor was probably due to a deafferentation mechanism (Klein 2013). These findings are consistent with the present proposal of reorganizations in the short loop (see Sect. 4.4.2). Tractography has been used successfully to target the dentato-rubro-thalamic tract to plan the implantation of electrodes for deep brain stimulation, in combination with traditional landmark-based targeting techniques (Coenen et al. 2011).

In essential tremor, a functional disconnection of dentate nuclei with cortical, subcortical, and cerebellar areas has been demonstrated recently (Tikoo et al. 2020). Changes in the cerebellum positively correlated with tremor amplitude, by contrast with changes in the bilateral thalamus which negatively correlated with tremor amplitude. The functional connectivity with the supplementary motor area, precentral and postcentral gyri, and prefrontal cortex negatively correlated with tremor scores. These observations confirm the importance of the cerebello-thalamo-cortical pathway in ET. These imaging studies favor the present hypothesis that a pathological synchronization of IO cells sparks a chain reaction in the cerebello-cerebral circuits (e.g., synchronous CS, rebound excitation of DN cells, and finally, rhythmical activation of M1 through the cerebello-thalamo-cortical pathway) (see Sect. 4.3.1). However, neuropathological studies have identified lesions in the cerebellar cortex, especially at the level of Purkinje neurons, hence the terminology of Purkinjopathy (Grimaldi and Manto 2013). The involvement of the cerebellar cortex might be a prime mover for ET. In the systematic literature search by Ceresa and Quattrone (2016), which combined the terms essential tremor with the following keywords MRI, VBM, MRS, DTI, fMRI, PET, and SPECT, a total of 51 neuroimaging studies met search criteria, divided into 19 structural and 32 functional studies. These studies showed similar findings without defining a precise topography of the neurodegenerative process. Most studies identified functional and structural abnormalities in several portions of the anterior and posterior cerebellar lobules. Still, the authors stressed the absence of correlation between these neural changes and the clinical symptoms of ET. The authors also highlighted the high variability in results.

We did not expand here on the numerous MRI reports describing the location of lesions in the G-M triangle and the involvement of ctt, the dentato-rubro-thalamic tract, the transaxonal degeneration, and Wallerian degeneration (see the recent work of Raeder et al. (2020) focusing on imaging characteristics of transaxonal degenerations involving cerebellar connections).

4.6 Conclusion

We propose an explanation of complex phenotypes of tremors or tremor-like movements based on two physiological principles related to the G-M triangle, pointing out the abnormal motor behavior based on errors in feedforward and feedback loops. The G-M triangle appears in our view as an interface between sensory and motor processes. Tremor is the result of errors in predictions executed by the posterior fossa structures, including the cerebellum, causing an unstable state. Although our hypothesis may not cover all tremors or tremor-like movement disorders, our approach integrates the latest theories of cerebellar physiology. It explains how various lesions in or around the G-M triangle result in tremors or tremor-like movements. These two elemental mechanisms can be extrapolated to the loops between dentate nuclei and reticular nuclei in the brainstem acting as

reverberating (Dietrichs et al. 1999). We did not speculate on the neurobiological mechanisms underlying the aberrant synaptogenesis in the G-M triangle (Sarnat et al. 2013).

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References

Bäss P, Jacobsen T, Schröger E. Suppression of the auditory N1 event-related potential component with unpredictable self-initiated tones: evidence for internal forward models with dynamic stimulation. Int J Psychophysiol. 2008;70:137–43.

Bastian AJ. Learning to predict the future: the cerebellum adapts feedforward movement control. Curr Opin Neurobiol. 2006;16:645–9.

Bastian AJ, Thach WT. Cerebelalr outflow lesions: a comparison of movement deficits resulting from lesions at the levels of the cerebellum and thalamus. Ann Neurol. 1995;38(6):881–92.

Baumel Y, Jacobson GA, Cohen D. Implications of functional anatomy on information processing in the deep cerebellar nuclei. Front Cell Neurosci. 2009;3:14.

Bazzigaluppi P, Ruigrok T, Saisan P, De Zeeuw CI, de Jeul M. Properties of the Nucleo-Olivary Pathway: an in vivo whole-cell patch clamp study. PLoS One. 2012;7(9):e46360.

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. From task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33(1):75–87.

Boonstra F, Florescu G, Evans A, Steward C, Mitchell P, Desmond P, et al. Tremor in multiple sclerosis is associated with cerebello-thalamoic pathology. J Neural Transm. 2017;124:1509–14.

Bostan AC, Dum RP, Strick PL. Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn Sci. 2013;17:241–54.

Brodal P, Bjaalie JG. Organization of the pontine nuclei. Neurosci Res. 1992;13:83–118.

Ceresa A, Quattrone A. Linking essential tremor to the cerebellum : neuroimaging evidence. Cerebellum. 2016;15(3):263–75.

Charcot JM. Séance du 14mars. CR Soc Biol (Paris). 1868;20:13.

Cheng MM, Tang G, Kuo S-H. Harmaline-induced tremor in mice: videotape documentation and open questions about the model. Tremor Other Hyperkinet Mov (N Y). 2013;3:tre-03-205-4668-1. https://doi.org/10.7916/D8H993W3.

Choe M, Cortés E, Vonsattel JG, Kuo S-H, Faust PL, Louis ED. Purkinje cell loss in essential tremor: Random sampling quantification and nearest neighbor analysis. Mov Disord. 2016;31(3):393–401.

Choi SM. Movement disorders following cerebrovascular lesions in cerebellar circuits. J Mov Disord. 2016;9(2):80–8.
Coenen VA, Allert N, Mädler B. A role of diffusion tensor imaging fiber tracking in deep brain stimulation surgery: DBS of the dentato-rubro-thalamic tract (drt) for the treatment of therapy-refractory tremor. Acta Neurochir. 2011;153(8):1579–85.
De Zeeuw CI, Holstege JC, Ruigrok TJ, Voogd J. Mesodiencephalic and cerebellar terminals terminate upon the same dendritic spines in the glomeruli of the cat and rat inferior olive: an ultrastructural study using a combination of [3H]leucine and wheat germ agglutinin coupled horseradish peroxidase anterograde tracing. Neuroscience. 1990;34:645–55.
De Zeeuw CI, Simpson JI, Hoogenraad CC, Galjart N, Koekkoek SKE, Ruigrok TJH. Microcircuitry and function of the inferior olive. Trends Neurosci. 1998;21:391–400.
Deuschl G, Bain P, Brin M. Consensus statement of the movement disorder society on tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13(Suppl 3):2–23.
Dietrichs E, Heier MS, Faye-Lund H, Nakstad PH. Bulbar myoclonus without palatal myoclonus. A hypothesis on pathophysiology. Eur J Neurol. 1999;6:367–70.
Droulez J, Cornílleau-Pérèz V. Application of the coherence scheme to the multisensory fusion problem. In: Berthoz A, editor. Multisensory control of movement. Oxford: Oxford University Press; 1993. p. 485–501.
Ebner TJ, Pasalar S. Cerebellum predicts the future motor state. Cerebellum. 2008;7:583–8.
Elble RJ. Animal models of action tremor. Mov Disord. 1998;13(Suppl 3):35–9.
Garcin R. The ataxias. In: Vinken PJ, Bruyn GW, editors. Handbook of Clinical Neurology, Volume 1 Disturbances of nervous function. Amsterdam, Nertherland: North Holland Publishing Company; 1969. p. 309–35.
Garifoli A, Scardilli G, Perciavalle V. Effects of cerebellar dentate nucleus GABAergic cells on rat inferior olivary neurons. Neuroreport. 2001;12:3709–13.
Gatlin JL, Wineman R, Schlakman B, Buciuc R, Khan M. Hypertrophic Olivary degeneration after resection of a pontine cavernous malformation: a case report. J Radiol Case Rep. 2011;5:24–9.
Grimaldi G, Manto M. Is essential tremor a Purkinjopathy? The role of the cerebellar cortex in its pathogenesis. Mov Disord. 2013;28:1759–61.
Haggard P, Wing A. Coordinate responses following mechanical perturbations of the arm during prehension. Exp Brain Res. 1995;102:483–94.
Haines DE, Manto MU. Cerebellar classic II. Cerebellum. 2007;6:141–56.
Handforth A. Linking essential tremor to the cerebellum-animal model evidence. Cerebellum. 2016;15:285–98.
Handforth A, Lang EJ. Increased Purkinje cell complex spike and deep cerebellar nucleus synchrony as a potential basis for syndromic essential tremor. A review and synthesis of the literature. Cerebellum. 2021;20:266–81.
Heinks-Maldonado TH, Nagarajan SS, Houde JF. Magnetoencephalographic evidence for a precise forward model in speech production. Neuroreport. 2006;17:1375–9.
Hoang H, Lang EJ, Hirata Y, Tokuda IT, Aihara K, Toyama K, Kawato M, Schweighofer N. Electrical coupling controls dimensionality and chaotic firing of inferior olive neurons. PLoS Comp Biol. 2020;16(7):e1008075.
Hoebeek FE, Witter L, Ruigrok TJH, De Zeeuw CI. Differential olivo-cerebellar cortical control of rebound activity in the cerebellar nuclei. PNAS. 2010;107:8410–5.
Holmes G. Clinical symptoms of cerebellar disease and their interpretation, Lecture I. Lancet. 1922a;202(1):1178–82.
Holmes G. Clinical symptoms of cerebellar disease and their interpretation, Lecture II. Lancet. 1922b;202(1):1232–7.
Ishikawa T, Tomatsu S, Tsunoda Y, Lee J, Hoffman DS, Kakei S. Releasing dentate nucleus cells from Purkinje cell inhibition generates output from the cerebrocerebellum. PLoS One. 2014;9:e108774.
Ishikawa T, Tomatsu S, Izawa J, Kakei S. The cerebro-cerebellum: Could it be loci of forward models? Neurosci Res. 2016;104:72–9.

Kakei S, Lee J, Mitoma H, Tanaka H, Manto M, Hampe CS. Contribution of the cerebellum to predictive motor control and its evaluation in ataxic patients. Front Hum Neurosci. 2019;13:216. https://doi.org/10.3389/fnhum.2019.00216.

Kakei S, Manto M, Tanaka H, Mitoma H. Pathophysiology of cerebellar tremor: the forward model-related tremor and the inferior olive oscillation-related tremor. Front Neurol. 2021a;12:694653.

Kakei S, Tanaka H, Ishikawa T, Tomatsu S, Lee J. The input-output organization of the cerebrocerebellum as Kalman filter. In: Mizusawa H, Kakei S, editors. Cerebellum as a CNS Hub. Cham: Springer; 2021b. p. 391–411.

Katsumaru H, Murakami F, Wu J-Y, Tsukahara N. Sprouting of GABAergic synapses in the red nucleus after lesions of the nucleus interpositus in the cat. J Neurosci. 1986;6:2864–74.

Kalman RE, Bucy RS. New results in linear filtering and prediction theory. J Basic Eng 1961:83:95–108. https://doi.org/10.1115/1.3658902.

Kelly RM, Strick PL. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosci. 2003;23:8432–44.

Kipfer S, Frigerio SB. Post-ischemic stroke Holmes' tremor of the upper limb. Mov Disord. 2013;28:1347.

Klein JC. Diffusion imaging in tremor. In: Grimaldi G, Manto M, editors. Mechanisms and emerging therapies in tremor disorders. New York: Springer; 2013. p. 391–401.

Krauss JK, Wakhloo AK, Nobbe F, Tränkle R, Mundinger F, Seeger W. Lesion of dentatothalamic pathways in severe post-traumatic tremor. Neurol Res. 1995;17(6):409–16.

Lang CE, Bastian AJ. Cerebellar subjects show impaired adaptation of anticipatory EMG during catching. J Neurophysiol. 1999;82(5):2108–19.

Lee J, Kagamihara Y, Tomatsu S, Kakei S. The functional role of the cerebellum in visually guided tracking movement. Cerebellum. 2012;11:426–33.

Lee J, Kagamihara Y, Kakei S. A new method for functional evaluation of motor commands in patients with cerebellar ataxia. PLoS One. 2015;10:e0132983. https://doi.org/10.1371/journal.pone.0132983.

Lehéricy S, Grand S, Pollak P, Poupon F, Le Bas JF, Limousin P, et al. Clinical characteristics and topography of lesions in movement disorders due to thalamic lesions. Neurology. 2001;57:1055–66.

Lesage E, Morgan BE, Olson AC, Meyer AS, Miall RC. Cerebellar rTMS disrupts predictive language processing. Curr Biol. 2012;22:R794–5.

Maki F, Sato S, Watanabe K, Yanagisawa T, Hagiwara Y, Shimizu T, Hasegawa Y. Vim thalamotomy in a patient with Holmes' tremor and palatal tremor – Pathophysiological considerations. BMC Neurol. 2015;15:26.

McNamee D, Wolpert DM. Internal models in biological control. Annu Rev Control Robot Auton Syst. 2019;2:339–64.

Miall RC, Weir DJ, Wolpert DM, Stein J. Is the cerebellum a Smith predictor? J Motor Behav. 1993;25:203–16.

Miall RC, Christensen LO, Cain O, Stanley J. Disruption of state estimation in the human lateral cerebellum. PLoS Biol. 2007;5:e316.

Mitoma H. Intention tremor exaggerated by visually guided movement. Eur Neurol. 1996;36(3):177–8.

Mitoma H, Adhikari K, Aeschlimann D, Chattopadhyay P, Hadjivassiliou M, Hampe CS, Honnorat J, Joubert B, Kakei S, Lee J, Manto M, Matsunaga A, Mizusawa H, Nanri K, Shanmugarajah P, Yoneda M, Yuki N. Consensus paper: neuroimmune mechanisms of cerebellar ataxias. Cerebellum. 2016;15:213–32.

Mitoma H, Buffo A, Gelfo F, Guell X, Fucà E, Kakei S, Lee J, Manto M, Petrosini L, Shaikh AG, Schmahmann JD. Consensus paper. Cerebellar reserve: from cerebellar physiology to cerebellar disorders. Cerebellum. 2019;19:131–53.

Na J, Sugihara I, Shinoda Y. The entire trajectories of single pontocerebellar axons and their lobular and longitudinal terminal distribution patterns in multiple aldolase C-positive compartments of the rat cerebellar cortex. J Comp Neurol. 2019;527:2488–511.

Nowak DA, Hermsdörfer J, Rost K, Timmann D, Topka H. Predictive and reactive finger force control during catching in cerebellar degeneration. Cerebellum. 2004;3:227–35.
Nowak DA, Topka H, Timmann D, Boecker H, Hermsdörfer J. The role of the cerebellum for predictive control of grasping. Cerebellum. 2007;6:7–17.
Nsengiyumva N, Barakat A, Macerollo A, Pullicino R, Bleakley A, Bonello M, Ellis RJB, Alusi SH. Thalamic versus midbrain tremor; two distinct types of Holmes' Tremor: a review of 17 cases. J Neurol. 2021;268:4152–62.
Paulin M. A Kalman filter theory of the cerebellum. In: Arbib MA, Amari S, editors. Dynamic interactions in neural networks: models and data. New York: Springer; 1989. p. 239–59.
Paulin M. Neural representations of moving systems. In: Schmahmann JD, editor. The cerebellum and cognition. San Diego: Academic Press; 1997. p. 515–33.
Pourfar M, Niethammer M, Eidelberg D. Metabolic networks in Parkinson's disease. In: Grimaldi G, Manto M, editors. Mechanisms and emerging therapies in tremor disorders. New York: Springer; 2013. p. 403–15.
Raeder MTL, Reis EP, Campos BM, Zamilute IAG, França Júnior MC, Reis F. Transaxonal degenerations of cerebellar connections: the value of anatomical knowledge. Arq Neuropsiquiatr. 2020;78(5):301–6.
Ruigrok TJH, Voogd J. Cerebellar nucleo-olivary projections in the rat: an anterograde tracing study with *Phaseolus vulgaris*-leucoagglutinin (PHA-L). J Comp Neurol. 1990;298:315–33.
Ruigrok TJH, Voogd J. Cerebellar influence on olivary excitability in the cat. Eur J Neurosci. 1995;7:679–93.
Sarnat HB, Flores-Sarnat L, Auer RN. Sequence of synaptogenesis in the fetal and neonatal cerebellar system - part 1: Guillain–Mollaret triangle (dentato-rubro-olivo-cerebellar circuit). Dev Neurosci. 2013;35:69–81.
Sasaki K, Gemba H. Cortical field potentials preceding self-paced and visually initiated hand movements in one and the same monkey and influences of cerebellar hemispherectomy upon the potentials. Neurosci Lett. 1981;25:287–92.
Sasaki K, Gemba H, Mizuno N. Cortical field potentials preceding visually initiated hand movements and cerebellar actions in the monkey. Exp Brain Res. 1982;46:29–36.
Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J Neuropsychiatry Clin Neurosci. 2004;16:367–78.
Schmolesky MT, Wang Y, Hanes DP, Thompson KG, Leutgeb S, Schall JD, Leventhal AG. Signal timing across the macaque visual system. J Neurophysiol. 1998;79:3272–8.
Seidel S, Kasprian G, Leutmezer F, Prayer D, Auff E. Disruption of nigrostriatal and cerebellothalamic pathways in dopamine responsive Holmes' tremor. J Neurol Neurosurg Psychiatry. 2009;80(8):921–3.
Solomon DH, Barohn RJ, Bazan C, Grissom J. The thalamic ataxia syndrome. Neurology. 1994;44(5):810–4.
Strick PL, Dum RP, Fiez JA. Cerebellum and nonmotor function. Annu Rev Neurosci. 2009;32:413–34.
Tanaka H, Ishikawa T, Kakei S. Neural evidence of the cerebellum as a state predictor. Cerebellum. 2019;18:349–71. https://doi.org/10.1007/s12311-018-0996-4.
Tanaka H, Ishikawa T, Lee J, Kakei S. The cerebre-cerebellum as a locus of forward model; a review. Front Syst Neurosci. 2020;14:19.
Thach WT. Timing of activity in cerebellar dentate nucleus and cerebral motor cortex during prompt volitional movement. Brain Res. 1975;88:233–41.
Thach WT. Correlation of neural discharge with pattern and force of muscular activity, joint position, and direction of intended next movement in motor cortex and cerebellum. J Neurophysiol. 1978;41:654–76.
Thier P, Markanday A. Role of the vermal cerebellum in visually guided eye movements and visual motion perception. Annu Rev Vis Sci. 2019;5:247–68.
Tikoo S, Pietracupa S, Tommasin S, Bologna M, Petsas N, Bharti K, Berardelli A, Pantano P. Functional disconnection of the dentate nucleus in essential tremor. J Neurol. 2020;267(5):1358–67.

Tomatsu S, Ishikawa T, Tsunoda Y, Lee J, Hoffman DS, Kakei S. Information processing in the hemisphere of the cerebellar cortex for control of wrist movement. J Neurophysiol. 2016;115:255–70.

Tsukahara N, Hultborn H, Murakami F, Fujito Y. Electrophysiological study of formation of new synapses and collateral sprouting in red nucleus neurons after partial denervation. J Neurophysiol. 1975;38:1359–72.

Wang H, Wang Y, Wang R, Li Y, Wang P, Li J, Du J. Hypertrophic olivary degeneration: a comprehensive review focusing on etiology. Brain Res. 2019;1718:53–63.

Witter L, Canto CB, Hoogland TM, de Gruijl JR, De Zeeuw CI. Strength and timing of motor responses mediated by rebound firing in the cerebellar nuclei after Purkinje cell activation. Front Neural Cricuits. 2013;7:133.

Wolpert DM, Miall RC. Forward models for physiological motor control. Neural Netw. 1996;9:1265–79.

Wolpert DM, Miall RC, Kawato M. Internal models in the cerebellum. Trends Cogn Sci. 1998;2:338–47.

Wu HS, Sugihara I, Shinoda Y. Projection patterns of single mossy fibers originating from the lateral reticular nucleus in the rat cerebellar cortex and nuclei. J Comp Neurol. 1999;411:97–118.

Zhang X, Santaniello S. Role of cerebellar GABAergic dysfunctions in the origins of essential tremor. PNAS. 2019;116:13592–601.

Chapter 5
Physiologic Tremor

Rodger J. Elble

Abstract Physiologic tremor is barely visible to the unaided eye unless it is enhanced by fatigue, anxiety, thyroxin, or a sympathomimetic drug. Consequently, physiologic tremor is assessed with sensitive motion transducers such as miniature accelerometers, gyroscopic angular velocity transducers, and force transducers. Muscle activity is recorded electromyographically, using skin electrodes for gross motor activity and needle electrodes for single motor unit activity. Using these methods, investigators have demonstrated mechanical-reflex and central-neurogenic mechanisms of physiologic tremor and have identified the involvement of central motor pathways with high-resolution electroencephalography and magnetoencephalography. Low-frequency 1–3 Hz aperiodic involuntary movement is the main source of positional error unless physiologic tremor is enhanced by fatigue, anxiety, or a medication. The study of physiologic tremor has provided important insight into mechanisms of normal motor control. These topics are reviewed in this chapter.

Keywords Physiologic tremor · Accelerometry · Electromyography · Oscillation · Stretch reflex · Biomechanics

5.1 Introduction

Physiologic tremor is barely visible to the unaided eye unless it is enhanced by fatigue, anxiety, thyroxin, or sympathomimetic drugs. Consequently, the study of physiologic tremor requires the use of sensitive motion transducers such as miniature accelerometers, gyroscopic angular velocity transducers, or force transducers, and muscle activity is recorded electromyographically, using skin electrodes for gross motor activity and needle electrodes for single motor unit activity (Elble and Deuschl 2002; Vial et al. 2019). Motion transducer and electromyographic

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(EMG) signals are usually recorded digitally with a computer and analyzed with spectral (Fourier) techniques to determine the amplitude and frequency of tremor and the coherence (linear correlation squared) between tremor and EMG activity (Elble and McNames 2016). These electrophysiologic methods are also used to quantify the effect of mass (inertial) and spring (elastic) loading on tremor frequency. Using these methods, investigators have demonstrated mechanical-reflex and central-neurogenic mechanisms of physiologic tremor and have identified central motor pathways with high-resolution electroencephalography and magnetoencephalography. These physiologic oscillations have provided important insight into the mechanisms of normal motor control, but low-frequency 1–3 Hz aperiodic involuntary movement is the main source of positional error unless physiologic tremor is enhanced with fatigue, anxiety, or a medication (Carignan et al. 2010). These phenomena are reviewed in this chapter.

5.2 Mechanical Resonant Tremor

Normal mechanical resonant oscillation is the principal component of physiologic tremor and is invariably present in tremor recordings (Elble and Randall 1978; Fox and Randall 1970; Stiles 1976). This oscillation is so named because it emerges primarily from the inertial, viscous, and elastic properties of the body. Small irregularities in muscle force produce damped joint oscillation at a frequency ω determined by the equation $\omega = \sqrt{K/I}$, where K is the stiffness of the joint and I is the inertia. Under normal circumstances, the response of somatosensory receptors (e.g., muscle spindles) to the mechanical oscillations of physiologic tremor is too weak to entrain motoneurons at the frequency of tremor (Hagbarth and Young 1979; Young et al. 1975). Consequently, the EMG and muscle force are not modulated at the frequency of tremor, and the rectified-filtered EMG spectrum is statistically flat (Fig. 5.1).

Normal elbow tremor has a frequency 3–5 Hz that is lower than the 7–10 Hz frequency of wrist tremor (Fig. 5.1) because the moment of inertia of forearm and hand, rotating about the elbow, is much greater than that of the hand rotating about the wrist (Elble and Randall 1978; Fox and Randall 1970; Stiles 1976). Similarly, a finger has much less mass (inertia) than the entire hand or forearm, so the frequency of metacarpophalangeal joint tremor is 17–30 Hz. Adding mass to a limb decreases tremor frequency, and additional stiffness K increases frequency in proportion to $\sqrt{K/I}$ (Takanokura and Sakamoto 2005). Similarly, voluntary cocontraction of the muscles about a joint produces a slight increase in tremor frequency due to increased joint stiffness, and gradual relaxation of the joint reduces the frequency of mechanical resonant tremor (Stiles and Randall 1967).

The musculoskeletal system does not oscillate in the absence of exogenous or endogenous forces or perturbations. Mechanical resonant tremor occurs in response to irregularities in muscle contraction, the pulsatile force of cardiac systole, and

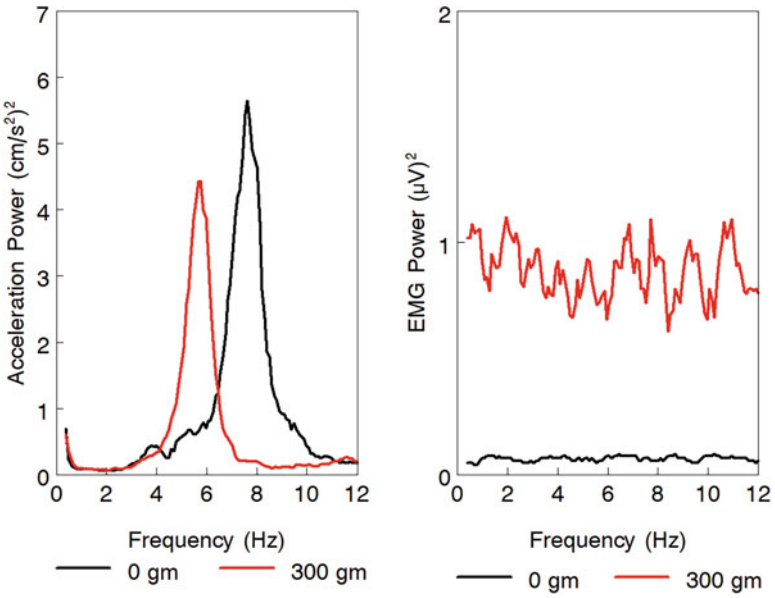

Fig. 5.1 Fourier power spectra of wrist (hand) tremor and rectified-filtered extensor carpi radialis brevis EMG with and without a 300-gm load attached to the dorsal surface of the horizontally extended pronated hand. The forearm was supported so motion was restricted to the wrist. The EMG spectra are statistically flat, indicating no entrainment of motor unit activity at the frequency of tremor. Tremor frequency decreased 2 Hz with mass (inertial) loading

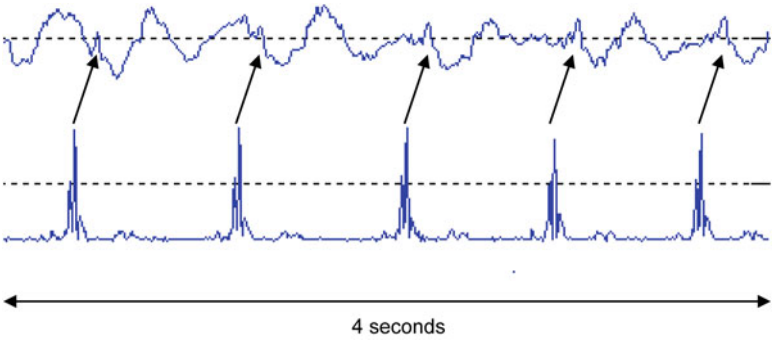

Fig. 5.2 Simultaneous recordings of head acceleration in the sagittal plane (upper trace) and the electrocardiogram (lower trace). The normal volunteer was seated in a chair with back supported. An accelerometer was mounted on the forehead. Following each QRS complex, there is a sharp perturbation of the head (arrows) and subsequent mechanical resonant oscillation

external perturbations (e.g., someone bumping the limb) (Elble and Randall 1978). Mechanical resonant oscillation at rest is caused almost entirely by the ejection of blood at cardiac systole (Elble and Randall 1978; Marsden et al. 1969) (Fig. 5.2).

5.3 Mechanical-Reflex Tremor

Steady voluntary muscle contractions are generally produced by orderly motor unit recruitment and little or no motor unit synchronization or entrainment, resulting in a fairly smooth EMG interference pattern and muscle force. However, muscle contractions are never perfectly smooth, and normal irregularities in motor unit firing and recruitment provide a broad-frequency forcing to the involved limb and any load that the limb may carry. Most of these irregularities in force cause damped mechanical oscillations that are not large enough to produce stretch reflex modulation of motor unit activity at the frequency of tremor (Hagbarth and Young 1979; Young et al. 1975; Logigian et al. 1988). However, occasional EMG/force irregularities are large enough to induce stretch reflex modulation of motor unit discharge (Young and Hagbarth 1980). Tremor produced by the interaction of mechanical resonance and the stretch reflex is called *mechanical-reflex tremor* and is most commonly observed when stretch reflex sensitivity is enhanced by factors such as drugs, fatigue, or anxiety (e.g., adrenaline) (see Sect. 5.4).

5.4 Central Neurogenic Tremor

In contrast to normal mechanical-reflex tremor, central neurogenic tremor is always associated with a modulation of motor unit activity, even when this tremor is much smaller than the mechanical resonant or mechanical-reflex oscillation (Fig. 5.3). Central neurogenic tremor in normal people occurs at frequencies of 8–12 Hz and at 15–30 Hz (Baker et al. 1999; Elble and Randall 1976; Halliday et al. 1999). The 8–12 Hz tremor is the stronger of the two oscillations, and the 15–30 Hz is difficult to record except in finger tremor. The frequency bands of both oscillations are not a function of limb mechanics (inertia and stiffness) or reflex loop time, hence the belief that these oscillations emerge from networks within the central nervous system.

In most individuals, the 8–12 Hz component of physiologic tremor is small and intermittent unless this tremor is enhanced with fatigue or beta-adrenergic agonists, and even then, most people do not exhibit 8–12 Hz tremor during the maintenance of a steady posture (Elble 2003). However, nearly all people exhibit 8–12 Hz bursts of EMG during slow voluntary movements, particularly in the wrist and finger extensors 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 to produce an EMG spectral peak during steady horizontal extension of the hand or finger (Elble 2003).

Motor units participating in the 8–12 Hz tremor are entrained at 8–12 Hz, regardless of their mean firing frequency (Elble and Randall 1976). The frequency of this tremor is not reduced by inertial loading and is independent of stretch reflex loop time. Rhythmic 8–12 Hz EMG activity is coherent with activity in motor cortex and the cerebellothalamocortical pathway (Köster et al. 1998; Raethjen et al. 2002,

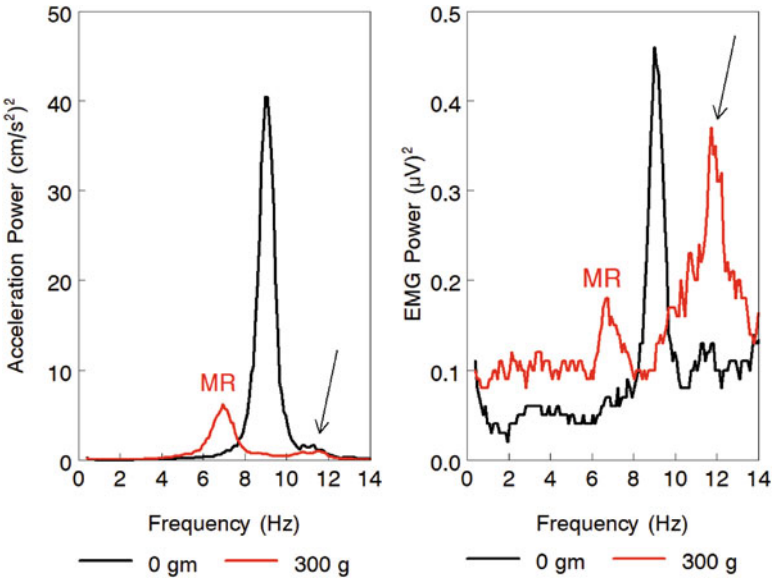

Fig. 5.3 Fourier power spectra of wrist (hand) tremor and rectified-filtered extensor carpi radialis brevis EMG with and without a 300-gm load attached to the dorsal surface of the horizontally extended pronated hand. The forearm was supported so motion was restricted to the wrist. With no mass load, there is a single peak in the tremor and EMG spectra. Mass loading reduced the frequency of the mechanical-reflex (MR) oscillation, thereby separating the mechanical-reflex oscillation (MR) and 8–12 Hz central neurogenic tremor (arrow) into two spectral peaks. Note that the 8–12 Hz EMG peak is much larger than the MR EMG peak, even though the 8–12 Hz tremor (acceleration) is much smaller than the MR tremor

2004; Ohara et al. 2001; Gross et al. 2002; Grosse et al. 2002), but the precise mechanism of this oscillation is unclear.

Halliday and coworkers demonstrated the presence of 15–30 Hz motor unit entrainment that was estimated to explain about 20% of finger tremor in this frequency band (Halliday et al. 1999). The contribution of 15–30 Hz motor unit entrainment to tremor in body parts with greater inertia (e.g., hand, forearm) is much smaller, and the strength of this motor unit entrainment is much weaker than in the 8–12 Hz tremor. This component of physiologic tremor is believed to emerge from normal cortical rhythmicity (Baker et al. 1997, 1999; Conway et al. 1995; Halliday et al. 1998; Salenius et al. 1997).

5.5 Enhanced Physiologic Tremor

Limb ischemia sufficient to suppress the stretch reflex causes a reduction in normal tremor (Lakie et al. 1994; Christakos et al. 2006), so the stretch reflex appears

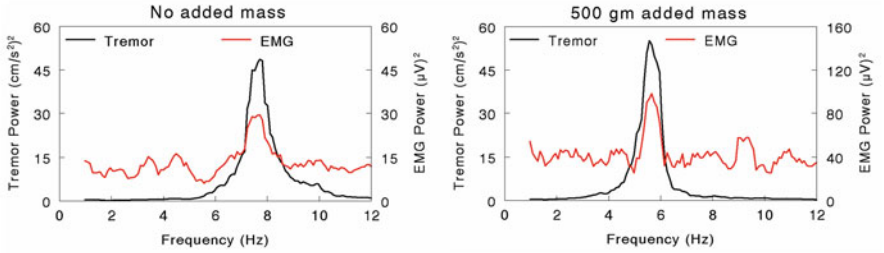

Fig. 5.4 Fourier power spectra of wrist (hand) tremor and rectified-filtered extensor carpi radialis brevis EMG with no added mass and with 500 gm added mass attached to the dorsal surface of the horizontally extended pronated hand. The forearm was supported so motion was restricted to the wrist. This is a classic example of enhanced mechanical-reflex tremor caused by mild thyrotoxicosis. There is entrainment of EMG activity at the tremor frequency, which decreased 2 Hz with mass loading

to contribute little to the control of physiologic postural tremor. Consistent with this hypothesis is the presence of little or no reflex-induced modulation of EMG in normal mechanical-reflex tremor. Reflex-induced modulation of EMG increases when stretch reflex gain is enhanced by fatigue, anxiety, thyrotoxicosis (Fig. 5.4), or beta-adrenergic drugs (Logigian et al. 1988; Stiles 1976; Stiles and Hahs 1991). The amplitude of tremor in fatigue may increase by a factor of 5–20, and the mechanical oscillation becomes associated with an entrainment of motor unit activity, produced by sensory feedback (Hagbarth and Young 1979; Stiles 1980). This enhanced physiologic tremor is primarily an enhanced mechanical-reflex oscillation because the natural (resonant) frequency of tremor is proportional to $\sqrt{K/I}$ (Fig. 5.4). Data from laboratory primates suggest that spinal and long-loop transcortical stretch reflex pathways and the cerebellothalamocortical pathway are probably involved in the control of enhanced mechanical-reflex tremor (Kuo et al. 2019; Elble et al. 1984), but the involvement of these pathways probably varies with the etiology of reflex enhancement.

The natural 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). Tremor frequency also becomes less dependent on joint stiffness and inertia with increasing tremor amplitude, consistent with an increasing contribution of reflex dynamics (Stiles 1976).

People with deafferented limbs exhibit broad-frequency arrhythmic fluctuations in limb position when their tremor is enhanced, but they do not exhibit the very rhythmic tremor and motor unit entrainment seen in normal people with enhanced mechanical-reflex tremor (Sanes 1985). Thus, sensory feedback tends to entrain or concentrate tremor at a particular frequency, resulting in rhythmic oscillation. Increasing stretch reflex involvement appears to increase physiologic tremor by

destabilizing the wrist and other joints at the mechanical resonant frequency (Milner and Cloutier 1998).

Central neurogenic tremor is enhanced by the same factors that enhance mechanical-reflex tremor, but the frequency of enhanced central neurogenic tremor is not proportional to $\sqrt{K/I}$, nor is it a function of reflex loop time. Without enhancement, the motor unit entrainment of central neurogenic tremor is often very intermittent, and the intermittent bursts of EMG activity do little more that perturb the mechanical-reflex system, producing damped mechanical oscillations that induce a reflex modulation of motor unit activity at a frequency that is sensitive to mechanical loading (Elble 1991; Deuschl et al. 1994). Studies in laboratory primates have found that 6–13 Hz sensory feedback is 180° antiphase with 6–13 Hz corticospinal activity, suggesting that the 8–12 Hz central neurogenic tremor is minimized in this manner (Kozelj and Baker 2014). Spinal interneurons such as Renshaw cells may have a similar effect (Williams and Baker 2009).

5.6 Low-Frequency Aperiodic Error

Tremor is defined as "an involuntary, rhythmic, oscillatory movement of a body part" (Bhatia et al. 2018). Physiologic tremor contributes far less than half 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, and the log spectral power (squared error) is inversely proportional to frequency (Carignan et al. 2010; Sutton and Sykes 1967a, b; Yoshitake and Shinohara 2013). The aperiodic error below 4 Hz is orders of magnitude greater than normal mechanical-reflex and central neurogenic oscillations, and this low-frequency error may not be appreciated when tremor is recorded with velocity and acceleration transducers because these transducers have the effect of taking the first and second derivatives of position, thus amplifying signals in proportion to $2\pi f$ and $(2\pi f)^2$ (Carignan et al. 2010).

The relative magnitudes of low-frequency aperiodic and higher-frequency rhythmic error in positional control are determined largely by the frequency-response characteristics of peripheral stretch reflex and central motor pathways (Fig. 5.5). As discussed in the preceding paragraphs, the motor unit drive during a postural task is not perfectly smooth and contains random, broad-frequency (0 to >40 Hz) irregularities with superimposed central neurogenic entrainment at 8–12 Hz and 15–30 Hz. The contractile properties of skeletal muscle attenuate irregularities and rhythms logarithmically at frequencies above 3 Hz, in the manner of a second-order low-pass filter (Milner-Brown and Stein 1975). Joints such as the wrist have underdamped spring-mass properties that allow resonant oscillation at the natural frequency (mechanical-resonant oscillation) and that attenuate irregularities and central neurogenic rhythms at frequencies above the natural frequency, like a low-pass filter (Milsum 1966). The error in position (joint angle) therefore consists of low-frequency arrhythmic error, the mechanical resonant component of tremor, and the two central neurogenic components, and the low-frequency aperiodic error is

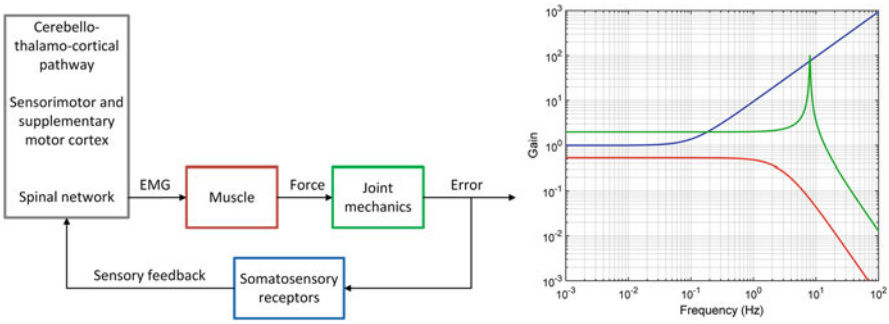

Fig. 5.5 A schematic diagram of the mechanical-reflex loop (left) is shown for a hypothetical task of maintaining a steady posture or position. The frequency-response (Bode) plots (right) for muscle (red; gain = force/EMG), joint (green; gain = error/force), and sensory receptors (blue; gain = sensory feedback/error) are linear approximations, based on data from decerebrate cats (Roberts et al. 1971; Matthews and Stein 1969). Muscle filters irregularities at frequencies >3 Hz, and the joint has a resonant frequency of 8 Hz and damping ratio of 0.01. Sensory receptors amplify error in proportion to frequency, at frequencies >0.1 Hz. The complex oscillatory and nonlinear dynamics of central pathways are not shown

least affected by the low-pass filtering properties of muscle and joint. These sources of error (tremor) induce somatosensory feedback in proportion to their amplitude, velocity (i.e., first derivative), and acceleration (second derivative) (Roberts et al. 1971). Somatosensory receptors (i.e., muscle spindles and Golgi tendon organs) have a sensitivity that is proportional to $2\pi f$ and $(2\pi f)^2$ (velocity and acceleration), so higher-frequency error will produce proportionally greater sensory feedback to the central nervous system (Roberts et al. 1971).

As already discussed, sensory feedback can attenuate or enhance mechanical-reflex and central neurogenic oscillation in ways that are still poorly understood. Feedback control of movement is clearly inadequate for most motor tasks, and the cerebellum plays a pivotal role in the feedforward control of movement (Kuo et al. 2019). It seems likely that low-frequency aperiodic error is limited primarily by feedforward control, in which sensory feedback and prior experience (motor learning) are used to anticipate and reduce error in movement and posture. Absent the cerebellum, a reliance solely on feedback control results in gross ataxia that far exceeds normal low-frequency aperiodic error (Bastian 2006).

5.7 Summary

The properties of tremor in healthy adults and adolescents are summarized in Table 5.1. These components of physiologic tremor and their relative importance have not been studied adequately in children and infants (Marshall 1959).

Table 5.1 Properties of tremor in healthy people

	Mechanical resonant tremor	Central neurogenic tremor	Enhanced mechanical-reflex tremor
Amplitude	Invisible or barely visible; not disabling	Invisible or barely visible; not disabling	Less than 1 cm hand tremor; may interfere with fine motor control
Frequency	A function of joint stiffness and inertia. Reduced by adding inertia to the limb. Increased by adding stiffness	Frequency does not vary with limb inertia or reflex arc length	A function of joint stiffness and inertia. Reduced by adding inertia to the limb. Increased by adding stiffness. Influenced by reflex arc length
Electromyogram	No motor unit entrainment or synchronization	Motor unit entrainment at 8–12 Hz and at 15–30 Hz	Motor unit entrainment at the frequency of tremor. Commonly associated with enhanced central neurogenic tremor at 8–12 Hz

In a one-minute recording of hand (wrist) tremor during steady horizontal posture, about 60% of adults exhibit only a pure mechanical resonant tremor with no evidence of motor unit entrainment, about 30% exhibit some evidence of motor unit entrainment at the mechanical resonant frequency, and about 10% exhibit a central neurogenic tremor at 8–12 Hz in addition to mechanical-reflex oscillation (Elble 2003). Motor unit entrainment at the mechanical resonant frequency and the 8–12 Hz central neurogenic tremor become more evident with fatigue and anxiety, which enhance reflex sensitivity. Physiologic tremor at rest (i.e., in the absence of voluntary muscle activation) is primarily a mechanical resonant oscillation in response to the force of cardiac systole.

The origins of 8–12 Hz and 15–30 Hz central oscillation are poorly defined, but there is good evidence that sensorimotor cortex, supplementary motor cortex, and cerebellothalamocortical pathways are involved (Gross et al. 2002; Raethjen et al. 2004; Ohara et al. 2000, 2001; Williams and Baker 2009). All sources of central oscillation, physiologic and pathologic, are coupled to segmental and transcortical reflex pathways (Kozelj and Baker 2014). Involved pathways can become collectively entrained in tremorogenic oscillation. Oscillatory entrainment of motor pathways is a feature of enhanced physiologic tremor and all forms of pathologic tremor (Schnitzler et al. 2006).

References

Agarwal GC, Gottlieb GL. Mathematical modeling and simulation of the postural control loop. Part III. Crit Rev Biomed Eng. 1984;12(1):49–93.

Baker SN, Olivier E, Lemon RN. Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. J Physiol-London. 1997;501(1):225–41. https://doi.org/10.1111/j.1469-7793.1997.225bo.x.

Baker SN, Kilner JM, Pinches EM, Lemon RN. The role of synchrony and oscillations in the motor output. Exp Brain Res. 1999;128(1–2):109–17. https://doi.org/10.1007/s002210050825

Bastian AJ. Learning to predict the future: the cerebellum adapts feedforward movement control. Curr Opin Neurobiol. 2006;16(6):645–9. https://doi.org/10.1016/j.conb.2006.08.016

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. From the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33(1):75–87. https://doi.org/10.1002/mds.27121

Carignan B, Daneault JF, Duval C. Quantifying the importance of high frequency components on the amplitude of physiological tremor. Exp Brain Res. 2010;202(2):299–306. https://doi.org/10.1007/s00221-009-2132-7

Christakos CN, Papadimitriou NA, Erimaki S. Parallel neuronal mechanisms underlying physiological force tremor in steady muscle contractions of humans. J Neurophysiol. 2006;95(1):53–66. https://doi.org/10.1152/jn.00051.2005

Conway BA, Halliday DM, Farmer SF, Shahani U, Maas P, Weir AI, et al. Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. J Physiol-London. 1995;489(3):917–24. https://doi.org/10.1113/jphysiol.1995.sp021104.

Deuschl G, Toro C, Valls-Sole J, Zeffiro T, Zee DS, Hallett M. Symptomatic and essential palatal tremor. 1. Clinical, physiological and MRI analysis. Brain. 1994;117(Pt 4):775–88. https://doi.org/10.1093/brain/117.4.775

Elble RJ. Inhibition of forearm EMG by palatal myoclonus. Mov Disord. 1991;6(4):324–9. https://doi.org/10.1002/mds.870060410

Elble RJ. Characteristics of physiologic tremor in young and elderly adults. Clin Neurophysiol. 2003;114(4):624–35. https://doi.org/10.1016/s1388-2457(03)00006-3

Elble RJ, Deuschl G. Tremor. In: Brown WF, Bolton CF, Aminoff M, editors. Neuromuscular function and disease: basic, clinical and electrodiagnostic aspects. Philadelphia: W. B. Saunders Co.; 2002. p. 1759–79.

Elble RJ, McNames J. Using portable transducers to measure tremor severity. Tremor Other Hyperkinet Mov (N Y). 2016;6:375. https://doi.org/10.7916/D8DR2VCC

Elble RJ, Randall JE. Motor-unit activity responsible for 8- to 12-Hz component of human physiological finger tremor. J Neurophysiol. 1976;39(2):370–83. https://doi.org/10.1152/jn.1976.39.2.370

Elble RJ, Randall JE. Mechanistic components of normal hand tremor. Electroencephalogr Clin Neurophysiol. 1978;44(1):72–82. https://doi.org/10.1016/0013-4694(78)90106-2

Elble RJ, Schieber MH, Thach WT Jr. Activity of muscle spindles, motor cortex and cerebellar nuclei during action tremor. Brain Res. 1984;323(2):330–4. https://doi.org/10.1016/0006-8993(84)90308-1

Fox JR, Randall JE. Relationship between forearm tremor and the biceps electromyogram. J Appl Physiol. 1970;29:103–8.

Gottlieb GL, Agarwal GC. Physiological clonus in man. Exp Neurol. 1977;54(3):616–21. https://doi.org/10.1016/0014-4886(77)90260-6

Gross J, Timmermann L, Kujala J, Dirks M, Schmitz F, Salmelin R, et al. The neural basis of intermittent motor control in humans. Proc Natl Acad Sci U S A. 2002;99(4):2299–302. https://doi.org/10.1073/pnas.032682099

Grosse P, Cassidy MJ, Brown P. EEG-EMG, MEG-EMG and EMG-EMG frequency analysis: physiological principles and clinical applications. Clin Neurophysiol. 2002;113(10):1523–31. https://doi.org/10.1016/s1388-2457(02)00223-7

Hagbarth KE, Young RR. Participation of the stretch reflex in human physiological tremor. Brain. 1979;102(3):509–26. https://doi.org/10.1093/brain/102.3.509

Halliday DM, Conway BA, Farmer SF, Rosenberg JR. Using electroencephalography to study functional coupling between cortical activity and electromyograms during voluntary contractions in humans. Neurosci Lett. 1998;241(1):5–8. https://doi.org/10.1016/S0304-3940(97)00964-6.

Halliday DM, Conway BA, Farmer SF, Rosenberg JR. Load-independent contributions from motor-unit synchronization to human physiological tremor. J Neurophysiol. 1999;82(2):664–75. https://doi.org/10.1152/jn.1999.82.2.664

Köster B, Lauk M, Timmer J, Winter T, Guschlbauer B, Glocker FX, et al. Central mechanisms in human enhanced physiological tremor. Neurosci Lett. 1998;241(2–3):135–8. https://doi.org/10.1016/s0304-3940(98)00015-9

Kozelj S, Baker SN. Different phase delays of peripheral input to primate motor cortex and spinal cord promote cancellation at physiological tremor frequencies. J Neurophysiol. 2014;111(10):2001–16. https://doi.org/10.1152/jn.00935.2012

Kuo SH, Louis ED, Faust PL, Handforth A, Chang SY, Avlar B, et al. Current opinions and consensus for studying tremor in animal models. Cerebellum. 2019;18(6):1036–63. https://doi.org/10.1007/s12311-019-01037-1

Lakie M, Walsh EG, Wright GW. Resonance at the wrist demonstrated by the use of a torque motor – an instrumental analysis of muscle tone in man. J Physiol-London. 1984;353(Aug):265–85. https://doi.org/10.1113/jphysiol.1984.sp015335.

Lakie M, Walsh EG, Arblaster LA, Villagra F, Roberts RC. Limb temperature and human tremors. J Neurol Neurosurg Psychiatry. 1994;57(1):35–42. https://doi.org/10.1136/jnnp.57.1.35

Logigian EL, Wierzbicka MM, Bruyninckx F, Wiegner AW, Shahahi BT, Young RR. Motor unit synchronization in physiologic, enhanced physiologic, and voluntary tremor in man. Ann Neurol. 1988;23(3):242–50. https://doi.org/10.1002/ana.410230306

Marsden CD, Meadows JC, Lange GW, Watson RS. The role of the ballistocardiac impulse in the genesis of physiological tremor. Brain. 1969;92(3):647–62. https://doi.org/10.1093/brain/92.3.647

Marshall J. Physiological tremor in children. J Neurol Neurosurg Psychiatry. 1959;22(1):33–5. https://doi.org/10.1136/jnnp.22.1.33

Matthews PB, Stein RB. The sensitivity of muscle spindle afferents to small sinusoidal changes of length. J Physiol. 1969;200(3):723–43. https://doi.org/10.1113/jphysiol.1969.sp008719

Milner TE, Cloutier C. Damping of the wrist joint during voluntary movement. Exp Brain Res. 1998;122(3):309–17. https://doi.org/10.1007/s002210050519

Milner-Brown HS, Stein RB. The relation between the surface electromyogram and muscular force. J Physiol. 1975;246(3):549–69. https://doi.org/10.1113/jphysiol.1975.sp010904

Milsum JH. Biological control systems analysis. McGraw-Hill electronic science series. New York: McGraw-Hill; 1966.

Ohara S, Nagamine T, Ikeda A, Kunieda T, Matsumoto R, Taki W, et al. Electrocorticogram-electromyogram coherence during isometric contraction of hand muscle in human. Clin Neurophysiol. 2000;111(11):2014–24. https://doi.org/10.1016/s1388-2457(00)00448-x

Ohara S, Mima T, Baba K, Ikeda A, Kunieda T, Matsumoto R, et al. Increased synchronization of cortical oscillatory activities between human supplementary motor and primary sensorimotor areas during voluntary movements. J Neurosci. 2001;21(23):9377–86.

Raethjen J, Lindemann M, Dumpelmann M, Wenzelburger R, Stolze H, Pfister G, et al. Cortico-muscular coherence in the 6-15 Hz band: is the cortex involved in the generation of physiologic tremor? Exp Brain Res. 2002;142(1):32–40. https://doi.org/10.1007/s00221-001-0914-7

Raethjen J, Lindemann M, Morsnowski A, Dumpelmann M, Wenzelburger R, Stolze H, et al. Is the rhythm of physiological tremor involved in cortico-cortical interactions? Mov Disord. 2004;19(4):458–65. https://doi.org/10.1002/mds.10686

Roberts WJ, Rosenthal NP, Terzuolo CA. A control model of stretch reflex. J Neurophysiol. 1971;34(4):620–34. https://doi.org/10.1152/jn.1971.34.4.620

Salenius S, Portin K, Kajola M, Salmelin R, Hari R. Cortical control of human motoneuron firing during isometric contraction. J Neurophysiol. 1997;77(6):3401–5. https://doi.org/10.1152/jn.1997.77.6.3401

Sanes JN. Absence of enhanced physiological tremor in patients without muscle or cutaneous afferents. J Neurol Neurosurg Psychiatry. 1985;48(7):645–9. https://doi.org/10.1136/jnnp.48.7.645.

Schnitzler A, Timmermann L, Gross J. Physiological and pathological oscillatory networks in the human motor system. J Physiol Paris. 2006;99(1):3–7. https://doi.org/10.1016/j.jphysparis.2005.06.010

Stiles RN. Frequency and displacement amplitude relations for normal hand tremor. J Appl Physiol. 1976;40(1):44–54. https://doi.org/10.1152/jappl.1976.40.1.44

Stiles RN. Mechanical and neural feedback factors in postural hand tremor of normal subjects. J Neurophysiol. 1980;44(1):40–59. https://doi.org/10.1152/jn.1980.44.1.40

Stiles RN, Hahs DW. Muscle-load oscillations: detection, analysis and models. In: Wise DL, editor. Bioinstrumentation and biosensors. New York: Marcel Dekker, Inc.; 1991. p. 75–119.

Stiles RN, Randall JE. Mechanical factors in human tremor frequency. J Appl Physiol. 1967;23(3):324–30. https://doi.org/10.1152/jappl.1967.23.3.324

Sutton GG, Sykes K. The effect of withdrawal of visual presentation of errors upon the frequency spectrum of tremor in a manual task. J Physiol. 1967a;190(2):281–293. https://doi.org/10.1113/jphysiol.1967.sp008208

Sutton GG, Sykes K. The variation of hand tremor with force in healthy subjects. J Physiol. 1967b;191(3):699–711. https://doi.org/10.1113/jphysiol.1967.sp008276

Takanokura M, Sakamoto K. Neuromuscular control of physiological tremor during elastic load. Med Sci Monit. 2005;11(4):CR143–52.

Vial F, Kassavetis P, Merchant S, Haubenberger D, Hallett M. How to do an electrophysiological study of tremor. Clin Neurophysiol Pract. 2019;4:134–42. https://doi.org/10.1016/j.cnp.2019.06.002

Wessberg J, Vallbo ÅB. Pulsatile motor output in human finger movements is not dependent on the stretch reflex. J Physiol Lond. 1996;493(3):895–908.

Williams ER, Baker SN. Renshaw cell recurrent inhibition improves physiological tremor by reducing corticomuscular coupling at 10 Hz. J Neurosci. 2009;29(20):6616–24. https://doi.org/10.1523/JNEUROSCI.0272-09.2009

Yoshitake Y, Shinohara M. Oscillations in motor unit discharge are reflected in the low-frequency component of rectified surface EMG and the rate of change in force. Exp Brain Res. 2013;231(3):267–276. https://doi.org/10.1007/s00221-013-3689-8

Young RR, Hagbarth KE. Physiological tremor enhanced by Maneuvers affecting the segmental stretch reflex. J Neurol Neurosurg Psychiatry. 1980;43(3):248–56. https://doi.org/10.1136/jnnp.43.3.248.

Young RR, Growdon JH, Shahani BT. Beta-adrenergic mechanisms in action tremor. N Engl J Med. 1975;293(19):950–3. https://doi.org/10.1056/NEJM197511062931902

Zahalak GI, Pramod R. Myoelectric response of the human triceps brachii to displacement-controlled oscillations of the forearm. Exp Brain Res. 1985;58(2):305–17. https://doi.org/10.1007/BF00235312

Chapter 6
Rest Tremor

Giuliana Grimaldi and Mario Manto

Abstract By definition, rest tremor is an involuntary oscillation occurring while the body segment is maintained at rest, fully supported against gravity. To look for a rest tremor, the patient is seated with the upper limbs relaxed and the forearms on the thighs, or the patient is lying horizontally in complete repose. Rest tremor is typically in the 3–6 Hz frequency range and may reach high levels of severity. Rest tremor is usually asymmetrical, in general starting distally in the arms and legs. Typically, tremor in the upper limbs reminds the 'pill rolling' movement. Lips and jaw can be affected, with a rhythmic clicking of teeth. Head and trunk are usually spared. Rest tremor may disappear or subside with action (posture, movement, maintaining an isometric force, exerting a specific task) and is associated with reciprocal activation in antagonistic muscles. In some cases, patients can reduce the tremor by holding one hand with the other or crossing the legs. Rest tremor often increases with mental stress (i.e. counting backwards) or contralateral motion (Froment manoeuvre). However, this feature is not specific. Rest tremor disappears during sleep, as most tremulous disorders. In addition to the clinical features, we discuss the pathogenesis and the therapies of rest tremor.

Keywords Rest · Frequency · Parkinson's disease · Cortico–subthalamo–pallido–thalamic loop · Dopamine · Levodopa · Dopamine agonists · Anticholinergic · Deep brain stimulation · Thalamotomy

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6.1 Definition and Clinical Description

By definition, rest tremor is an involuntary oscillation occurring while the body segment is maintained at rest, fully supported against gravity (see Axis 1 of Bhatia et al. 2018). To look for a rest tremor, the patient is seated with the upper limbs relaxed and the forearms on the thighs, or the patient is lying horizontally in complete repose. Rest tremor is typically in the 3–6 Hz frequency range (Fig. 6.1) and may reach high levels of severity. Rest tremor is usually asymmetrical, in general starting distally in the arms and legs. Typically, tremor in the upper limbs reminds the 'pill rolling' movement. Lips and jaw can be affected, with a rhythmic clicking of teeth. Head and trunk are usually spared. Rest tremor may disappear or subside with action (posture, movement, maintaining an isometric force, exerting a specific task) and is associated with reciprocal activation in antagonistic muscles. In some cases, patients can reduce the tremor by holding one hand with the other or crossing the legs. Rest tremor often increases with mental stress (i.e. counting backwards) or contralateral motion (Froment manoeuvre). Rest tremor may appear or increase while walking. However, this feature is not specific. Rest tremor disappears during sleep, as most tremulous disorders.

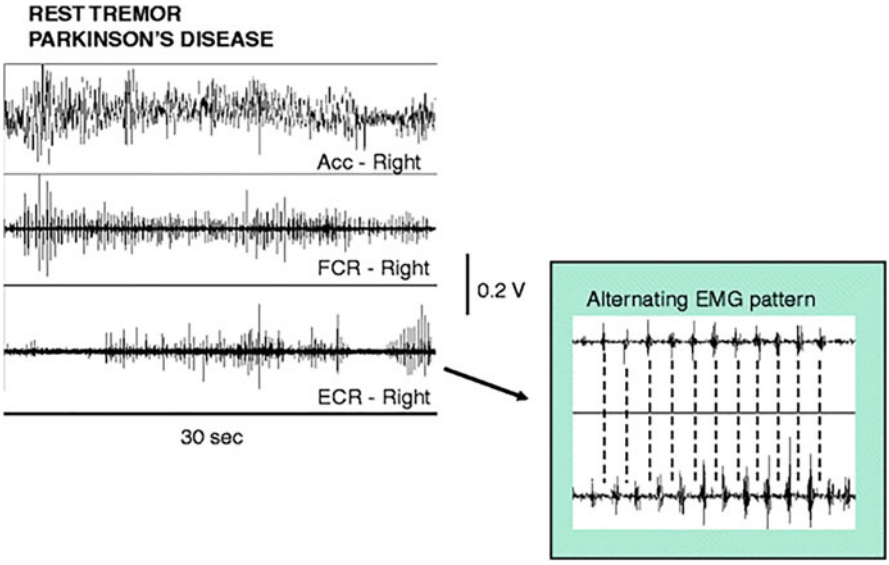

Fig. 6.1 Rest tremor in a patient with idiopathic Parkinson's disease. Dopamine transporter SPECT confirmed a decreased uptake in striatum in this patient. Single-axis accelerometer (Acc) fixed on right index. Surface EMG recordings at the level of the right flexor carpi radialis (FCR) and extensor carpi radialis (ECR) show an alternating EMG pattern in the agonist/antagonist EMG pair (*dotted lines* show that bursts of EMG in the FCR muscle occur when the ECR muscle is electrically silent). Note the fluctuation over time of the intensities of burst of EMG activities

A physiological rest tremor may be present (see Chap. 8), but in this case the acceleration power spectrum does not show a clear dominant peak in most cases, and its magnitude is low (the tremor is barely perceptible). The enhanced physiological tremor may worsen with emotions or volitional movements.

Rest tremor is a cause of social embarrassment, interfering with dexterous hand movements and causing various degrees of disability. However, because rest tremor often decreases with action, it causes a greater social embarrassment than a functional deficit during daily life. The patient may not report tremor himself at the beginning. Rather a family member may be the first to note the involuntary movement. In other cases, the patient may feel a 'trembling sensation' at the very beginning in the absence of visible contractions. Anxiety and stress exacerbate rest tremor, and a very mild tremor may be brought up by stress during the office interview.

6.2 Disorders Associated with Rest Tremor

Rest tremor is mainly associated with Parkinson's disease (PD) and related disorders. The term 'parkinsonism' refers to a symptomatology characterized by rest tremor, rigidity and bradykinesia that is not in the frame of PD (atypical Parkinson's disease). The causes of parkinsonism include extrapyramidal neurodegenerative diseases such as progressive supranuclear palsy (PSP), multiple systemic atrophy (MSA), corticobasal degeneration (CBD) or Lewy body disease (LBD), rare genetic forms of PD, metabolic disorders such as Wilson's disease (Figs. 6.2 and 6.3), vascular damage, drugs, toxic agents such as neuroleptics or antidepressants and rarely antibiotics (cotrimoxazole, amphotericin B), brain infections (especially abscesses) and brain trauma (see also dementia pugilistica) (Abbruzzese 2003). Dystonia may present with an atypical rest tremor, often with a jerky component. However, the most common type of tremor reported in dystonic patients is postural and kinetic (Gupta and Pandey 2020).

PD is a progressive neurodegenerative disorder originally described by James Parkinson in 1817 (see also Chaps. 4 and 22). Distal resting tremor ('pill rolling') of 3–6 Hz, rigidity (sustained increase of resistance throughout the range of passive movement at a joint), bradykinesia, impaired postural reflexes and asymmetrical onset are cardinal features of PD. The classical parkinsonian tremor is typically asymmetrical, at least initially, and affects the upper limb before involving the ipsilateral leg after a period of about 2 years. Regardless of tremor presentation at disease onset or during the clinical follow-up, the upper limb is the most common tremor localization, rest tremor will develop faster in the upper limbs than in other sites and the age of onset above 63 years is associated with a greater risk of tremor spreading (Gigante et al. 2017). Tremor of the lips, jaw or tongue may also occur. Head or voice tremor is rare, unlike in essential tremor (ET). A postural tremor is also present in most cases, with heterogeneity in terms of severity (Habib-ur-Rehman 2000). Re-emergent tremor refers to a postural tremor appearing after a

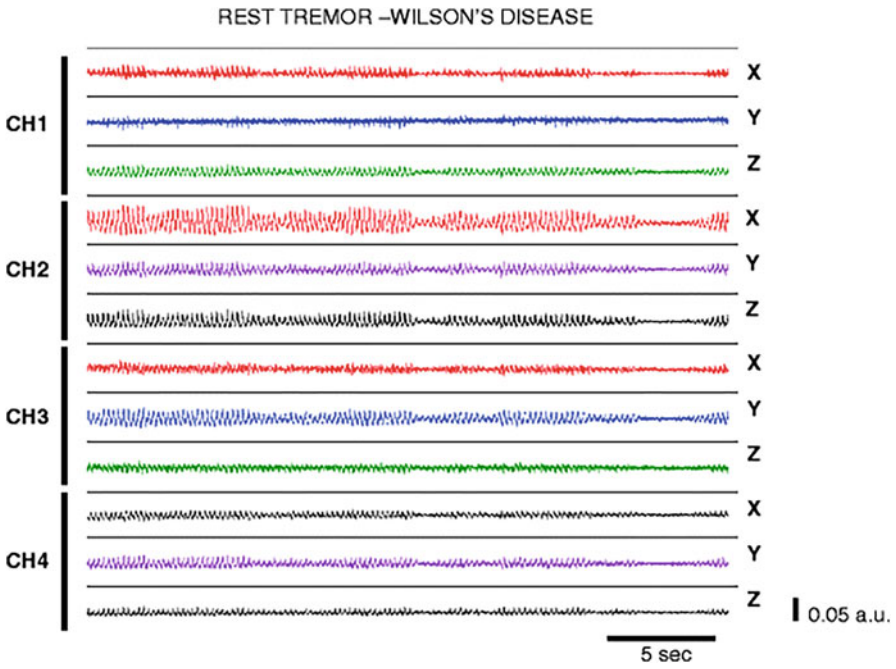

Fig. 6.2 Rest tremor affecting the whole upper limb in a patient with Wilson's disease. Triaxial (X,Y,Z) accelerometers affixed along the left upper limb from index (upper traces) to shoulder (lower traces). A distal and proximal tremor is clearly visible. This patient also exhibited a postural and kinetic tremor. The patient had very low serum ceruloplasmin levels and increased excretion of copper in urine

delay of a few seconds in PD. Patients with re-emergent tremor and patients with isolated rest tremor likely represent the same clinical subtype, whereas patients with action tremor (isolated or with rest tremor) might belong to another subgroup, which is clinically worse (Belvisi et al. 2017). Re-emergent tremor is related to the activity of the primary motor cortex (Leodori et al. 2020). Mechanisms of postural tremor likely differ between patients with and those without tremor suppression, as shown by the group of Berardelli (Leodori et al. 2022). Kinetic tremor is uncommon in PD (Kraus et al. 2006). Isolated lower leg rest tremor is an uncommon symptom of neurological disease and is considered as an unusual presentation of PD. It should raise suspicion for MSA, psychogenic tremor or drug-induced parkinsonism (Hellmann et al. 2010).

PD presentation is heterogeneous, and clinicians often distinguish a 'tremor-dominant' from an 'akineto-rigid' form mainly because this phenotypic distinction might predict the clinical course and the response to medications (Foltynie et al. 2002). The clinical progression is more rapid, and the mental status declines more rapidly in the akineto-rigid form.

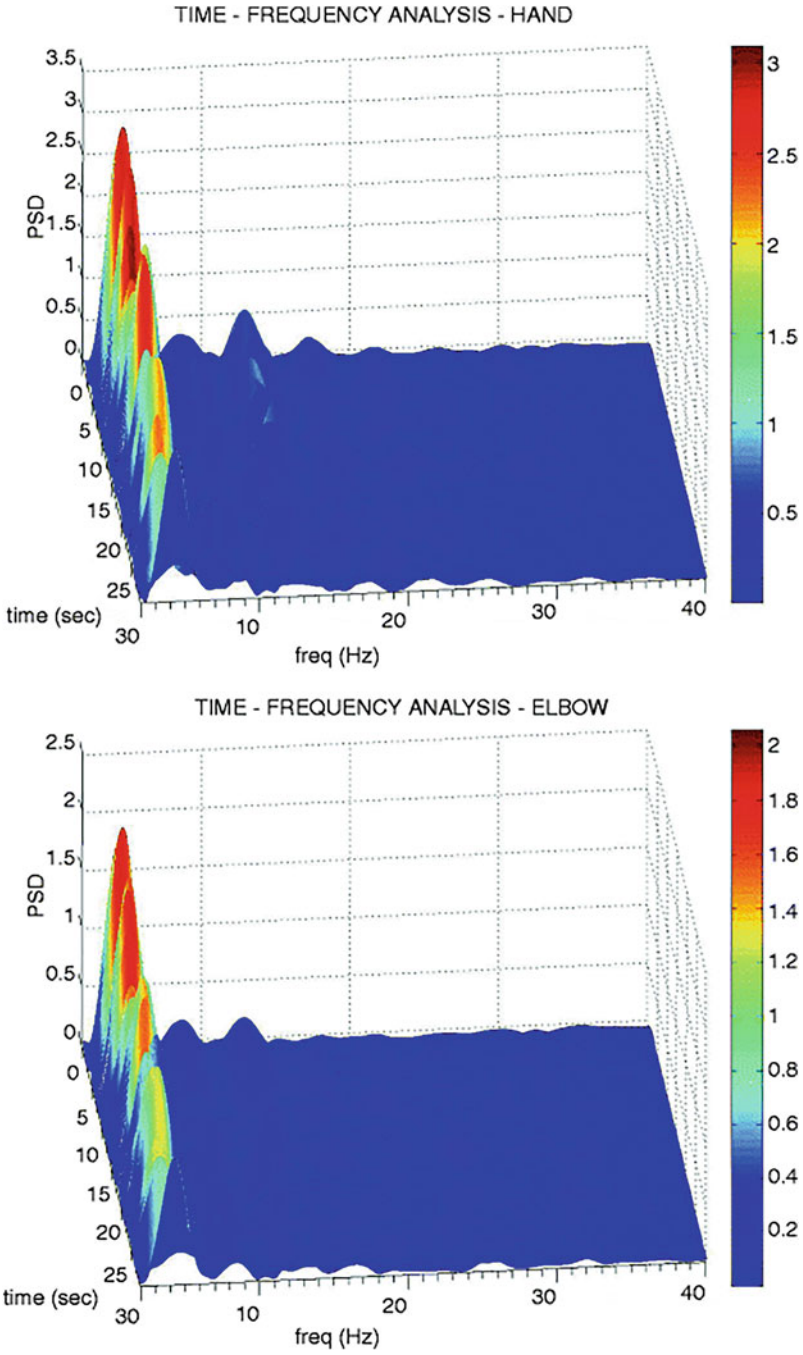

Fig. 6.3 Time–frequency analysis of the rest tremor illustrated in Fig. 6.2. A 4-Hz tremor is identified on power spectra. The generator is relatively stable over time. Windows of 1 s duration are used

Other well-known clinical signs of PD include persistence of primitive reflexes (glabellar reflex, palmar grasp reflex) and micrographia (small handwriting). Parkinsonian patients often present an abnormal posture called camptocormia (ranging from mild to severe) characterized by an excessive anterior flexion of the spine (Bonneville et al. 2008).

Response to an adequate therapeutic challenge of levodopa or a dopamine agonist is one of the key features for the diagnosis (Guidelines for the diagnosis of Parkinson's disease 2003). However, a positive response to levodopa can also be observed in MSA patients (Wüllner et al. 2007).

PD also includes nonmotor signs and symptoms, involving cognitive and autonomic functions. Decreased scores in cognitive tests are associated with greater impairment in motor performances (Verbaan et al. 2007). Among the symptoms autonomic failure, orthostatic dizziness, bladder dysfunction and constipation are considered to have great impact on daily life (Magerkurth et al. 2005). A decreased olfactory function has been reported.

Vascular parkinsonism (VP), accounting for 4.4–12% of all cases of parkinsonism, is considered as a distinct clinicopathological entity due to cerebrovascular disease. Parkinsonism tends to be bilaterally symmetrical, affecting the lower limbs more than the upper limbs in some patients (Thanvi et al. 2005). Patients with VP are usually older than PD patients, with a shorter duration of illness, often presenting with symmetrical gait difficulties. Rest tremor is often mild. VP patients are less responsive to levodopa, and more prone to postural instability, falls and dementia. Concomitant pyramidal signs, pseudobulbar palsy and incontinence are not rare. Structural neuroimaging is abnormal in VP (Kalra et al. 2010; Fig. 6.4).

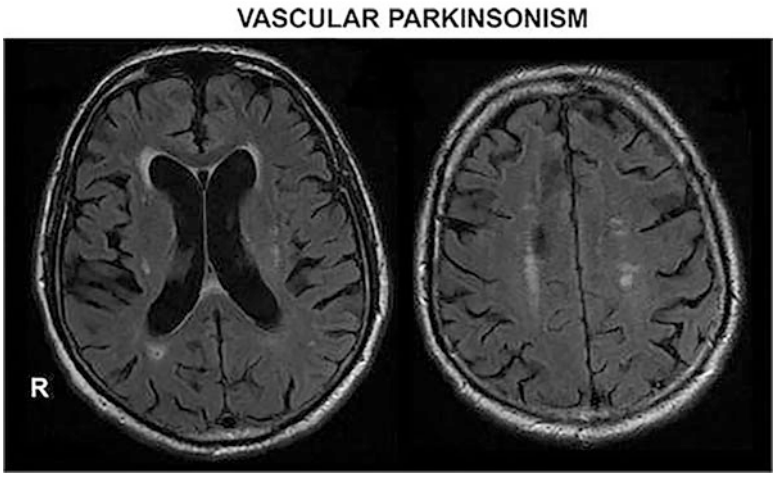

Fig. 6.4 Axial flair images show multiple hypersignals in a patient with vascular parkinsonism exhibiting a rest tremor on the left side. *R* right

Rest tremor may also be associated with essential tremor (see Chap. 10), especially in advanced cases (about 15% of advanced ET present a rest tremor), thus posing challenges in the diagnosis. Nisticò and colleagues proposed that the electromyographic (EMG) pattern of rest tremor may help to differentiate PD from ET. In fact, by comparing the electrophysiological parameters of tremor in PD patients and in ET patients with rest tremor, the authors found that the amplitude of rest tremor amplitude in PD patients was significantly higher as compared to patients with ET, whereas burst duration and frequency were significantly higher in the ET group. All patients with ET had a synchronous EMG pattern (cocontractions between agonist and antagonist EMG bursts), whereas PD patients showed an alternating pattern between agonist and antagonist muscles (Nisticò et al. 2011; see also Fig. 6.1). Rest tremor in ET is not associated with Lewy body pathology, indicating that the pathogenesis differs from a deficit in dopamine (Louis et al. 2011). SPECT studies show normal striatal dopamine uptake in ET with rest tremor, unlike in PD (Marshall et al. 2009).

Rest tremor in dystonia is a late-onset phenomenon which most commonly affects the arm and tends to be asymmetrical (Gupta and Pandey 2020). The majority of patients show a multifocal segmental dystonia. The differential diagnosis with other forms of rest tremor may be challenging. Other neurological signs and neurophysiological techniques may be helpful.

Rest tremor may occur in combination with other presentations of tremor, for instance in the case of midbrain tremor, also called Holmes' tremor or rubral tremor. Midbrain tremor is characterized by a combination of 2–5 Hz rest, postural and kinetic tremor (Hopfensperger et al. 1995; Findley and Koller 1995), affecting predominantly proximal segments in upper limbs. Midbrain tremor often results from a combined lesion of the nigrostriatal and cerebellothalamic pathways around the contralateral red nucleus (see also Chap. 1).

6.3 Pathophysiology of Rest Tremor

Three main neuronal mechanisms have been hypothesized: a cortico–subthalamo–pallido–thalamic loop-generating tremor (see also Chap. 1), a pacemaker activity emerging from the external pallidum and the subthalamic nucleus, and an abnormal synchronization within the whole striato–pallido–thalamic pathway leading to a loss of segregation (Deuschl et al. 2000).

The arguments against the hypothesis of a pure peripheral mechanism generating rest tremor are the following (Llinas and Paré 1995):

- Rest tremor is not abolished by sectioning the dorsal roots, indicating that it does not reflect the sole action of a pure spinal reflex loop.
- It is very difficult to reset rest tremor by a mechanical perturbation, and the phase shift lasts for a few cycles only.

- Recordings of Ia afferents show patterns similar to the one found during a voluntary alternating movement.

Neurons of the VLa nucleus are rhythmically active at the frequency of tremor but are not sensitive to sensory feedback or voluntary movements (Llinas and Paré 1995). Importantly, the main input to the VLa neurons originates from the GPi (Globus pallidus, internal segment), whose lesions reduce rest tremor, and VLa neurons project to the premotor cortex. In monkeys, the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine) causes a parkinsonian syndrome associated with changes in the patterns of neuronal discharges in the GPi and which is abolished by subthalamic lesions (Bergman et al. 1990). The intrinsic features of thalamic neurons, in particular the fact that their firing modes change with the membrane potential, contribute to the genesis of rest tremor. Interactions between cation current, low-threshold calcium conductance, and changes in potassium conductance trigger oscillations between 0.5 and 4 Hz in thalamic nuclei, as demonstrated by in vitro and in vivo experiments.

Typical PD resting tremor (4–6 Hz) is associated with strong coherence between the EMG of forearm muscles and activity in the contralateral primary motor cortex (M1) not only at tremor frequency but also at double tremor frequency. Tremor-related oscillatory activity within a cerebral network has been demonstrated. There is an abnormal coupling in a cerebello–diencephalic–cortical loop, including cortical motor (primary motor cortex, cingulated/supplemental motor area, lateral premotor cortex) and sensory (secondary somatosensory cortex, posterior parietal cortex) areas contralaterally to the tremor hand (Timmermann et al. 2003).

In a study on coherence in 22 subjects affected by PD, no consistent pattern across patients was found, suggesting that rest tremor is generated by multiple oscillatory circuits which tend to operate on similar frequencies (Ben-Pazi et al. 2001; Raethjen et al. 2000). PD tremor is coupled within but not between limbs. Oscillating neurons in one or multiple localizations within the basal ganglia–thalamo–cortical loop may cause rest tremor. The anatomy of basal ganglia loops may explain the presence of several generators.

Force oscillations share common origins. Christakos et al. have demonstrated that the motor unit synchrony in PD shares features with the physiological tremor (Christakos et al. 2009). However, the authors have noted that occurrence of rhythmical doublets, and triplets is observed in frequencies between 5 and 7.5 Hz. These doublets/triplets are very rarely found in healthy subjects. It is suggested that doublets/triplets might be a common behaviour in Parkinson's disease, and could correspond to responses of motoneurons to a rhythmical synaptic input exhibiting multiple local peaks per cycle. They might be specific for parkinsonian tremors, hence the importance of identifying them in the future to test the hypothesis that they might represent electrophysiological signatures (Christakos et al. 2009).

The analysis of the dynamics of oscillatory activity in the subthalamic nucleus (STN) during functional neurosurgery in PD patients with rest tremor has revealed an altered balance between beta and gamma oscillations in the motor circuits of STN. Ratios of the beta (13–35 Hz) to gamma (40–80 Hz) coherence are

significantly lower in periods with stronger tremor as compared with periods of no/weak tremor. The ratio between high-frequency 200–300 and 300–400 Hz oscillation power increases when tremor becomes manifest and occurs in medication on and off (Hirschmann et al. 2016). This ratio might be a better neurophysiological marker than low gamma power. The simultaneous recording of neuronal firing and local field potential (LFP) activity has shown that neurons exhibiting oscillatory activity at tremor frequency are located in the dorsal region of STN (where neurons with beta oscillatory activity are found) and that their activity is coherent with LFP oscillations in the beta frequency range. Furthermore, the coherence of two LFPs recorded simultaneously increased in the gamma range with increased amplitudes of tremor (Weinberger et al. 2009). Coherence analysis in the STN has revealed a specific topography of 'tremor clusters' for rest and postural tremors in tremor-dominant and akinetic-rigid PD (coherence at single tremor frequency during rest in both subgroups of DP; coherence at double tremor frequency during postural tremor only in patients with akinetic-rigid PD), suggesting that symptoms in patients with tremor-dominant and akinetic-rigid PD are related to different degrees of the same tremor mechanisms (Reck et al. 2010).

The most striking differences between parkinsonian patients and healthy subjects imitating the resting tremor are a reduction of the coupling between primary sensorimotor cortex and a diencephalic structure—most likely the thalamus—and an enhancement of the coupling between premotor and primary sensorimotor cortex (Pollok et al. 2004). These results indicate that the coupling of oscillatory activity within a cerebello–diencephalic–cortical loop constitutes a basic feature of physiological motor control, sustaining the hypothesis that parkinsonian resting tremor involves oscillatory cerebro–cerebral coupling in a physiologically pre-existing network.

The network perspective has grown these last years (Helmich 2018). Parkinsonian tremor would result from increased interactions between basal ganglia and the cerebello–thalamo–cortical circuit, driven by impaired dopaminergic projections to nodes within the circuit, under a modulatory effect of the context such as stress occurring in daily conditions. This is particularly relevant given the recent demonstration of a disynaptic projection from the STN to the cerebellum via the pons and from cerebellar nuclei to striatum via thalamic nuclei (Bostan et al. 2010; Caligiore et al. 2017). There is a dynamic dynamical interplay between cerebellum, basal ganglia and cortical areas with reciprocal influences between cerebellum, basal ganglia and cortex in control processes (Caligiore et al. 2017). Possible roles of the cerebellum in basal ganglia movement disorders sur as PD or dystonia are being scrutinized (Caligiore et al. 2017; Shakkottai et al. 2017).

The nigrostrial dopamine deficiency correlates with bradykinesia, but the correlation is less clear for rest tremor. However, in a recent study an association between rest tremor in PD and contralateral reduction in striatal dopamine binding was identified (Fois et al. 2021). A specific pattern of neuronal loss in the substantia nigra of PD patients with rest tremor has been reported (Jellinger 1999). Autopsy studies in PD and controls have shown that dopamine (DA) levels in the external globus pallidus (GPe) of normal brains are greater than in the GPi. In PD, the mean

loss of DA is marked (−82%) in GPe and moderate (−51%) in Gpi. However, DA levels are nearly normal in the ventral (rostral and caudal) GPi of PD cases with prominent tremor. There is a marked loss of DA (−89%) in the caudate and a severe loss (−98.4%) in the putamen in PD. The pattern of pallidal DA loss does not match the putaminal DA loss. The possible functional disequilibrium between GABAergic and DAergic influences the balance in favour of DA in the caudoventral parts of the Gpi, which may contribute to rest tremor in tremor-dominant and classic PD cases (Rajput et al. 2008). The study of noradrenergic neurotransmission using PET technique shows that noradrenergic neurons are relatively preserved in PD with rest tremor as compared to PD without rest tremor (Kinnerup et al. 2021). Noradrenergic neurons in locus coeruleus and thalamus would be more affected in patients without rest tremor.

The involvement of the cerebellum and cerebello–thalamo–cortical circuit in the pathogenesis of parkinsonian rest tremor has been highlighted during the last decade. An active contribution of the cerebellum and the cerebello–thalamo–cortical projections in the pathogenesis of parkinsonian rest tremor has been recently suggested on the basis of voxel-based morphometry (VBM). This technique has revealed morphological changes in the cerebellum of PD patients with rest tremor, when compared with PD patients without rest tremor (Benninger et al. 2009). Grey matter volume is decreased in the right quadrangular lobe and declive of the cerebellum in PD with tremor as compared to those without. Interestingly, there is a correlation between rest tremor and an increased metabolic and oscillatory activity in the cerebellum, thalamus and motor cortex (Antonini et al. 1998). Anatomically, the posterior quadrangular lobule (lobule VI) of the cerebellar cortex projects indirectly into the hand area of the motor cortex (Kelly and Strick 2003). Vim, a target of cerebellar projections, is an efficacious target to suppress rest tremor with deep brain stimulation (DBS, see Chap. 25). This is another argument for a role of cerebellar projections in the pathogenesis of rest tremor. Still, additional studies are required to clarify the contribution of the cerebellar circuitry in rest tremor and possible therapeutical interventions. Alpha-synuclein aggregates in Purkinje neurons and cerebellar glial cells have been shown, but their clinical correlate remains unclear (Piao et al. 2003).

6.4 Therapy of Rest Tremor

The therapy of rest tremor is often based on anticholinergics (biperiden 2–6 mg/day, trihexyphenidyl 5–10 mg/day) in the absence of contra-indications. However, the assumption that anticholinergics exert a selective effect upon rest tremor is not based on scientific evidence. The efficacy is similar to levodopa (see below), but safety profile of anticholinergic agents is lower. Side effects are common (in particular dry mouth, blurred vision, constipation). Therefore, they may be used either as monotherapy in young patients with predominant PD rest tremor, or as adjunctive therapy to levodopa (Jiménez and Vingerhoets 2012).

Levodopa-based medications (Levodopa + carbidopa; Levodopa + COMT inhibitors) and dopamine agonists (pramipexole, ropinirole) are beneficial to reduce tremor intensity. Once a day sustained release preparations and transdermal applications of dopaminergic therapies are increasingly used. Dopamine agonists are very likely associated with a significant delay in the rate of decline of nigrostriatal function (The Parkinson Study Group 2002; Whone et al. 2003). Dopamine agonists reduce levodopa refractory rest tremor when used as adjunct treatment in fluctuating patients (Fishman 2008). While rest tremor in PD is usually improved by dopaminergic drugs, the response of the postural component is usually relatively poor (Raethjen et al. 2005). Although the response of bradykinesia and rigidity to levodopa is excellent in PD, rest tremor responds less and the interindividual benefits are variable. Responders show a response up to 50% of tremor reduction (Henderson et al. 1994).

Inhibitors of monoamine oxidase B (selegiline 10 mg/day, rasagiline 0.5–1 mg/day) as adjunctive therapies of levodopa reduce tremor intensity (Parkinson Study Group 2005). Safinamide has a dual mechanism of action. The drug is a highly selective and fully reversible inhibitors of monoamine oxidase B, with a selectivity superior to selegiline and rasagiline, as well as a blocker of voltage-gated Na + channels, with inhibition of stimulated glutamate release (Alborghetti and Nicoletti 2018; Kulisevsky 2014). The drug is prescribed mainly for motor fluctuations but also shows antitremor effects. Results from phase III trials have shown beneficial effects upon tremor (Abbruzzese et al. 2021). The effects of amantadine are unclear. The sparing effect upon doses of levodopa remains doubtful.

Clozapine may be useful in resistant parkinsonian tremor, but requires a close hematologic follow-up due to the risk of agranulocytosis.

Other therapeutic options include beta-blockers such as propranolol, primidone and zonizamide. However, the effectiveness of propranolol in parkinsonian tremor remains a matter of debate (Crosby et al. 2003). Botulinum toxin may be useful for hand tremor (Niemann and Jankovic 2018). Doses and sites of administration should be individualized. Adverse events (pain, paresia) are transient.

Surgical procedures such as conventional thalamotomy and DBS (targets: Vim, GPi, STN, PPN or pedunculopontine nucleus, zona incerta) are discussed elsewhere in the book. These techniques may decrease substantially rest tremor, providing a long-lasting alleviation (Jiménez and Vingerhoets 2012). They are proposed in advanced cases refractory to medications. DBS of the Vim is the usual target for tremor (Lake et al. 2019). Paresthesias, dysarthria and less often ataxia are common side effects. Closed-loop stimulation is moving from research laboratories to the clinic. Overall, rest tremor usually responds better to surgery than to drugs.

Gamma-knife thalamotomy may be considered in a subset of patients who are not eligible for open surgical procedures or who opt to avoid them (Monaco et al. 2018). The noninvasive MRI-guided focused ultrasound thalamotomy (MRgFUS) of the Vim is associated with a significant, immediate and sustained improvement of the contralateral tremor score (Fasano et al. 2017). Side effects include hemitongue numbness and hemiparesis with hemihypoesthesia. A recent analysis suggests a similar efficacy of DBS and MRgFUS in parkinsonian tremor suppression (Lin et al. 2021).

References

Abbruzzese G. Malattie del sistema extrapiramidale. In: Loeb C, Favale E, editors. Neurologia di Fazio Loeb. Roma: Società Editrice Universo; 2003.

Abbruzzese G, Barone P, Lopiano L, Stocchi F. The current evidence for the use of safinamide for the treatment of Parkinson's disease. Drug Des Devel Ther. 2021;15:2507–17.

Alborghetti M, Nicoletti F. Different generations of type-B monoamine oxidase inhibitors in parkinson's disease: from bench to bedside. Curr Neuropharmacol. 2018;16:1–13.

Antonini A, Moeller JR, Nakamura T, Spetsieris P, Dhawan V, Eidelberg D. The metabolic anatomy of tremor in Parkinson's disease. Neurology. 1998;51:803–10.

Belvisi D, Conte A, Bologna M, Bloise MC, Suppa A, Formica A, Costanzo M, Cardone P, Fabbrini G, Berardelli A. Re-emergent tremor in Parkinson's disease. Parkinsonism Relat Disord. 2017;36:41–6.

Benninger DH, Thees S, Kollias SS, Bassetti CL, Waldvogel D. Morphological differences in Parkinson's disease with and without rest tremor. J Neurol. 2009;256(2):256–63.

Ben-Pazi H, Bergman H, Goldberg JA, Giladi N, Hansel D, Reches A, Simon ES. Synchrony of rest tremor in multiple limbs in parkinson's disease: evidence for multiple oscillators. J Neural Transm. 2001;108(3):287–96.

Bergman H, Wichmann T, De Long M. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science. 1990;249:1436–8.

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM. Deuschl G; tremor task force of the International Parkinson and Movement Disorder Society. Consensus statement on the classification of tremors. From the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33(1):75–87.

Bonneville F, Bloch F, Kurys E, du Montcel ST, Welter ML, Bonnet AM, Agid Y, Dormont D, Houeto JL. Camptocormia and Parkinson's disease: MR imaging. Eur Radiol. 2008;18(8):1710–9.

Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. Proc Natl Acad Sci U S A. 2010;107(18):8452–6.

Caligiore D, Pezzulo G, Baldassarre G, Bostan AC, Strick PL, Doya K, Helmich RC, Dirkx M, Houk J, Jörntell H, Lago-Rodriguez A, Galea JM, Miall RC, Popa T, Kishore A, Verschure PF, Zucca R, Herreros I. Consensus paper: towards a systems-level view of cerebellar function: the interplay between cerebellum, basal ganglia, and cortex. Cerebellum. 2017;16(1):203–29.

Christakos CN, Erimaki S, Anagnostou E, Anastasopoulos D. Tremor-related motor unit firing in Parkinson's disease: implications for tremor genesis. J Physiol. 2009;587(Pt 20):4811–27.

Crosby NJ, Deane KH, Clarke CE. Beta-blocker therapy for tremor in Parkinson's disease. Cochrane Database Syst Rev. 2003;1:CD003361.

Deuschl G, Raethjen J, Baron R, Lindemann M, Wilms H, Krack P. The pathophysiology of parkinsonian tremor: a review. J Neurol. 2000;247(Suppl 5):V33–48.

Fasano A, Llinas M, Munhoz RP, Hlasny E, Kucharczyk W, Lozano AM. MRI-guided focused ultrasound thalamotomy in non-ET tremor syndromes. Neurology. 2017;89(8):771–5.

Findley LJ, Koller WC. Handbook of tremor disorders. New York: Marcel Dekker; 1995.

Fishman PS. Paradoxical aspects of parkinsonian tremor. Mov Disord. 2008;23(2):168–73.

Fois AF, Chang FC, Barnett R, London K, Mahant N, Ha A, Aldaajani Z, Cruse B, Morales-Briceno H, Ma KK, Farlow D, Fung VS. Rest tremor correlates with reduced contralateral striatal dopamine transporter binding in Parkinson's disease. Parkinsonism Relat Disord. 2021;85:102–8.

Foltynie T, Brayne C, Barker RA. The heterogeneity of idiopathic Parkinson's disease. J Neurol. 2002;249:138–45.

Gigante AF, Pellicciari R, Iliceto G, Liuzzi D, Mancino PV, Custodero GE, Guido M, Livrea P, Defazio G. Rest tremor in Parkinson's disease: Body distribution and time of appearance. J Neurol Sci. 2017;15(375):215–9.

Gupta N, Pandey S. Rest tremor in dystonia: epidemiology, differential diagnosis, and pathophysiology. Neurol Sci. 2020;41(9):2377–2388.

Habib-ur-Rehman. Diagnosis and management of tremor. Arch Intern Med. 2000;160(16):2438–44.

Hellmann MA, Melamed E, Steinmetz AP, Djaldetti R. Unilateral lower limb rest tremor is not necessarily a presenting symptom of Parkinson's disease. Mov Disord. 2010;25(7):924–7.

Helmich R. The cerebral basis of Parkinsonian tremor: A network perspective. Mov Disord. 2018;33(2):219–231.

Henderson JM, Yiannikas C, Morris JG, Einstein R, Jackson D, Byth K. Postural tremor of Parkinson's disease. Clin Neuropharmacol. 1994;17(3):277–85.

Hirschmann J, Butz M, Hartmann CJ, Hoogenboom N, Özkurt TE, Vesper J, Wojtecki L, Schnitzler A. Parkinsonian rest tremor is associated with modulations of subthalamic high-frequency oscillations. Mov Disord. 2016;31(10):1551–9.

Hopfensperger KJ, Busenbark K, Koller WC. Midbrain tremor. In: Findley LJ, Koller WC, editors. Handbook of tremor disorders. New York: Marcel Dekker; 1995. p. 455–9.

Italian Neurological Society; Italian Society of Clinical Neurophysiology. Guidelines for the treatment of Parkinson's disease 2002. The diagnosis of Parkinson's disease. Neurol Sci. 2003;24(3):S157–64.

Jellinger KA. Post mortem studies in Parkinson's disease – is it possible to detect brain areas for specific symptoms? J Neural Transm. (Supplement). 1999:1–29.

Jiménez MC, Vingerhoets FJ. Tremor revisited: treatment of PD tremor. Parkinsonism Relat Disord. 2012;18(Suppl 1):S93–5.

Kalra S, Grosset DG, Benamer HT. Differentiating vascular parkinsonism from idiopathic Parkinson's disease: a systematic review. Mov Disord. 2010;25(2):149–56.

Kelly RM, Strick PL. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosci. 2003;23:8432–44.

Kinnerup MB, Sommerauer M, Damholdt MF, Schaldemose JL, Ismail R, Terkelsen AJ, Stær K, Hansen A, Fedorova TD, Knudsen K, Skjærbæk C, Borghammer P, Pavese N, Brooks DJ, Nahimi A. Preserved noradrenergic function in Parkinson's disease patients with rest tremor. Neurobiol Dis. 2021;152:105295.

Kraus PH, Lemke MR, Reichmann H. Kinetic tremor in Parkinson's disease–an underrated symptom. J Neural Transm. 2006;113(7):845–53.

Kulisevsky J. Emerging role of safinamide in parkinson's disease therapy. Eur Neurol Rev. 2014;9(2):108–12.

Lake W, Hedera P, Konrad P. Deep brain stimulation for treatment of tremor. Neurosurg Clin N Am. 2019;30(2):147–59.

Leodori G, Belvisi D, De Bartolo MI, Fabbrini A, Costanzo M, Vial F, Conte A, Hallett M, Berardelli A. Re-emergent tremor in parkinson's disease: The role of the motor cortex. Mov Disord. 2020;35(6):1002–1011.

Leodori G, De Bartolo MI, Fabbrini A, Costanzo M, Mancuso M, Belvisi D, Conte A, Fabbrini G, Berardelli A. The role of the motor cortex in tremor suppression in parkinson's disease. J Parkinsons Dis. 2022;12(6):1957–1963.

Lin F, Wu D, Yu J, Weng H, Chen L, Meng F, Chen Y, Ye Q, Cai G. Comparison of efficacy of deep brain stimulation and focused ultrasound in parkinsonian tremor: a systematic review and network meta-analysis. J Neurol Neurosurg Psychiatry. 2021:jnnp-2020-323656.

Llinas R, Paré D. Role of intrinsic neuronal oscillations and network ensembles in the genesis of normal and pathological tremors. In: Findley LJ, Koller WC, editors. Handbook of tremor disorders. New York: Marcel Dekker; 1995.

Louis ED, Asabere N, Agnew A, et al. Rest tremor in advanced essential tremor: a post-mortem study of nine cases. J Neurol Neurosurg Psychiatry. 2011;82(3):261–5.

Magerkurth C, Schnitzer R, Braune S. Symptoms of autonomic failure in Parkinson's disease: prevalence and impact on daily life. Clin Auton Res. 2005;15(2):76–82.

Marshall VL, Reininger CB, Marquardt M, et al. Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study with repeat [123I]FP-CIT SPECT. Mov Disord. 2009;24:500–8.

Monaco EA III, Shin SS, Niranjan A, Lunsford LD. Radiosurgical thalamotomy. Prog Neurol Surg. 2018;33:135–48.

Niemann N, Jankovic J. Botulinum toxin for the treatment of hand tremor. Toxins (Basel). 2018;10(7):299.

Nisticò R, Pirritano D, Salsone M, Novellino F, Del Giudice F, Morelli M, Trotta M, Bilotti G, Condino F, Cherubini A, Valentino P, Quattrone A. Synchronous pattern distinguishes resting tremor associated with essential tremor from rest tremor of Parkinson's disease. Parkinsonism Relat Disord. 2011;17(1):30–3.

Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch Neurol. 2005;62(2):241–8.

Piao YS, Mori F, Hayashi S, Tanji K, Yoshimoto M, Kakita A, Wakabayashi K, Takahashi H. Alpha-synuclein pathology affecting Bergmann glia of the cerebellum in patients with alphasynucleinopathies. Acta Neuropathol. 2003;105:403–9.

Pollok B, Gross J, Dirks M, Timmermann L, Schnitzler A. The cerebral oscillatory network of voluntary tremor. J Physiol. 2004;554(Pt 3):871–8.

Raethjen J, Lindemann M, Schmaljohann H, Wenzelburger R, Pfister G, Deuschl G. Multiple oscillators are causing parkinsonian and essential tremor. Mov Disord. 2000;15(1):84–94.

Raethjen J, Pohle S, Govindan RB, Morsnowski A, Wenzelburger R, Deuschl G. Parkinsonian action tremor: interference with object manipulation and lacking levodopa response. Exp Neurol. 2005;194(1):151–60.

Rajput AH, Sitte HH, Rajput AH, Fenton ME, Pifl C, Hornykiewicz O. Globus pallidus dopamine and Parkinson motor subtypes. Clinical and brain biochemical correlation. Neurology. 2008;70(16 Pt 2):1403–10.

Reck C, Himmel M, Florin E, Maarouf M, Sturm V, Wojtecki L, Schnitzler A, Fink GR, Timmermann L. Coherence analysis of local field potentials in the subthalamic nucleus: differences in parkinsonian rest and postural tremor. Eur J Neurosci. 2010;32(7):1202–14.

Shakkottai VG, Batla A, Bhatia K, Dauer WT, Dresel C, Niethammer M, Eidelberg D, Raike RS, Smith Y, Jinnah HA, Hess EJ, Meunier S, Hallett M, Fremont R, Khodakhah K, LeDoux MS, Popa T, Gallea C, Lehericy S, Bostan AC, Strick PL. Current opinions and areas of consensus on the role of the cerebellum in dystonia. Cerebellum. 2017;16(2):577–94.

Thanvi B, Lo N, Robinson T. Vascular parkinsonism–an important cause of parkinsonism in older people. Age Ageing. 2005;34(2):114–9.

The Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs. levodopa on Parkinson disease progression. JAMA. 2002;287:1653–61.

Timmermann L, Gross J, Dirks M, Volkmann J, Freund HJ, Schnitzler A. The cerebral oscillatory network of parkinsonian resting tremor. Brain. 2003;126:199–212.

Verbaan D, Marinus J, Visser M, van Rooden SM, Stiggelbout AM, Middelkoop HA, van Hilten JJ. Cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007;78(11):1182–7.

Weinberger M, Hutchison WD, Lozano AM, Hodaie M, Dostrovsky JO. Increased gamma oscillatory activity in the subthalamic nucleus during tremor in Parkinson's disease patients. J Neurophysiol. 2009;101(2):789–802.

Whone AL, Watts RL, Stoessl AJ, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: the REALPET study. Ann Neurol. 2003;54:93–101.

Wüllner U, Schmitz-Hübsch T, Abele M, Antony G, Bauer P, Eggert K. Features of probable multiple system atrophy patients identified among 4770 patients with parkinsonism enrolled in the multicentre registry of the German Competence Network on Parkinson's disease. J Neural Transm. 2007;114(9):1161–5.

Chapter 7
Postural Tremors

Jean-François Daneault and Christian Duval

Abstract Tremor can be observed in every individual. Its amplitude and frequency are dependent on mechanical as well as neural components, and can be modified by disease. The objective of this chapter is to discuss the specific characteristics of postural tremor in healthy persons and in different pathologies. Postural tremor deserves attention since limbs are rarely completely at rest. Accordingly, postural tremor may provide important information about the state of the system. Furthermore, in some pathologies, postural and rest tremor may present different characteristics. Identifying the origins of postural tremor and its relationship with rest tremor characteristics may be helpful for diagnostic purposes. We will discuss the possible origins of those tremor oscillations, as well as current controversies. While we acknowledge that tremor, either physiological or pathological, can be observed in the lower limbs, head and even trunk just as often as in the upper limbs, this chapter will focus on finger or hand tremor. More specifically, we will compare some of the most common postural tremors with their resting tremor equivalents. Physiological tremor (PT), enhanced physiological tremor (EPT) and essential tremor (ET) will be discussed. We will also consider the possible link between these different types of postural tremors. Finally, we will discuss postural tremor in the context of Parkinson's disease (PD) and its possible relation to ET.

Keywords Posture · Physiological tremor · Enhanced physiological tremor · Essential tremor · Parkinson tremor

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7.1 Introduction

Tremor can be observed in every individual. Its amplitude and frequency are dependent on mechanical as well as neural components, which can be modified by disease. The objective of this chapter is to discuss the specific characteristics of postural tremor in healthy individuals and in people with different pathologies. Several studies have shown that by examining postural tremor, it is possible to gather important information about the state of the system. For instance, in some pathologies, identifying the origins of postural tremor, and its relationship with other symptoms such as rest tremor, may be helpful for diagnostic purposes and can help pinpoint therapeutic targets. In this chapter, we will discuss the possible origins of those tremor oscillations, as well as current controversies. While we acknowledge that tremor, either physiological or pathological, can be observed in the lower limbs, head and even trunk just as often as in the upper limbs, this chapter will focus on finger or hand tremor. Pathological distal tremor of the hands and fingers affect the performance of activities of daily living and can lead to major impairments in quality of life. As such, we will first describe normal postural physiological tremor (PT) and identify how it differs from enhanced physiological tremor (EPT) and essential tremor (ET). Next, we will consider the possible link between these different types of postural tremors and how they differ from rest tremor. Finally, we will discuss postural tremor in the context of Parkinson's disease (PD) and its possible relation to ET. Figure 7.1 illustrates the importance of the postural component of tremor in PT, EPT, ET and PD as well as the possible relationship between those types of tremor and disorders.

7.2 Postural Physiological Tremor

Postural PT can be described as involuntary oscillations of a limb with sinusoidal properties (Elble and Koller 1990). These oscillations are present in every limb but are of such small amplitude that they are difficult to see with the naked eye. In young healthy adults, postural PT amplitude of the finger normally ranges from 0.1 to 0.2 mm (Duval and Jones 2005; Carignan et al. 2009, 2010, 2012). Interestingly, a recent study found that PT components in the *x*-, *y*- and *z*-dimensions are not independent time series, and there exists a subject-specific and task-specific coupling between axes in the frequency domain (Adhikari et al. 2016). Raethjen et al. (2000) demonstrated that age does not seem to influence postural PT amplitude, but there is a decrease in median power frequency with age (Marshall 1961; Marsden et al. 1969; Wade et al. 1982; Birmingham et al. 1985; Lakie 1995). The origin of PT is still unclear but recent work suggests that the primary motor cortex and cerebellum may be involved (Mehta et al. 2014).

Postural PT comprises oscillations between 1 and 40 Hz (Brumlik 1962; Allum et al. 1978; Isokawa-Akesson and Komisaruk 1985). In the acceleration power

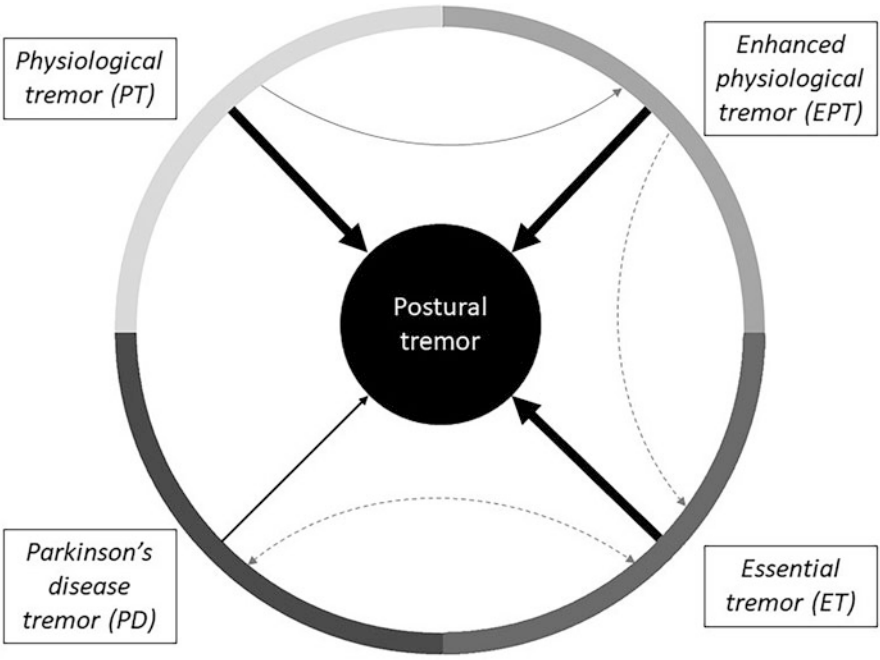

Fig. 7.1 Graph illustrating the importance of the postural component of tremor (*black arrows*) in physiological tremor (PT), enhanced physiological tremor (EPT), essential tremor (ET) and Parkinson's disease (PD). The thicker black arrows indicate a greater importance of the postural component of tremor. Additionally, the potential relationship between PT, EPT, ET and PD is highlighted by the grey lines where the arrow indicates the direction of the relationship and a dashed line indicates that the relationship is not yet well established

spectrum of postural PT of the finger, a predominance of oscillations between 16 and 30 Hz can be observed (Carignan et al. 2010). Additionally, a peak between 8 and 12 Hz can also be seen (Fig. 7.2). However, the systematic presence of an 8–12 Hz peak is still debated. For instance, Raethjen et al. (2004) observed this peak in the majority of their subjects whereas in their other study (Raethjen et al. 2000), they observed the 8–12 Hz peak in less than 20% of subjects. Similarly, another study did not observe this peak in most subjects (Carignan et al. 2010). Most importantly, they demonstrated that the majority of acceleration power lies within the oscillations located between 16 and 30 Hz and that analytically removing the oscillations located between 8 and 12 Hz led to only a 7% reduction in total acceleration power (Carignan et al. 2010).

In addition to postural PT, rest PT can also be observed in healthy individuals and shares many characteristics with postural PT. However, the amplitude of rest PT is significantly smaller than in postural PT and when examining the acceleration power spectrum of rest PT, the relative distribution of power stemming from the oscillations between 1 and 40 Hz diverges from what can be observed in postural

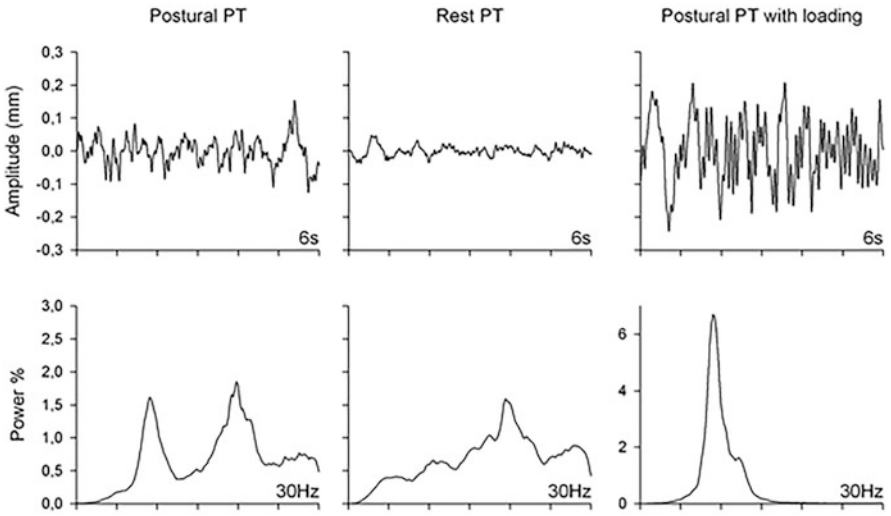

Fig. 7.2 Finger tremor was recorded from a 43-year-old female without any known neurological disorders. A laser displacement sensor was used to measure tremor during a postural condition, a rest condition and while loading (70 g) was applied to the finger during a postural condition. *Top*: Example of finger tremor displacement over a 6 s window within a 60 s trial. *Bottom*: Acceleration power spectra of the complete trial from which each of the above examples were taken. Here the 8–12 Hz peak is identifiable in the postural condition. More details on the analysis can be obtained from Carignan et al. (2010) and Daneault et al. (2010)

PT. For instance, the acceleration power spectrum of rest PT usually does not present any dominant oscillations (Fig. 7.2).

While both rest and postural PT probably stem from the same systems, it is reasonable to suggest that it is the different level of activation within those systems that causes the inherent differences. According to most studies, the oscillations can be divided into two categories: those stemming from central origins and those that are derived from mechanical reflex sources. Studies have shown that for finger tremor, frequencies below 7 Hz are associated with reflex activities influenced by mechanical properties of the limb involved (Van Buskirk et al. 1966; Yap and Boshes 1967; Jalaleddini et al. 2017). Since mechanical properties, such as unfused motor-unit activity (De Luca and Erim 1994) or sensorimotor control processes (Morrison et al. 2006), are inherently different while maintaining posture when compared to rest, this can explain some of the differences observed between postural and rest PT. Recent work has shown that the amplitude of PT increases as muscles shorten and that this stems from the modulation of γ-static fusimotor drive (Jalaleddini et al. 2017). The ballistocardiac impulse is also involved in the generation of low-frequency oscillations (Marsden et al. 1969; Wade et al. 1982; Lakie et al. 1986; Elble and Koller 1990). However, it has been demonstrated that this phenomenon only accounts minimally for the low-frequency oscillations in rest PT (Morrison and Newell 2000). Since postural PT stems from higher activation of other systems, the

minimal implication of the ballistocardiac impulse to rest PT is even less significant in postural PT.

As for frequencies between 8 and 12 Hz, they have been associated with centrally originating oscillations (Halliday and Redfearn 1956; Lamarre et al. 1975; Llinas 1984; Köster et al. 1998). The most common method to identify whether oscillations stem from central structures is to load the limb being examined. By loading the limb, its mechanical properties are altered. This modifies the power spectrum (Fig. 7.2). While the frequency of the centrally generated oscillations is unaffected by loading, their amplitude increases (Halliday and Redfearn 1956; Marshall and Walsh 1956; Randall and Stiles 1964; Elble 1995; Vaillancourt and Newell 2000), suggesting an increased central drive to counteract the additional load. As such, these centrally generated oscillations should be present both during postural PT and rest PT. Yet, the peak between 8 and 12 Hz, when present, is much more prominent in postural PT. This can be explained by the fact that rest PT requires little activation while postural PT requires muscular activation to hold the limb against gravity. This has previously been observed as coherence between postural PT and electromyography (EMG) occurs in the 8–12 Hz frequency band (Elble and Randall 1976). Furthermore, recent work has also demonstrated that there is no significant difference in PT characteristics in the 8–12 Hz range between the dominant and non-dominant hands during an isometric finger abduction (Novak and Newell 2017), suggesting that this component is centrally generated and linked to muscle activation. However, limited work has been done to conclusively link central nervous system activity to postural and rest PT. Some studies have demonstrate that 10 Hz oscillations are present in the inferior olive (Armstrong 1974; Llinás et al. 2015). It was suggested that these oscillations could be transmitted to the periphery by the olivo-cerebellar (Poirier et al. 1966; Lamarre et al. 1975; Llinas 1984; Llinas and Paré 1995) and the cerebello-thalamo-cortical tracts (Duval et al. 2000, 2005; Duval 2006). One compelling argument for the central genesis of these oscillations is that, in patients having undergone a thalamotomy, in addition to the elimination of the pathological central oscillations, the 8–12 Hz component of postural PT is also absent when tremor amplitude reached normal values (Duval et al. 2000, 2005).

The other component of PT comprises the oscillations in the 16–30 Hz range, which are suggested to originate from the mechanical resonance of the finger (Stiles and Randall 1967) as well as cortical oscillations (Conway et al. 1995; McAuley et al. 1997) modulated by the mechanical properties of the finger (Vaillancourt and Newell 2000). This component was also shown to be affected by a thalamotomy (Duval et al. 2000, 2005), which argues for central involvement in generating these oscillations. The mechanical resonance frequency of a limb (f_0) has been demonstrated to be directly proportional to the square root of its rigidity (K) (Robson 1959) and inversely proportional to the square root of its inertia (I) (Stiles and Randall 1967):

$$f_0 = \sqrt{\frac{K}{I}}$$

Since the limb's inertia remains unchanged when examining postural and rest PT, some of the observed changes could be due to slight changes in rigidity brought forward by increased muscular activation. Based on the aforementioned evidence, postural PT oscillations likely stem from mechanical as well as central structures and are different from rest PT in terms of amplitude and spectral characteristics, because the relative involvement of the different mechanical and central components varies depending on whether the limb is held or not against gravity.

It is also important to note, however, that recent studies have suggested that the central drive is not required to generate the spectral characteristics of PT (Vernooij et al. 2013, 2015). Instead, they suggest that PT is primarily a result of broadband nonlinear resonance, regardless of the frequency band being examined. As such, more work is needed to clarify the origin of these oscillations.

7.3 Postural Enhanced Physiological Tremor

It was previously demonstrated that in some cases, the mechanical component of PT can be enhanced by reflex activity (Young and Hagbarth 1980; Deuschl et al. 2001). This phenomenon can be best observed by loading the limb while in a postural position. The peak observed between 16 and 30 Hz in the tremor acceleration power spectrum shifts towards lower frequencies as the load is applied, while the frequency of the 8–12 Hz peak remains unchanged (Fig. 7.3). Interestingly, young individuals can present with tremor whose amplitude is slightly above normal when assuming posture. Whereas there is often no prominent EMG peak in postural PT, there is an easily identifiable 8–12 Hz EMG peak that is independent from loading in enhanced physiological tremor (EPT) (Elble 1986; Deuschl et al. 2001), which could be of cortical origin (Köster et al. 1998). Since EPT is not usually a burden to people, except in situations where precision is required, only few studies have examined its characteristics. Most evaluated EPT during posture (Young and Hagbarth 1980; Köster et al. 1998; Lauk et al. 1999; Deuschl et al. 2001) and to our knowledge only one examined it during rest (Lauk et al. 1999). Interestingly, the prominent peak in the tremor power spectrum fades in the rest condition, resulting in a relatively flatter curb similar to rest PT (Fig. 7.3). Lauk et al. (1999) observed a higher coherence between bilateral EPT during rest and posture than for PT, essential tremor (ET), or Parkinson's disease (PD) tremor. This may indicate a shared or linked central process generating these dominating oscillations. Although EPT can be induced experimentally through muscular fatigue (Young and Hagbarth 1980), loading (Young and Hagbarth 1980; Köster et al. 1998; Gironell et al. 2004), manoeuvres influencing the stretch reflex (Young and Hagbarth 1980), and the injection of various drugs such as adrenaline (Marsden and Meadows 1968), isoproterenol (Young and Hagbarth 1980) and salbutamol (Köster et al. 1998), the pathophysiological basis of its unprovoked presence in some individuals is yet unknown. Studies using loading (Köster et al. 1998; Gironell et al. 2004) and transcranial magnetic stimulation (Köster et al. 1998) seem to suggest that the

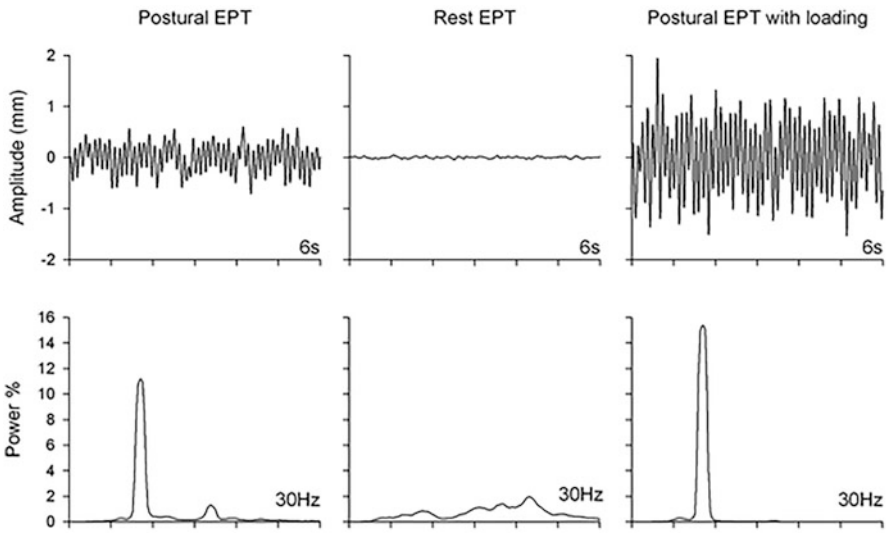

Fig. 7.3 *Top:* Finger tremor from a 41-year-old male presenting with clinically visible tremor was recorded using a laser displacement sensor during a postural condition, a rest condition and a postural condition while a mechanical load (70 g) was added to the finger. *Bottom:* Acceleration power spectra of the complete trial from which each of the above examples were taken. Note again that the *y*-axis of the power spectrum represents the percentage of total power for each frequency, with a resolution of 0.2 Hz

cortex is not involved in the generation of EPT, but that peripheral mechanisms do play an important role in generating these oscillations. However, a recent study has demonstrated that frequency decrease upon loading is a specific (95%) but not sensitive (42%) test for EPT (van der Stouwe et al. 2016). It was also suggested that EPT could be an intermediate step to progress from PT to ET, which can be first identified through frequency-invariant motor-unit entrainment below 8 Hz (Elble et al. 2005). This hypothesis will be discussed in Sect. 7.5.

7.4 Essential Tremor

Although ET is the most common movement disorder (Louis et al. 1998b, 2009; Louis 2000; Louis and Ferreira 2010; Louis and Ottman 2014), its pathophysiology is still debated. ET asymmetrically affects the upper limbs in 95% of patients (Louis et al. 1998a) and it classically occurs during posture and movement (Hubble et al. 1997; Louis et al. 1998a; Brennan et al. 2002; Elble and Deuschl 2009) (Fig. 7.4) but it can also be observed during rest in as many as 20–30% of cases (Cohen et al. 2003; Burne et al. 2004; Gironell et al. 2004; Louis et al. 2005; Dotchin and Walker 2008) (Fig. 7.5). Some argue that rest tremor is merely present in advanced

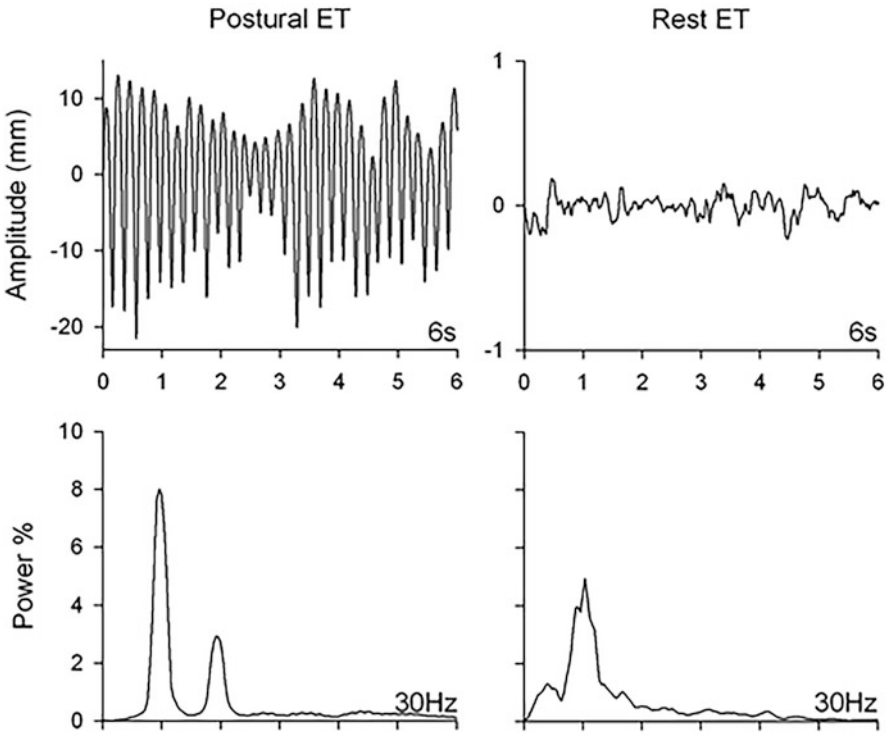

Fig. 7.4 Graph representing an example of advanced classical essential tremor (ET) where postural tremor can be observed and there is no visible rest tremor. Finger tremor was recorded using a laser displacement sensor during both a postural and a rest condition. These recordings were made from a 62-year-old female diagnosed with ET and scheduled to undergo stereotactic neurosurgery to alleviate her tremor. *Top:* Example of finger tremor displacement over a 6 s window within a 30 s trial. *Bottom:* Velocity power spectra of the complete trial from which each of the above examples were taken. Note again that the *y*-axis of the power spectrum represents the percentage of total power for each frequency, with a resolution of 0.2 Hz. The velocity power spectra are displayed since double differentiation of the displacement signal amplifies the harmonics as can already be seen from the postural ET power spectrum (i.e. the second peak is the first upper harmonic of the dominant oscillations located at 5 Hz). Note also that even though there is no visible tremor, a peak is detectable at the same frequency for both postural and rest tremor. This could indicate that although tremor is not clinically detectable, abnormal oscillations can still be detected at rest in this patient with advanced ET

ET and that it is in fact postural tremor caused by incomplete muscle relaxation, which would disappear if the patient was lying or seated in a position with complete body support (Elble and Deuschl 2009). Others (Louis et al. 2005, 2011) suggest that when both rest and postural tremor are present in ET, they stem from a common process. A possible reason for the prevailing postural tremor in ET is that the load-dependent component of tremor is dominant (Burne et al. 2004). Thus, holding the limb against gravity activates load-bearing muscles, which in turn activates tremor.

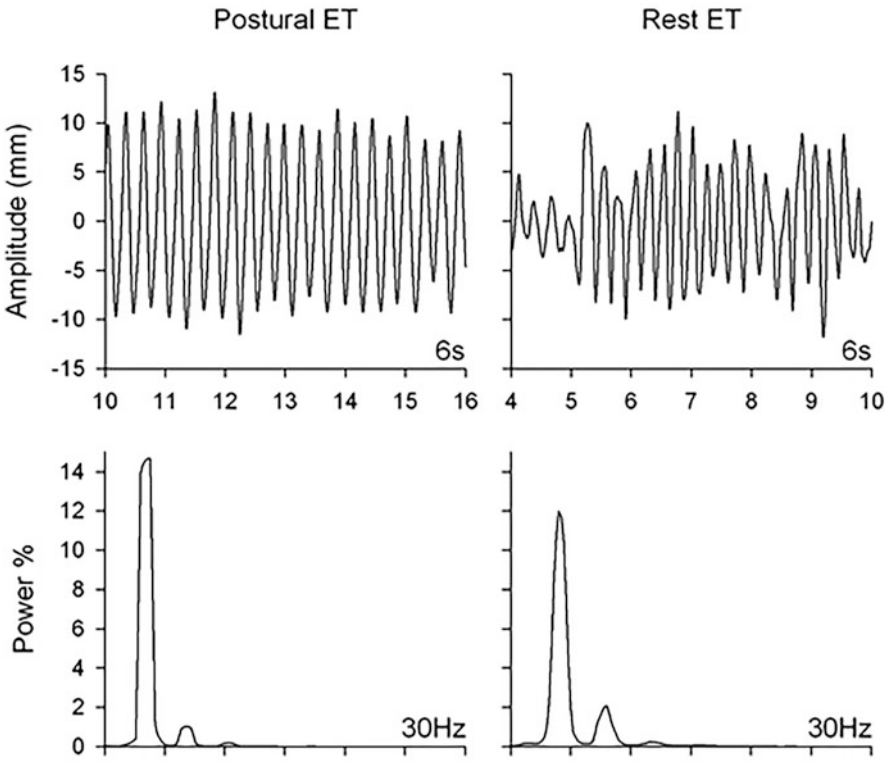

Fig. 7.5 Graph representing an example of advanced essential tremor (ET) where postural tremor and rest tremor can both be observed. Finger tremor was recorded using a laser displacement sensor during both a postural and a rest condition. These recordings were made from an 85-year-old female diagnosed with ET and scheduled to undergo stereotactic neurosurgery to alleviate her tremor. *Top:* Example of finger tremor displacement over a 6 s window within a 30 s trial. *Bottom:* Velocity power spectra of the complete trial from which each of the above examples were taken. Note again that the *y*-axis of the power spectrum represents the percentage of total power for each frequency, with a resolution of 0.2 Hz. The velocity power spectra are displayed since double differentiation of the displacement signal amplifies the harmonics as can already be seen from both power spectra (i.e. the second peak is the first upper harmonic of the dominant oscillations located at 4 Hz)

ET amplitude is quite variable between patients as well as within and across days for any given patient (Tamás et al. 2004). Tremor amplitude tends to increase with advancing age (Zesiewicz and Hauser 2001) and can become functionally incapacitating for some patients (Louis et al. 2001a). When examining the spectral characteristics of postural ET, one can observe a distinct high-amplitude peak over a wide range between 5 and 12 Hz (Deuschl et al. 1998; Bhatia et al. 2017). This is probably due to the fact that ET frequency has been shown to decrease over time (Hellwig et al. 2009). Indeed, in early ET, the prominent peak is usually located closer to 10 Hz while in advanced ET, this peak shifts closer to 5 Hz. In

contrast to PT or EPT, ET peak frequency does not change when loading the limb while in a postural position (Zeuner et al. 2003; Gironell et al. 2004). This can be explained by the fact that a central generator contributes to setting the dominant tremor frequency in ET. While loading does not significantly modify postural PT amplitude, interestingly, it significantly reduces its amplitude (Héroux et al. 2009).

Héroux et al. (2009) suggested that in ET, the centrally generated component determines tremor frequency whereas the synergistic and/or competitive interaction between central and mechanical reflex components determines tremor amplitude. Furthermore, it was demonstrated that the central component itself might stem from stochastically interacting central structures that cause large intra- and inter-subject variability in tremor characteristics (Tamás et al. 2004). Some have suggested that these central structures most likely do not involve primary motor areas (Halliday et al. 2000; Tamás et al. 2004) but rather lower-order regions. Nonetheless, others have shown that metabolic activation of the contralateral supplementary motor area and bilateral cerebellum (Colebatch et al. 1990; Jenkins et al. 1993) as well as contralateral thalamus (Jenkins et al. 1993) is observed during ET. The sensorimotor cortex has also been implicated in the generation of the oscillations observed in ET (Hellwig et al. 2001). The thalamus plays an important part in ET circuitry since lesioning of the posterior portion of the ventral lateral nucleus, which receives deep proprioceptive input, as well as cerebellar projections, eliminates ET (Akbostanci et al. 1999; Zesiewicz et al. 2005; Kondziolka et al. 2008; Young et al. 2010). Overactivity of the cerebellum and its projections may be induced by the abnormal oscillatory activity arising as afferent input from the inferior olive, which would then be conducted via the thalamus and cortex to the periphery via the corticospinal tract (Jenkins et al. 1993; Hellwig et al. 2001). Note that these activation patterns were observed in ET patients without rest tremor. Whether this pattern is also present when rest ET is present is yet to be determined. The relationship between ET and other forms of tremor is discussed below.

7.5 Relationships Between PT, EPT and ET

While the characteristics of different tremors have been described above, one might wonder if there is a link between PT, EPT and ET. PT is the normal behaviour observed in every limb in the absence of any pathological condition. If a link exists between these tremors, it should start from this normal physiological process. EPT is thought to stem from similar origins as PT with its increased amplitude resulting from abnormal central activity as evident on EMG spectra (Elble 1986; Deuschl et al. 2001). Since only two variables are modified over the tremor signal, it is plausible that EPT is merely the initial manifestation of abnormal oscillations within the central nervous system. As mentioned above, it has been suggested that EPT could be an intermediate step to progress from PT to ET (Elble et al. 2005). Much work remains to be done however to confirm this hypothesis. Patients having been diagnosed with ET often present with asymmetrical symptoms (Louis et al. 1998a;

Bhatia et al. 2017). Whereas one side presents with definite ET characteristics, it is not uncommon to observe some form of EPT on the contralateral side. This could indicate that EPT is more prevalent in ET patients, or that EPT should be included as a precursor of ET. Interestingly, simple linear analytical techniques cannot differentiate between these types of tremor based on the tremor signals (Morrison et al. 2017). On the other hand, nonlinear approaches can distinguish between the postural PT of healthy older adults (potentially EPT) and ET (Ayache et al. 2014; Morrison et al. 2017), suggesting that the relationship between these types of tremor is complex.

7.6 Postural Parkinson's Disease Tremor

Rest tremor is a cardinal symptom of Parkinson's disease (PD) (Deuschl et al. 1998; Jankovic 2008; Postuma et al. 2015; Bhatia et al. 2017), but postural tremor can also be observed in some patients with PD (Fig. 7.6) (Duval 2006; Daneault et al. 2013). In advanced PD, tremor may remain present in patients during postural tasks or movement (Lance et al. 1963; Teravainen and Calne 1980; Duval et al. 2000, 2005, 2006; Forssberg et al. 2000; Wenzelburger et al. 2000; Daneault et al. 2013). Interestingly, even some patients with PD presenting with mild tremor exhibit a postural component (Duval 2006). Importantly, one must also keep in mind that some have suggested that there are different types of postural tremor in PD (pure postural tremor and re-emergent postural tremor [a manifestation of PD rest tremor during posture]) (Jankovic et al. 1999; Mailankody et al. 2016; Aytürk et al. 2017; Belvisi et al. 2017, 2018; Dirkx et al. 2018). Recently, Belvisi et al. (2017) demonstrated that re-emergent postural tremor was present in about 20% of their sample and that this type of tremor had a latency of 3–16 s from posture onset. Another study observed that 81% of their sample exhibited re-emergent tremor while 19% exhibited pure postural tremor (Dirkx et al. 2018). However, since most studies that have examined postural PD tremor did not differentiate between re-emergent and pure postural tremor, they will be discussed as one entity here, highlighting differences when possible. Future work should identify those differences in more details.

When examining rest and postural PD tremor amplitude, as for ET, much variation exists between patients, as well as within and between days for a given patient (Beuter and Vasilakos 1995a, b; Agapaki et al. 2018). In patients with tremor, as the disease progresses, tremor shifts from being unilateral to bilateral and its amplitude tends to increase. However, one study reported that tremor eventually subsides completely in up to 10% of patients (Hughes et al. 1993). Duval et al. (2006) demonstrated that the amplitude of postural and rest PD tremor is strongly correlated in patients exhibiting mild PD tremor. A prominent peak between 4 and 8 Hz can be observed when examining the spectral characteristics of postural PD tremor (Fig. 7.5) (Rajput et al. 1991; Deuschl et al. 1998; Duval et al. 2000, 2005, 2006; Duval 2006; Bhatia et al. 2017). This same prominent peak is a hallmark

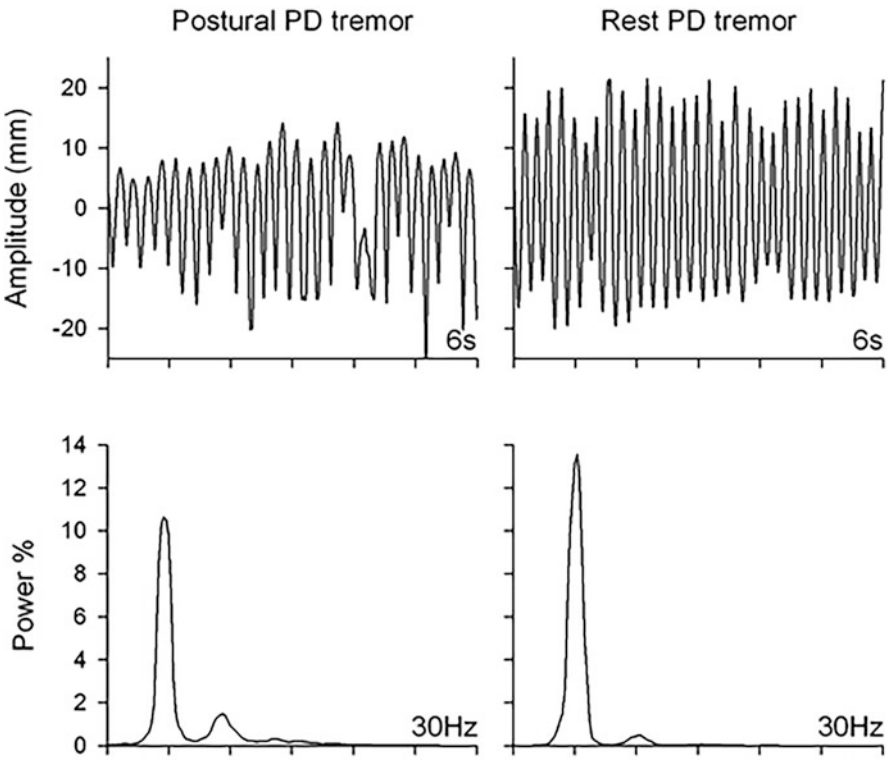

Fig. 7.6 Graph representing an example of advanced Parkinson's disease (PD) tremor where postural tremor and rest tremor can both be observed. Finger tremor was recorded using a laser displacement sensor during both a postural and a rest condition. These recordings were made from a 62-year-old male diagnosed with PD and scheduled to undergo stereotactic neurosurgery to alleviate his tremor. More details on the analysis can be obtained from Carignan et al. (2010) and Daneault et al. (2010). *Top*: Example of finger tremor displacement over a 6 s window within a 30 s trial. *Bottom*: Velocity power spectra of the complete trial from which each of the above examples were taken. The velocity power spectra are displayed since double differentiation of the displacement signal amplifies the harmonics as can already be seen from both power spectra (i.e. the second peak is the first upper harmonic of the dominant oscillations located at 5 Hz (Gresty and Buckwell 1990))

of rest PD tremor (Deuschl et al. 1998; Bhatia et al. 2017), contrasting with PT and EPT where the prominent frequency peak is not always present. Furthermore, in both PT and EPT, the respective rest and postural tremor characteristics differ (Homberg et al. 1987; Raethjen et al. 2000). In PD (Henderson et al. 1994; Jankovic et al. 1999) and ET (Burne et al. 2002; Cohen et al. 2003), the respective rest and postural tremor characteristics are similar.

Agapaki et al. (2018) found that there is increased motor-unit synchrony at the frequency of the primary tremor component, which leads to patient-specific spike doublets and triplets within the beta range with short inter-spike intervals that

bear a one-to-one relationship to each overt tremor cycle. They also observed that the frequency of the primary and secondary components of the PD tremor signal did not significantly change whether patients were at rest or maintaining a stable posture (Agapaki et al. 2018). Dirkx et al. (2018) did compare re-emergent and pure postural tremor characteristics in PD. They observed that re-emergent tremor had a lower amplitude, a frequency peak matching rest tremor and a dopamine response. On the other hand, pure postural tremor had a larger amplitude, a peak frequency about 3.5 Hz higher than rest tremor, and no dopamine response. This may suggest that previous work that did not observe differences between rest and postural PD tremor may have been assessing re-emergent tremor rather than pure postural tremor. Thus, while the pathophysiology of postural PD tremor has not yet been definitively defined, it is suggested that the mechanisms involved in the generation and/or propagation of rest PD tremor may remain active despite voluntary muscle activation (Jankovic et al. 1999; Duval et al. 2004; Duval 2006).

While loading the limb lowers the frequency of oscillations markedly in PT and EPT (Elble and Deuschl 2002; Raethjen et al. 2004) without changing their acceleration amplitude significantly (Raethjen et al. 2000, 2004; Elble 2003) because of the important contribution of the mechanical components of tremor, ET and PD tremor have major frequency-invariant central tremor components. Still, loading can affect these tremors through the interaction of these frequency-invariant components with mechanical resonance and mechanical reflex components, depending on the relative amplitude of these components. For instance, loading reduces amplitude of ET postural tremor and usually separates central and mechanical components in the power spectrum (Elble et al. 2005; Héroux et al. 2009) depending on the magnitude of the inertial load. In PD, some researchers have reported marginal effect of loading on amplitude and frequency of rest (Homberg et al. 1987; Deuschl et al. 1996) and postural (Meshack and Norman 2002) tremor while others reported significant loading effects on PD tremor characteristics (Forssberg et al. 2000; Burne et al. 2004). Specifically, Burne et al. (Burne et al. 2004) demonstrated that there is a large load-independent component in rest PD tremor that remains present during posture. In addition to this load-independent component, a load-dependent component is also present during postural PD tremor, which could explain the amplitude difference often seen between rest and postural PD tremor (Burne et al. 2004).

Some imaging studies have suggested that PD tremor is, at least partially, generated through a network encompassing the supplementary motor area, sensorimotor cortex, cerebellum and thalamus (Parker et al. 1992; Deiber et al. 1993; Boecker et al. 1997; Tasker et al. 1997; Fukuda et al. 2004). Other imaging studies have also implicated structures such as the subthalamic nucleus and since subsets of subthalamic nucleus neurons are tuned to the tremor frequency; it is suggested that PD tremor is generated by these neurons (Amtage et al. 2008, 2009). Others observed that subsets of neurons within the globus pallidus have oscillatory activity within the PD tremor range (Hurtado et al. 1999), suggesting that this structure could also provide abnormal oscillations leading to PD tremor. Other studies have observed that some spectral characteristics of tremor were no longer present after a thalamotomy (Duval et al. 2000, 2005, 2006) indicating that the thalamus is involved

in generating—or at least in relaying—tremor oscillations. Recent work highlights a consensus that one or several supraspinal oscillators generate PD tremor (Helmich et al. 2011, 2012; Cagnan et al. 2014; Brittain et al. 2015; Duval et al. 2016). However, the actual network responsible for PD tremor is still debated. For instance, some suggest that PD tremor is generated by the basal ganglia but is modulated by the cerebello-thalamo-cortical network (Helmich et al. 2012) while others suggest that PD tremor is induced by abnormal basal ganglia activity; it is generated by the thalamus, and modulated or reinforced by the cerebellum (Duval et al. 2016). More work is needed to conclusively identify the network(s) underlying PD tremor.

Furthermore, there is still much debate if rest and postural PD tremor share common neural networks. Some have suggested that it is indeed the case (Henderson et al. 1994; Jankovic et al. 1999; Moore et al. 2000) while other studies (Reck et al. 2010) emphasize the differences between rest and postural PD tremor. Contrary to classic PD rest tremor with a single peak on the frequency spectrum (about 4–6 Hz), PD action tremor (which includes postural tremor) exhibits one or two frequency peaks (Findley et al. 1981; Forssberg et al. 2000; Raethjen et al. 2005) in a wide frequency range of 4.8–12 Hz (Lance et al. 1963; Findley et al. 1981; Hadar and Rose 1993; Forssberg et al. 2000). However, since amplitude and spectral characteristics seem to overlap, it is suggested that the neural network involved in rest PD tremor may simply remain active during posture. Some researchers believe that PD postural (action) tremor might not be distinguishable from enhanced (or exaggerated) PT (Forssberg et al. 2000; Raethjen et al. 2005). Others, however, have instead suggested that some patients may concomitantly exhibit both ET and PD simultaneously, as discussed below. Thus, several hypotheses may be brought forward. The first is that the neural network responsible for rest PD tremor described above remains active during posture. In that case, the basal ganglia-cerebello-thalamo-cortical pathway would be crucial to the generation of this postural PD tremor. Another possibility is that some patients may also exhibit ET as well as PD. In this case, however, postural PD tremor would rather involve the olivo-cerebellar-thalamo-cortical network. Whether this is indeed the case remains to be determined and the possible relationship between both pathologies will be discussed below.

7.7 Relationships Between ET and PD

Existence of a possible link between ET and PD tremors has been debated for many years (Koller et al. 1994; Tan et al. 2008; Adler et al. 2011; Fekete and Jankovic 2011; Algarni and Fasano 2018). Some studies have observed a link between both pathologies (Hornabrook and Nagurney 1976; Geraghty et al. 1985; Koller et al. 1994; Louis and Frucht 2007; Rocca et al. 2007; Tan et al. 2008), while others have not (Marttila et al. 1984; Cleeves et al. 1988). Another issue confounding the link between both disorders is that both pathologies can be present in the same patient (Geraghty et al. 1985; Yahr et al. 2003; Shahed and Jankovic 2007; Minen and Louis 2008). In this subgroup of patients, the side exhibiting the majority of

ET tremor also exhibits most of the PD motor symptoms and more evidence is coming to light regarding an association between ET and distinct subgroups of patients with PD as initially suggested by Barbeau and Pourcher (1982). Rocca et al. (2007) observed a significantly increased risk of developing ET in relatives of young-onset patients with PD. This risk was further increased for relatives of patients with PD presenting with tremor-dominant or a mixed form of PD when compared to akinetic-rigid patients. Similarly, Louis et al. (2003) also observed an increased risk of action tremor in relatives of patients with PD having a tremor-dominant form of the disease, but not in those exhibiting postural instability and gait disorders. Therefore, current data suggest a significant relationship between ET and PD, mainly within the subgroup of patients with PD exhibiting tremor as their dominant motor manifestation.

Aside from the limited number of patients presenting with both disorders, the idea that they are linked likely stems from the similar clinical features between ET and PD as is evident by the misdiagnosis rates close to 30% between PD and ET in the early stages (Hughes et al. 1992; Poewe and Wenning 2002; Fekete and Jankovic 2011). In addition, a study considering the overlap in the clinical features of the two pathologies suggested that the two movement disorders are pathogenically related (Fekete and Jankovic 2011). This may be related to the complex interconnection between the basal ganglia and the cerebellum (Bostan et al. 2010, 2013; Bostan and Strick 2018), with plausible interaction between aberrant neural activity of the basal ganglia-cerebello-thalamo-cortical network associated with PD tremor and those associated with olivo-cerebellar network in ET.

As mentioned above, in addition to the typical rest tremor, a postural tremor resembling ET can be observed in many patients with PD (Jankovic et al. 1999; Louis et al. 2001b). Furthermore, tremor frequency in both ET and PD decreases with disease progression (Hellwig et al. 2009). Although ET is characterized by a postural and kinetic tremor of higher frequency, PD tremor, especially in posture, can occur in a frequency range that overlaps with ET. Moreover, patients with ET can exhibit rest tremor with disease progression (Benito-León and Louis 2006). Tremor amplitude is also not a differentiating factor between ET and PD. Yet, recent studies performing more detailed evaluations of clinical features identified differences between ET and PD postural tremor (Sternberg et al. 2013; Jombík et al. 2018, 2020). They observed that during arm extension, patients with ET exhibited more wrist than finger tremor compared to patients with PD (Sternberg et al. 2013). Also, ET tremor was more present in the flexion-extension plane while PD tremor was more present in the pronation-supination axis/abduction-adduction plane (Sternberg et al. 2013; Jombík et al. 2018, 2020). This indicates that precise evaluations of tremor characteristics may help in differentiating ET and PD tremor.

There are promising methods for discriminating the two types of tremor based on the analysis of the tremor signals using a variety of experimental (e.g. mobile and wearable devices) and statistical methods (e.g. machine learning) (Muthuraman et al. 2011; Daneault et al. 2013; Woods et al. 2014; Dror et al. 2014; Dai et al. 2015; Kostikis et al. 2015; Barrantes et al. 2017; Rovini et al. 2017; Zheng et al. 2017; Morrison et al. 2017; Lipsmeier et al. 2018; Mehrang et al. 2018;

Mirabella et al. 2018; Hossen et al. 2020), or based on the analysis of muscle activity (Zhang et al. 2017), such as the examination of EMG firing pattern of antagonistic muscle groups (Milanov 2001; Nisticò et al. 2011). This could lead to improved identification of tremor subtypes and better identify the overlap in these disorders in large community samples. Determining when postural PD tremor is the result of activation of neural circuits generating rest PD tremor (basal ganglia-cerebello-thalamo-cortical networks), or the results of the activation of neural networks involved in ET (olivo-cerebellar networks), could ultimately provide the best avenue to determine whether ET and PD are indeed present concomitantly within the same patient. This is important information to determine the best course of action for treatment.

7.8 Conclusion

As demonstrated above, differential diagnosis of postural tremors remains a formidable challenge. In the future, longitudinal examination of subclinical aspects of different forms of postural tremor using novel wearable approaches may eventually provide clues about their respective origins, hence helping clinicians better assess these different forms of tremor and provide insight into the best treatment approach.

References

Adhikari K, Tatinati S, Ang WT, Veluvolu KC, Nazarpour K. A quaternion weighted Fourier linear combiner for modeling physiological tremor. IEEE Trans Biomed Eng. 2016;63:2336–46.

Adler CH, Shill HA, Beach TG. Essential tremor and Parkinson's disease: Lack of a link. Mov Disord. 2011;26:372. Available at: /pmc/articles/PMC3070808/. Accessed 25 Mar 2022.

Agapaki OM, Christakos CN, Anastasopoulos D. Characteristics of rest and postural tremors in parkinson's disease: An analysis of motor unit firing synchrony and patterns. Front Human Neurosci. 2018;12:179.

Akbostanci MC, Slavin KV, Burchiel KJ. Stereotactic ventral intermedial thalamotomy for the treatment of essential tremor: results of a series of 37 patients. Stereotact Funct Neurosurg. 1999;72:174–7. Available at: https://pubmed.ncbi.nlm.nih.gov/10853074/. Accessed 25 Mar 2022.

Algarni M, Fasano A) The overlap between Essential tremor and Parkinson disease. Parkinsonism Relat Disord. 2018;46:S101–S104. Available at: https://doi.org/10.1016/j.parkreldis.2017.07.006. Accessed 14 Feb 2022.

Allum JHJ, Dietz V, Freund HJ. Neuronal mechanisms underlying physiological tremor. J Neurophysiol. 1978;41:557–71. Available at: https://pubmed.ncbi.nlm.nih.gov/660226/. Accessed 25 Mar 2022.

Amtage F, Henschel K, Schelter B, Vesper J, Timmer J, Lücking CH, Hellwig B. Tremor-correlated neuronal activity in the subthalamic nucleus of Parkinsonian patients. Neurosci Lett. 2008;442:195–9. Available at: https://pubmed.ncbi.nlm.nih.gov/18634849/. Accessed 25 Mar 2022.

Amtage F, Henschel K, Schelter B, Vesper J, Timmer J, Lücking CH, Hellwig B. High functional connectivity of tremor related subthalamic neurons in Parkinson's disease. Clin Neurophysiol. 2009;120:1755–61.

Armstrong DM. Functional significance of connections of the inferior olive. Physiol Rev. 1974;54:358–417. Available at: https://pubmed.ncbi.nlm.nih.gov/4362162/. Accessed 25 Mar 2022.

Ayache SS, Al-ani T, Lefaucheur JP. Distinction between essential and physiological tremor using Hilbert-Huang transform. Neurophysiol Clin Neurophysiol. 2014;44:203–12.

Aytürk Z, Yilmaz R, Akbostanci MC. Re-emergent tremor in Parkinson's disease: Clinical and accelerometric properties. J Clin Neurosci. 2017;37:31–3.

Barbeau A, Pourcher E. New data on the genetics of Parkinson's disease. Can J Neurol Sci. 1982;9:53–60. Available at: https://pubmed.ncbi.nlm.nih.gov/7093827/. Accessed 25 Mar 2022.

Barrantes S, Sánchez Egea AJ, González Rojas HA, Martí MJ, Compta Y, Valldeoriola F, Mezquita ES, Tolosa E, Valls-Solè J. Differential diagnosis between Parkinson's disease and essential tremor using the smartphone's accelerometer. PLoS One. 2017;12

Belvisi D, Conte A, Bologna M, Bloise MC, Suppa A, Formica A, Costanzo M, Cardone P, Fabbrini G, Berardelli A. Re-emergent tremor in Parkinson's disease. Parkinsonism Relat Disord. 2017;36:41–6. Available at: https://pubmed.ncbi.nlm.nih.gov/28007517/. Accessed 28 Mar 2022.

Belvisi D, Conte A, Cutrona C, Costanzo M, Ferrazzano G, Fabbrini G, Berardelli A. Re-emergent tremor in Parkinson's disease: the effect of dopaminergic treatment. Eur J Neurol. 2018;25:799–804.

Benito-León J, Louis ED. Essential tremor: emerging views of a common disorder. Nat Clin Pract Neurol. 2006;2:666–78. Available at: https://pubmed.ncbi.nlm.nih.gov/17117170/. Accessed 25 Mar 2022.

Beuter A, Vasilakos K. Tremor: Is Parkinson's disease a dynamical disease? Chaos. 1995a;5:35–42. Available at: https://ui.adsabs.harvard.edu/abs/1995Chaos...5...35B/abstract. Accessed 28 Mar 2022.

Beuter A, Vasilakos K. Fluctuations in tremor and respiration in patients with Parkinson's disease. Parkinsonism Relat Disord. 1995b;1:103–11. Available at: https://pubmed.ncbi.nlm.nih.gov/18591009/. Accessed 28 Mar 2022.

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM, Deuschl G. Consensus Statement on the classification of tremors, from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2017;33:75–87. Available at: https://pubmed.ncbi.nlm.nih.gov/29193359/. Accessed 25 Mar 2022.

Birmingham AT, Wharrad HJ, Williams EJ. The variation of finger tremor with age in man. J Neurol Neurosurg Psychiatry. 1985;48:788–98. Available at: https://pubmed.ncbi.nlm.nih.gov/4031931/. Accessed 25 Mar 2022.

Boecker H, Wills AJ, Ceballos-Baumann A, Samuel M, Thomas DGT, Marsden CD, Brooks DJ. Stereotactic thalamotomy in tremor-dominant Parkinson's disease: an H2(15)O PET motor activation study. Ann Neurol. 1997;41:108–11. Available at: https://pubmed.ncbi.nlm.nih.gov/9005873/. Accessed 25 Mar 2022.

Bostan AC, Strick PL. The basal ganglia and the cerebellum: nodes in an integrated network. Nat Rev Neurosci. 2018;19:338–50. Available at: https://pubmed.ncbi.nlm.nih.gov/29643480/. Accessed 4 Apr 2022.

Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. Proc Natl Acad Sci. 2010;107:8452–6. Available at: http://www.pnas.org/cgi/doi/10.1073/pnas.1000496107.

Bostan AC, Dum RP, Strick PL. Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn Sci. 2013;17:241. Available at: /pmc/articles/PMC3645327/. Accessed 4 Apr 2022.

Brennan KC, Jurewicz EC, Ford B, Pullman SL, Louis ED. Is essential tremor predominantly a kinetic or a postural tremor? A clinical and electrophysiological study. Mov Disord.

2002;17:313–6. Available at: https://pubmed.ncbi.nlm.nih.gov/11921117/. Accessed 25 Mar 2022.

Brittain J-S, Cagnan H, Mehta AR, Saifee TA, Edwards MJ, Brown P. Distinguishing the central drive to tremor in Parkinson's disease and essential tremor. J Neurosci. 2015;35

Brumlik J. On the nature of normal tremor. Neurology. 1962;12:159. Available at: https://n.neurology.org/content/12/3/159. Accessed 25 Mar 2022.

Burne JA, Hayes MW, Fung VSC, Yiannikas C, Boljevac D. The contribution of tremor studies to diagnosis of parkinsonian and essential tremor: a statistical evaluation. J Clin Neurosci. 2002;9:237–42. Available at: https://pubmed.ncbi.nlm.nih.gov/12093126/. Accessed 25 Mar 2022.

Burne JA, Blanche T, Morris JJ. Muscle loading as a method to isolate the underlying tremor components in essential tremor and Parkinson's disease. Muscle and Nerve. 2004;30:347–55. Available at: https://pubmed.ncbi.nlm.nih.gov/15318346/. Accessed 25 Mar 2022.

Cagnan H, Little S, Foltynie T, Limousin P, Zrinzo L, Hariz M, Cheeran B, Fitzgerald J, Green AL, Aziz T, Brown P. The nature of tremor circuits in parkinsonian and essential tremor. Brain. 2014;137:3223. Available at: /pmc/articles/PMC4240284/. Accessed 28 Mar 2022.

Carignan B, Daneault JF, Duval C. The amplitude of physiological tremor can be voluntarily modulated. Exp Brain Res. 2009;194:309–16.

Carignan B, Daneault J-FF, Duval C. Quantifying the importance of high frequency components on the amplitude of physiological tremor. Exp Brain Res. 2010;202:299–306. Available at: http://link.springer.com/10.1007/s00221-009-2132-7. Accessed 25 Mar 2022.

Carignan B, Daneault J-F, Duval C. The organization of upper limb physiological tremor. Eur J Appl Physiol. 2012;112:1269–84. Available at: http://link.springer.com/10.1007/s00421-011-2080-3.

Cleeves L, Findley LJ, Koller W. Lack of association between essential tremor and Parkinson's disease. Ann Neurol. 1988;24:23–6. Available at: https://pubmed.ncbi.nlm.nih.gov/3415197/. Accessed 25 Mar 2022.

Cohen O, Pullman S, Jurewicz E, Watner D, Louis ED. Rest tremor in patients with essential tremor: Prevalence, clinical correlates, and electrophysiologic characteristics. Arch Neurol. 2003;60:405–10. Available at: https://pubmed.ncbi.nlm.nih.gov/12633153/. Accessed 25 Mar 2022.

Colebatch JG, Frackowiak RSJ, Brooks DJ, Colebatch JG, Findley LJ, Marsden CM. Preliminary report: activation of the cerebellum in essential tremor. Lancet (London, England). 1990;336:1028–30. Available at: https://pubmed.ncbi.nlm.nih.gov/1977019/. Accessed 25 Mar 2022.

Conway BA, Halliday DM, Farmer SF, Shahani U, Maas P, Weir AI, Rosenberg JR. Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. J Physiol. 1995;489:–917. Available at: /pmc/articles/PMC1156860/?report=abstract. Accessed 25 Mar 2022.

Dai H, Zhang P, Lueth TC. Quantitative assessment of parkinsonian tremor based on an inertial measurement unit. Sensors (Switzerland). 2015:15.

Daneault JFJFJF, Carignan B, Duval C. Bilateral effect of a unilateral voluntary modulation of physiological tremor. Clin Neurophysiol. 2010;121:734–43. Available at: https://pubmed.ncbi.nlm.nih.gov/20185364/ Accessed 25 Mar 2022.

Daneault JF, Carignan B, Codère CE, Sadikot AF, Duval C. Using a smart phone as a standalone platform for detection and monitoring of pathological tremors. Front Hum Neurosci. 2013;6. Available at: http://journal.frontiersin.org/article/10.3389/fnhum.2012.00357/abstract.

De Luca CJ, Erim Z. Common drive of motor units in regulation of muscle force. Trends Neurosci. 1994;17:299–305. Available at: https://pubmed.ncbi.nlm.nih.gov/7524216/. Accessed 25 Mar 2022.

Deiber MP, Pollak P, Passingham R, Landais P, Gervason C, Cinotti L, Friston K, Frackowiak R, Mauguière F, Benabid AL. Thalamic stimulation and suppression of parkinsonian tremor. Evidence of a cerebellar deactivation using positron emission tomography. Brain. 1993;116(Pt 1):267–79. Available at: https://pubmed.ncbi.nlm.nih.gov/8453462/. Accessed 25 Mar 2022.

Deuschl G, Krack P, Lauk M, Timmer J. Clinical neurophysiology of tremor. J Clin Neurophysiol. 1996;13:110–21. Available at: https://pubmed.ncbi.nlm.nih.gov/8849966/. Accessed 25 Mar 2022.

Deuschl G et al. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13 Suppl 3:2–23. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed4&AN=1998383967%5Cn; http://doi.wiley.com/10.1002/mds.870131303%5Cn; http://www.ncbi.nlm.nih.gov/pubmed/9827589. Accessed 25 Mar 2022.

Deuschl G, Raethjen J, Lindemann M, Krack P. The pathophysiology of tremor. Muscle Nerve. 2001;24:716–35. Available at: https://pubmed.ncbi.nlm.nih.gov/11360255/. Accessed 25 Mar 2022.

Dirkx MF, Zach H, Bloem BR, Hallett M, Helmich RC. The nature of postural tremor in Parkinson disease. Neurology. 2018;90:e1095–103. Available at: https://n.neurology.org/content/90/13/e1095. Accessed 14 Feb 2022.

Dotchin CL, Walker RW. The prevalence of essential tremor in rural northern Tanzania. J Neurol Neurosurg Psychiatry. 2008;79:1107–9. Available at: https://jnnp.bmj.com/content/79/10/1107. Accessed 25 Mar 2022.

Dror B, Yanai E, Frid A, Peleg N, Goldenthal N, Schlesinger I, Hel-Or H, Raz S. Automatic assessment of Parkinson's disease from natural hands movements using 3D depth sensor. In: 2014 IEEE 28th Convention of Electrical and Electronics Engineers in Israel, IEEE 2014; 2014.

Duval C. Rest and postural tremors in patients with Parkinson's disease. Brain Res Bull. 2006;70:44–8. Available at: https://pubmed.ncbi.nlm.nih.gov/16750481/. Accessed 25 Mar 2022.

Duval C, Jones J. Assessment of the amplitude of oscillations associated with high-frequency components of physiological tremor: impact of loading and signal differentiation. Exp brain Res. 2005;163:261–6. Available at: https://pubmed.ncbi.nlm.nih.gov/15912372/. Accessed 25 Mar 2022.

Duval C, Panisset M, Bertrand G, Sadikot AF. Evidence that ventrolateral thalamotomy may eliminate the supraspinal component of both pathological and physiological tremors. Exp brain Res. 2000;132:216–22. Available at: https://pubmed.ncbi.nlm.nih.gov/10853946/. Accessed 25 Mar 2022.

Duval C, Sadikot AF, Panisset M. The detection of tremor during slow alternating movements performed by patients with early Parkinson's disease. Exp Brain Res. 2004;154:395–8. Available at: https://pubmed.ncbi.nlm.nih.gov/14666394/. Accessed 25 Mar 2022.

Duval C, Strafella AP, Sadikot AF. The impact of ventrolateral thalamotomy on high-frequency components of tremor. Clin Neurophysiol. 2005;116:1391–9. Available at: https://pubmed.ncbi.nlm.nih.gov/15978501/. Accessed 25 Mar 2022.

Duval C, Panisset M, Strafella AP, Sadikot AF. The impact of ventrolateral thalamotomy on tremor and voluntary motor behavior in patients with Parkinson's disease. Exp Brain Res. 2006;170:160–71. Available at: https://pubmed.ncbi.nlm.nih.gov/16328283/. Accessed 25 Mar 2022.

Duval C, Daneault J, Hutchison WD, Sadikot AF. A brain network model explaining tremor in Parkinson's disease. Neurobiol Dis. 2016;85:49–59. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0969996115300656.

Elble RJ. Physiologic and essential tremor. Neurology. 1986;36:225–31. Available at: https://pubmed.ncbi.nlm.nih.gov/3945394/. Accessed 25 Mar 2022.

Elble R. Mechanisms of physiological tremor and relationship to essential tremor. In: Findley LJ, Koller WC, editors. Handbook of tremor disorders. New York: Dekker; 1995.

Elble RJ. Characteristics of physiologic tremor in young and elderly adults. Clin Neurophysiol. 2003;114:624–35. Available at: https://pubmed.ncbi.nlm.nih.gov/12686271/. Accessed 25 Mar 2022.

Elble R, Deuschl G. Tremor. In: Brown WF, Bolton CF, Aminoff M, editors. Neuromuscular function and disease: Basic, clinical and electrodiagnostic aspects. Philadelphia; 2002.

Elble RJ, Deuschl G. An update on essential tremor. Curr Neurol Neurosci Rep. 2009;9:273–7. Available at: https://pubmed.ncbi.nlm.nih.gov/19515278/. Accessed 25 Mar 2022.

Elble RJ, Koller WC. Tremor. Baltimore: Johns Hopkins University Press; 1990.

Elble RJ, Randall JE. Motor-unit activity responsible for 8- to 12-Hz component of human physiological finger tremor. J Neurophysiol. 1976;39:370–83. Available at: https://pubmed.ncbi.nlm.nih.gov/943474/. Accessed 25 Mar 2022.

Elble RJ, Higgins C, Elble S. Electrophysiologic transition from physiologic tremor to essential tremor. Mov Disord. 2005;20:1038–42. Available at: https://pubmed.ncbi.nlm.nih.gov/15852370/. Accessed 25 Mar 2022.

Fekete R, Jankovic J. Revisiting the relationship between essential tremor and Parkinson's disease. Mov Disord. 2011;26:391–8. Available at: https://pubmed.ncbi.nlm.nih.gov/21462256/. Accessed 25 Mar 2022.

Findley LJ, Gresty MA, Halmagyi GM. Tremor, the cogwheel phenomenon and clonus in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1981;44:534–46. Available at: https://pubmed.ncbi.nlm.nih.gov/7276968/. Accessed 25 Mar 2022.

Forssberg H, Ingvarsson PE, Iwasaki N, Johansson RS, Gordon A. Action tremor during object manipulation in Parkinson's disease. Mov Disord. 2000;15:244–54.

Fukuda M, Barnes A, Simon ES, Holmes A, Dhawan V, Giladi N, Fodstad H, Ma Y, Eidelberg D. Thalamic stimulation for parkinsonian tremor: correlation between regional cerebral blood flow and physiological tremor characteristics. Neuroimage. 2004;21:608–15. Available at: https://pubmed.ncbi.nlm.nih.gov/14980563/. Accessed 25 Mar 2022.

Geraghty JJ, Jankovic J, Zetusky WJ. Association between essential tremor and Parkinson's disease. Ann Neurol. 1985;17:329–33. Available at: https://pubmed.ncbi.nlm.nih.gov/4004153/. Accessed 25 Mar 2022.

Gironell A, Kulisevsky J, Pascual-Sedano B, Barbanoj M. Routine neurophysiologic tremor analysis as a diagnostic tool for essential tremor: A prospective study. J Clin Neurophysiol. 2004;21:446–50. Available at: https://pubmed.ncbi.nlm.nih.gov/15622132/. Accessed 25 Mar 2022.

Gresty M, Buckwell D. Spectral analysis of tremor: understanding the results. J Neurol Neurosurg Psychiatry. 1990;53:976. Available at: /pmc/articles/PMC488280/?report=abstract. Accessed 25 Mar 2022.

Hadar U, Rose FC. Is parkinsonian arm tremor a resting tremor? Eur Neurol. 1993;33:221–8. Available at: https://pubmed.ncbi.nlm.nih.gov/8467842/. Accessed 25 Mar 2022.

Halliday AM, Redfearn JW. An analysis of the frequencies of finger tremor in healthy subjects. J Physiol. 1956;134:600. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1359164/. Accessed 25 Mar 2022.

Halliday DM, Conway BA, Farmer SF, Shahani U, Russell AJC, Rosenberg JR. Coherence between low-frequency activation of the motor cortex and tremor in patients with essential tremor. Lancet (London, England). 2000;355:1149–53. Available at: https://pubmed.ncbi.nlm.nih.gov/10791378/. Accessed 25 Mar 2022.

Hellwig B, Häußler S, Schelter B, Lauk M, Guschlbauer B, Timmer J, Lücking CH. Tremor-correlated cortical activity in essential tremor. Lancet (London, England). 2001;357:519–523. Available at: https://pubmed.ncbi.nlm.nih.gov/11229671/ Accessed 25 Mar 2022.

Hellwig B, Mund P, Schelter B, Guschlbauer B, Timmer J, Lücking CH. A longitudinal study of tremor frequencies in Parkinson's disease and essential tremor. Clin Neurophysiol. 2009;120:431–5. Available at: https://pubmed.ncbi.nlm.nih.gov/19101200/. Accessed 25 Mar 2022.

Helmich RC, Janssen MJR, Oyen WJG, Bloem BR, Toni I (2011) Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. Ann Neurol 69:269–281. Available at: https://pubmed.ncbi.nlm.nih.gov/21387372/. Accessed 28 Mar 2022.

Helmich RC, Hallett M, Deuschl G, Toni I, Bloem BR. Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? Brain. 2012;135:3206–26. Available at: https://pubmed.ncbi.nlm.nih.gov/22382359/. Accessed 28 Mar 2022.

Henderson JM, Yiannikas C, Morris JGL, Einstein R, Jackson D, Byth K. Postural tremor of Parkinson's disease. Clin Neuropharmacol. 1994;17:277–85. Available at: https://pubmed.ncbi.nlm.nih.gov/9316673/. Accessed 25 Mar 2022.

Héroux ME, Pari G, Norman KE. The effect of inertial loading on wrist postural tremor in essential tremor. Clin Neurophysiol. 2009;120:1020–9. Available at: https://pubmed.ncbi.nlm.nih.gov/19383570/. Accessed 25 Mar 2022.

Homberg V, Hefter H, Reiners K, Freund HJ (1987) Differential effects of changes in mechanical limb properties on physiological and pathological tremor. J Neurol Neurosurg Psychiatry 50:568–579. Available at: https://pubmed.ncbi.nlm.nih.gov/3585382/. Accessed 25 Mar 2022.

Hornabrook RW, Nagurney JT. Essential tremor in Papua, New Guinea. Brain. 1976;99:659–72. Available at: https://pubmed.ncbi.nlm.nih.gov/1024690/. Accessed 25 Mar 2022.

Hossen A, Deuschl G, Groppa S, Heute U, Muthuraman M. Discrimination of physiological tremor from pathological tremor using accelerometer and surface EMG signals. Technol Heal Care. 2020;28:461–76.

Hubble JP, Busenbark KL, Pahwa R, Lyons K, Koller WC. Clinical expression of essential tremor: effects of gender and age. Mov Disord. 1997;12:969–72. Available at: https://pubmed.ncbi.nlm.nih.gov/9399222/. Accessed 25 Mar 2022.

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55:181–4. Available at: https://pubmed.ncbi.nlm.nih.gov/1564476/. Accessed 25 Mar 2022.

Hughes AJ, Lees AJ, Daniel SE, Blankson S. A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol. 1993;50:140–8. Available at: https://pubmed.ncbi.nlm.nih.gov/8431132/. Accessed 25 Mar 2022.

Hurtado JM, Gray CM, Tamas LB, Sigvardt KA. Dynamics of tremor-related oscillations in the human globus pallidus: a single case study. Proc Natl Acad Sci U S A. 1999;96:1674–9. Available at: https://pubmed.ncbi.nlm.nih.gov/9990083/. Accessed 25 Mar 2022.

Isokawa-Akesson M, Komisaruk BR. Tuning the power spectrum of physiological finger tremor frequency with flickering light. J Neurosci Res. 1985;14:373–80. Available at: https://pubmed.ncbi.nlm.nih.gov/4057289/. Accessed 25 Mar 2022.

Jalaleddini K, Nagamori A, Laine CM, Golkar MA, Kearney RE, Valero-Cuevas FJ (2017) Physiological tremor increases when skeletal muscle is shortened: implications for fusimotor control. J Physiol 595:7331–7346. Available at: https://onlinelibrary.wiley.com/doi/full/10.1113/JP274899. Accessed 14 Feb 2022.

Jankovic J. Parkinson's disease: Clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008;79:368–76. Available at: https://jnnp.bmj.com/content/79/4/368. Accessed 25 Mar 2022.

Jankovic J, Schwartz KS, Ondo W. Re-emergent tremor of Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;67:646–50. Available at: https://jnnp.bmj.com/content/67/5/646. Accessed 25 Mar 2022.

Jenkins IH, Bain PG, Colebatch JG, Thompson PD, Findley LJ, Frackowiak RSJ, Marsden CD, Brooks DJ. A positron emission tomography study of essential tremor: evidence for overactivity of cerebellar connections. Ann Neurol. 1993;34:82–90. Available at: https://pubmed.ncbi.nlm.nih.gov/8517685/. Accessed 25 Mar 2022.

Jombík P, Spodniak P, Bahýľ V, Necpál J. Analysis of 3D spatial trajectories in Parkinsonian, essential and physiological tremors. J Neural Transm. 2018;125:681–7.

Jombík P, Spodniak P, Bahýľ V, Necpál J. Visualisation of Parkinsonian, essential and physiological tremor planes in 3Dspace. Physiol Res. 2020;69:331–7. Available at: https://pubmed.ncbi.nlm.nih.gov/32199005/. Accessed 28 Mar 2022.

Koller WC, Busenbark K, Miner K (1994) The relationship of essential tremor to other movement disorders: Report on 678 patients. Ann Neurol 35:717–723. Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/ana.410350613. Accessed 25 Mar 2022.

Kondziolka D, Ong JG, Lee JYKK, Moore RY, Flickinger JC, Lunsford LD. Gamma Knife thalamotomy for essential tremor. J Neurosurg. 2008;108:111–7. Available at: https://pubmed.ncbi.nlm.nih.gov/18173319/. Accessed 25 Mar 2022.

Köster B, Lauk M, Timmer J, Winter T, Guschlbauer B, Glocker FX, Danek A, Deuschl G, Lücking CH. Central mechanisms in human enhanced physiological tremor. Neurosci Lett. 1998;241:135–8. Available at: https://pubmed.ncbi.nlm.nih.gov/9507939/. Accessed 25 Mar 2022.

Kostikis N, Hristu-Varsakelis D, Arnaoutoglou M, Kotsavasiloglou C. A smartphone-based tool for assessing parkinsonian hand tremor. IEEE J Biomed Heal Informatics. 2015;19

Lakie M. Is essential tremor physiological? In: Findley LJ, Koller WC, editors. Handbook of tremor disorders. New York: Dekker; 1995.

Lakie M, Walsh EG, Wright GW. Passive mechanical properties of the wrist and physiological tremor. J Neurol Neurosurg Psychiatry. 1986;49:669–76. Available at: https://pubmed.ncbi.nlm.nih.gov/3734824/. Accessed 25 Mar 2022.

Lamarre Y, Joffroy AJ, Dumont M, De Montigny C, Grou F, Lund JP. Central mechanisms of tremor in some feline and primate models. Can J Neurol Sci. 1975;2:227–33. Available at: https://www.cambridge.org/core/journals/canadian-journal-of-neurological-sciences/article/central-mechanisms-of-tremor-in-some-feline-and-primate-models/627AB71AB6267C92632D7117480A3C01. Accessed 25 Mar 2022.

Lance JW, Schwab RS, Peterson EA. Action tremor and the cogwheel phenomenon in Parkinson's disease. Brain. 1963;86:95–110. Available at: https://pubmed.ncbi.nlm.nih.gov/13928399/. Accessed 25 Mar 2022.

Lauk M, Köster B, Timmer J, Guschlbauer B, Deuschl G, Lücking CH. Side-to-side correlation of muscle activity in physiological and pathological human tremors. Clin Neurophysiol. 1999;110:1774–83. Available at: https://pubmed.ncbi.nlm.nih.gov/10574292/. Accessed 25 Mar 2022.

Lipsmeier F, et al. Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial. Mov Disord. 2018;

Llinas R. Rebound excitation as the physiological basis for tremor: a biophysical study of the oscillatory properties of mammalian central neurons in vitro. In: Findley LJ, Capildeo R, editors. Movement disorders: tremor. London: Macmillan; 1984.

Llinás R, research RV-E brain, 1973 undefined. The olivo-cerebellar system: functional properties as revealed by harmaline-induced tremor. Springer. 2015;18:69–87. Available at: https://link.springer.com/article/10.1007/BF00236557. Accessed 25 Mar 2022.

Llinas R, Paré D. Role of intrinsic neuronal oscillations and network ensembles in the genesis of normal and pathological tremors. In: Findley LJ, Koller WC, editors. Handbook of tremor disorders. New York: Dekker; 1995.

Louis ED. Essential tremor. Arch Neurol. 2000;57:1522–4. Available at: https://pubmed.ncbi.nlm.nih.gov/11030809/. Accessed 25 Mar 2022.

Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010;25:534–41.

Louis ED, Frucht SJ. Prevalence of essential tremor in patients with Parkinson's disease vs. Parkinson-plus syndromes. Mov Disord. 2007;22:1402–7. Available at: https://pubmed.ncbi.nlm.nih.gov/17516475/. Accessed 25 Mar 2022.

Louis ED, Ottman R. How many people in the USA have essential tremor? Deriving a population estimate based on epidemiological data. Tremor Other Hyperkinet Mov (N Y). 2014;4:259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25157323%5Cn; http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4137360.

Louis ED, Ford B, Wendt KJ, Cameron G. Clinical characteristics of essential tremor: data from a community-based study. Mov Disord. 1998a;13:803–8. Available at: https://pubmed.ncbi.nlm.nih.gov/9756149/. Accessed 25 Mar 2022.

Louis ED, Ottman R, Allen Hauser W. How common is the most common adult movement disorder? Estimates of the prevalence of essential tremor throughout the world. Mov Disord. 1998b;13:5–10. Available at: https://pubmed.ncbi.nlm.nih.gov/9452318/. Accessed 25 Mar 2022.

Louis ED, Barnes L, Albert SM, Cote L, Schneier FR, Pullman SL, Yu Q. Correlates of functional disability in essential tremor. Mov Disord. 2001a;16:914–20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11746622.

Louis ED, Levy G, Côte LJ, Mejia H, Fahn S, Marder K. Clinical correlates of action tremor in Parkinson disease. Arch Neurol. 2001b;58:1630–4. Available at: https://jamanetwork.com/journals/jamaneurology/fullarticle/780602. Accessed 25 Mar 2022.

Louis ED, Levy G, Mejia-Santana H, Cote L, Andrews H, Harris J, Waters C, Ford B, Frucht S, Fahn S, Ottman R, Marder K. Risk of action tremor in relatives of tremor-dominant and postural instability gait disorder PD. Neurology. 2003;61:931–6. Available at: https://pubmed.ncbi.nlm.nih.gov/14557562/. Accessed 25 Mar 2022.

Louis ED, Applegate LK, Factor-Litvak P, Parides MK. Factor structure of motor signs in essential tremor. Neuroepidemiology. 2005;25:42–7. Available at: https://www.karger.com/Article/FullText/85312. Accessed 25 Mar 2022.

Louis ED, Thawani SP, Andrews HF. Prevalence of essential tremor in a multiethnic, community-based study in northern Manhattan, New York, N.Y. Neuroepidemiology. 2009;32:208–14.

Louis ED, Asabere N, Agnew A, Moskowitz CB, Lawton A, Cortes E, Faust PL, Vonsattel JPG. Rest tremor in advanced essential tremor: a post-mortem study of nine cases. J Neurol Neurosurg Psychiatry. 2011;82:261–5. Available at: https://pubmed.ncbi.nlm.nih.gov/20802027/. Accessed 25 Mar 2022.

Mailankody P, Thennarasu K, Nagaraju BC, Yadav R, Pal PK. Re-emergent tremor in Parkinson's disease: A clinical and electromyographic study. J Neurol Sci. 2016;366:33–6.

Marsden CD, Meadows JC. The effect of adrenaline on the contraction of human muscle–one mechanism whereby adrenaline increases the amplitude of physiological tremor. J Physiol. 1968;194:70.

Marsden CD, Meadows JC, Lange GW, Watson RS. The role of the ballistocardiac impulse in the genesis of physiological tremor. Brain. 1969;92:647–62.

Marshall J. The effect of ageing upon physiological tremor. J Neurol Neurosurg Psychiatry. 1961;24:14–7. Available at: https://jnnp.bmj.com/content/24/1/14. Accessed 25 Mar 2022.

Marshall J, Walsh EG. Physiological tremor. J Neurol Neurosurg Psychiatry. 1956;19:260. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC497216/. Accessed 25 Mar 2022.

Marttila RJ, Rautakorpi I, Rinne UK. The relation of essential tremor to Parkinson's disease. J Neurol Neurosurg Psychiatry. 1984;47:734–5. Available at: https://jnnp.bmj.com/content/47/7/734. Accessed 25 Mar 2022.

McAuley JH, Rothwell JC, Marsden CD. Frequency peaks of tremor, muscle vibration and electromyographic activity at 10 Hz, 20 Hz and 40 Hz during human finger muscle contraction may reflect rhythmicities of central neural firing. Exp brain Res. 1997;114:525–41. Available at: https://pubmed.ncbi.nlm.nih.gov/9187289/. Accessed 25 Mar 2022.

Mehrang S, Jauhiainen M, Pietil J, Puustinen J, Ruokolainen J, Nieminen H. Identification of Parkinson's Disease Utilizing a Single Self-recorded 20-step Walking Test Acquired by Smartphone's Inertial Measurement Unit. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS; 2018.

Mehta AR, Brittain JS, Brown P. The selective influence of rhythmic cortical versus cerebellar transcranial stimulation on human physiological tremor. J Neurosci. 2014;34:7501–8. Available at: https://www.jneurosci.org/content/34/22/7501. Accessed 14 Feb 2022.

Meshack RP, Norman KE. A randomized controlled trial of the effects of weights on amplitude and frequency of postural hand tremor in people with Parkinson's disease. Clin Rehabil. 2002;16:481–92. Available at: https://pubmed.ncbi.nlm.nih.gov/12194619/. Accessed 25 Mar 2022.

Milanov I. Electromyographic differentiation of tremors. Clin Neurophysiol. 2001;112:1626–32. Available at: https://pubmed.ncbi.nlm.nih.gov/11514245/. Accessed 25 Mar 2022.

Minen MT, Louis ED. Emergence of Parkinsons disease in essential tremor: A study of the clinical correlates in 53 patients. Mov Disord. 2008;23:1602. Available at: /pmc/articles/PMC2683412/. Accessed 25 Mar 2022.

Mirabella G, Pisani A, Zhang D, Zhang B, Huang F, Liu J. A Novel Posture for Better Differentiation Between Parkinson's Tremor and Essential Tremor A Novel Posture for Better Tremor Differentiation. Front Neurosci | www.frontiersin.org. 2018;1:317. Available at: www.frontiersin.org.

Moore GP, Ding L, Bronte-Stewart HM. Concurrent Parkinson tremors. J Physiol. 2000;529:273. Available at: /pmc/articles/PMC2270175/. Accessed 25 Mar 2022.

Morrison S, Newell KM. Postural and resting tremor in the upper limb. 2000;111:651–63. Available at: https://pubmed.ncbi.nlm.nih.gov/10727916/. Accessed 14 Feb 2022.

Morrison S, Mills P, Barrett R. Differences in multiple segment tremor dynamics between young and elderly persons. J Gerontol A Biol Sci Med Sci. 2006;61:982–90. Available at: https://pubmed.ncbi.nlm.nih.gov/16960031/. Accessed 25 Mar 2022.

Morrison S, Newell KM, Kavanagh JJ. Differences in postural tremor dynamics with age and neurological disease. Exp Brain Res. 2017;235:1719–29. Available at: https://link.springer.com/article/10.1007/s00221-017-4924-5. Accessed 14 Feb 2022.

Muthuraman M, Hossen A, Heute U, Deuschl G, Raethjen J. A new diagnostic test to distinguish tremulous Parkinson's disease from advanced essential tremor. Mov Disord. 2011;26:1548–52. Available at: https://pubmed.ncbi.nlm.nih.gov/21520285/. Accessed 25 Mar 2022.

Nisticò R, Pirritano D, Salsone M, Novellino F, Del Giudice F, Morelli M, Trotta M, Bilotti G, Condino F, Cherubini A, Valentino P, Quattrone A. Synchronous pattern distinguishes resting tremor associated with essential tremor from rest tremor of Parkinson's disease. Parkinsonism Relat Disord. 2011;17:30–3. Available at: https://pubmed.ncbi.nlm.nih.gov/21071257/. Accessed 25 Mar 2022.

Novak T, Newell KM. Physiological tremor (8–12 Hz component) in isometric force control. Neurosci Lett. 2017;641:87–93.

Parker F, Tzourio N, Blond S, Petit H, Mazoyer B. Evidence for a common network of brain structures involved in parkinsonian tremor and voluntary repetitive movement. Brain Res. 1992;584:11–7. Available at: https://pubmed.ncbi.nlm.nih.gov/1515931/. Accessed 25 Mar 2022.

Poewe W, Wenning G. The differential diagnosis of Parkinson's disease. Eur J Neurol. 2002;9(Suppl 3):23–30. Available at: https://pubmed.ncbi.nlm.nih.gov/12464118/. Accessed 25 Mar 2022.

Poirier LJ, Sourkes TL, Bouvier G, Boucher R, Carabin S. Striatal amines, experimental tremor and the effect of harmaline in the monkey. Brain. 1966;89:37–52. Available at: https://pubmed.ncbi.nlm.nih.gov/4956264/. Accessed 25 Mar 2022.

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30:1591–601. Available at: https://pubmed.ncbi.nlm.nih.gov/26474316/. Accessed 13 Jan 2022.

Raethjen J, Pawlas F, Lindemann M, Wenzelburger R, Deuschl G. Determinants of physiologic tremor in a large normal population. Clin Neurophysiol. 2000;111:1825–37. Available at: https://pubmed.ncbi.nlm.nih.gov/11018499/. Accessed 25 Mar 2022.

Raethjen J, Lauk M, Köster B, Fietzek U, Friege L, Timmer J, Lücking CH, Deuschl G. Tremor analysis in two normal cohorts. Clin Neurophysiol. 2004;115:2151–6. Available at: https://pubmed.ncbi.nlm.nih.gov/15294218/. Accessed 25 Mar 2022.

Raethjen J, Pohle S, Govindan RB, Morsnowski A, Wenzelburger R, Deuschl G. Parkinsonian action tremor: interference with object manipulation and lacking levodopa response. Exp Neurol. 2005;194:151–60. Available at: https://pubmed.ncbi.nlm.nih.gov/15899252/. Accessed 25 Mar 2022.

Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism–a prospective study. Can J Neurol Sci. 1991;18:275–8. Available at: https://pubmed.ncbi.nlm.nih.gov/1913360/. Accessed 28 Mar 2022.

Randall JE, Stiles RN. Power spectral analysis of finger acceleration tremor. J Appl Physiol. 1964;19:357–60. Available at: https://pubmed.ncbi.nlm.nih.gov/14155314/. Accessed 25 Mar 2022.

Reck C, Himmel M, Florin E, Maarouf M, Sturm V, Wojtecki L, Schnitzler A, Fink GR, Timmermann L. Coherence analysis of local field potentials in the subthalamic nucleus: differences in parkinsonian rest and postural tremor. Eur J Neurosci. 2010;32:1202–14. Available at: https://pubmed.ncbi.nlm.nih.gov/21039956/. Accessed 25 Mar 2022.

Robson JG. The effect of loading on the frequency of muscle tremor. J Physiol. 1959;149:29–30.

Rocca WA, Bower JH, Ahlskog JE, Elbaz A, Grossardt BR, McDonnell SK, Schaid DJ, Maraganore DM. Increased risk of essential tremor in first-degree relatives of patients with Parkinson's disease. Mov Disord. 2007;22:1607–14. Available at: https://pubmed.ncbi.nlm.nih.gov/17546668/. Accessed 25 Mar 2022.

Rovini E, Maremmani C, Cavallo F. How wearable sensors can support parkinson's disease diagnosis and treatment: a systematic review. Front Neurosci. 2017;11

Shahed J, Jankovic J. Exploring the relationship between essential tremor and Parkinson's disease. Parkinsonism Relat Disord. 2007;13:67–76. Available at: https://pubmed.ncbi.nlm.nih.gov/16887374/. Accessed 25 Mar 2022.

Sternberg EJ, Alcalay RN, Levy OA, Louis ED, Foki T, Klebe S. Postural and intention tremors: a detailed clinical study of essential tremor vs. Parkinson's disease; 2013. Available at: www.frontiersin.org.

Stiles RN, Randall JE. Mechanical factors in human tremor frequency. J Appl Physiol. 1967;23:324–30. Available at: https://pubmed.ncbi.nlm.nih.gov/6047952/. Accessed 25 Mar 2022.

Tamás G, Pálvölgyi L, Takáts A, Szirmai I, Kamondi A. Contralateral voluntary hand movement inhibits human parkinsonian tremor and variably influences essential tremor. Neurosci Lett. 2004;357:187–90. Available at: https://pubmed.ncbi.nlm.nih.gov/15003281/. Accessed 25 Mar 2022.

Tan EK, Lee SS, Fook-Chong S, Lum SY. Evidence of increased odds of essential tremor in Parkinson's disease. Mov Disord. 2008;23:993–7. Available at: https://pubmed.ncbi.nlm.nih.gov/18383536/. Accessed 25 Mar 2022.

Tasker RR, Munz M, Junn FSCK, Kiss ZHT, Davis K, Dostrovsky JO, Lozano AM. Deep brain stimulation and thalamotomy for tremor compared. Acta Neurochir Suppl. 1997;68:49–53. Available at: https://pubmed.ncbi.nlm.nih.gov/9233413/. Accessed 25 Mar 2022.

Teravainen H, Calne DB. Action tremor in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1980;43:257. Available at: /pmc/articles/PMC490518/?report=abstract. Accessed 25 Mar 2022.

Vaillancourt DE, Newell KM. Amplitude changes in the 8-12, 20-25, and 40 Hz oscillations in finger tremor. Clin Neurophysiol. 2000;111:1792–801. Available at: https://pubmed.ncbi.nlm.nih.gov/11018494/. Accessed 25 Mar 2022.

Van Buskirk C, Wolbarsht ML, Stecher K. The nonnervous causes of normal physiologic tremor. Neurology. 1966;16:217. Available at: https://n.neurology.org/content/16/2_Part_1/217. Accessed 25 Mar 2022.

van der Stouwe AMM, Elting JW, van der Hoeven JH, van Laar T, Leenders KL, Maurits NM, Tijssen MAJ. How typical are 'typical' tremor characteristics? Sensitivity and specificity of five tremor phenomena. Parkinsonism Relat Disord. 2016;30:23–8.

Vernooij CA, Reynolds RF, Lakie M. A dominant role for mechanical resonance in physiological finger tremor revealed by selective minimization of voluntary drive and movement. J Neurophysiol. 2013;109:2317–26. Available at: https://journals.physiology.org/doi/abs/10.1152/jn.00926.2012. Accessed 14 Feb 2022.

Vernooij CA, Lakie M, Reynolds RF. The complete frequency spectrum of physiological tremor can be recreated by broadband mechanical or electrical drive. J Neurophysiol. 2015;113:647–56. Available at: https://journals.physiology.org/doi/abs/10.1152/jn.00519.2014. Accessed 14 Feb 2022.

Wade P, Gresty MA, Findley LJ. A normative study of postural tremor of the hand. Arch Neurol. 1982;39:358–62. Available at: https://jamanetwork.com/journals/jamaneurology/fullarticle/580802. Accessed 25 Mar 2022.

Wenzelburger R, Raethjen J, Loffler K, Stolze H, Illert M, Deuschl G. Kinetic tremor in a reach-to-grasp movement in Parkinson's disease. Mov Disord. 2000;15:1084–94.

Woods AM, Nowostawski M, Franz EA, Purvis M. Parkinson's disease and essential tremor classification on mobile device. Pervasive Mob Comput. 2014;13:1–12.

Yahr MD, Orosz D, Purohit DP. Co-occurrence of essential tremor and Parkinson's disease: clinical study of a large kindred with autopsy findings. Parkinsonism Relat Disord. 2003;9:225–31. Available at: https://pubmed.ncbi.nlm.nih.gov/12618058/. Accessed 25 Mar 2022.

Yap CB, Boshes B. The frequency and pattern of normal tremor. Electroencephalogr Clin Neurophysiol. 1967;22:197–203.

Young RR, Hagbarth KE. Physiological tremor enhanced by manoeuvres affecting the segmental stretch reflex. J Neurol Neurosurg Psychiatry. 1980;43:248. Available at: /pmc/articles/PMC490517/?report=abstract. Accessed 25 Mar 2022.

Young RF, Li F, Vermeulen S, Meier R. Gamma Knife thalamotomy for treatment of essential tremor: long-term results. J Neurosurg. 2010;112:1311–7. Available at: https://pubmed.ncbi.nlm.nih.gov/19895197/. Accessed 25 Mar 2022.

Zesiewicz TA, Hauser RA. Phenomenology and treatment of tremor disorders. Neurol Clin. 2001. Available at: https://pubmed.ncbi.nlm.nih.gov/11532648/. Accessed 25 Mar 2022.

Zesiewicz TA, Elble R, Louis ED, Hauser RA, Sullivan KL, Dewey RB, Ondo WG, Gronseth GS, Weiner WJ. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2005;64:2008–20. Available at: https://pubmed.ncbi.nlm.nih.gov/15972843/. Accessed 25 Mar 2022.

Zeuner KE, Shoge RO, Goldstein SR, Dambrosia JM, Hallett M. Accelerometry to distinguish psychogenic from essential or parkinsonian tremor. Neurology. 2003;61:548–50. Available at: https://pubmed.ncbi.nlm.nih.gov/12939436/. Accessed 25 Mar 2022.

Zhang J, Xing Y, Ma X, Feng L. Differential diagnosis of Parkinson disease, essential tremor, and enhanced physiological tremor with the tremor analysis of EMG. Parkinsons Dis. 2017;2017

Zheng X, Campos AV, Ordieres-Meré J, Balseiro J, Marcos SL, Aladro Y. Continuous monitoring of essential tremor using a portable system based on smartwatch. Front Neurol. 2017;8

Chapter 8
Isometric Tremor

Jan Raethjen and Dennis A. Nowak

Abstract Isometric tremor is an action tremor, which occurs during isometric contraction. It typically accompanies postural and kinetic tremor at virtually the same frequency in many pathological tremor syndromes. Its contribution to the loss of manual dexterity can be considerable as it specifically interferes with delicate object manipulation. Orthostatic tremor is the only pathological tremor syndrome in which isometric tremor is the dominant clinical presentation. Specific data on treatment responses of the isometric tremor component in different action tremor syndromes is scarce. But clinical experience and the little available evidence suggest that effective treatments for postural and kinetic tremors similarly improve isometric tremor.

Keywords Isometric · Action tremor · Resonance frequency · Loading

8.1 Introduction

Tremor is a rhythmic mechanical oscillation of at least one functional body region (Deuschl et al. 2007). It is usually considered to be pathologic, but one should keep in mind that any voluntary movement is accompanied by a physiological tremor, which is believed to be necessary to facilitate fast voluntary motion. The borderline between pathological and physiological tremors is less strictly delineated than most clinicians wished to. This is particularly true for isometric tremor, a

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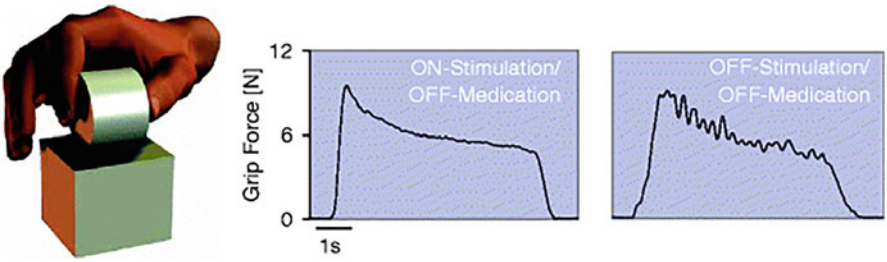

Fig. 8.1 Example of an isometric tremor in a subject with Parkinson's disease off dopaminergic medication lifting an instrumented object between the index finger and thumb under stimulation of the subthalamic nucleus (on-stimulation) and with subthalamic nucleus stimulation switched off (off-stimulation). The instrumented object incorporates a grip force to register grip forces exerted normally to the grip surfaces and linear acceleration sensors to register accelerations in three dimensions. The isometric tremor is evident only when subthalamic nucleus stimulation is switched off and occurs after the lifting movement when the object is held stationary in the air. The tremor is directed normally to the axis of grasping and shows a frequency of 5 Hz

subtype of action tremor. Isometric tremor can occur in isolation, but it is most frequently associated with other types of (action) tremor. Isometric tremor is a common symptom in a variety of clinical tremor syndromes and may vary regarding its frequency and amplitude depending on the underlying condition.

8.2 Definition and Phenomenology of Isometric Tremor

Classification of tremor is based on the activation condition in which it appears or is most pronounced (Deuschl et al. 1998; Bhatia et al. 2018). In isolated tremors without prominent additional symptoms, the activation condition along with other features of the tremor (e.g. affected body parts, frequency and regularity) defines the clinical tremor syndrome according to the clinical axis 1 of the new tremor classification (see chapters 1 and 7, Bhatia et al. 2018). As a subtype of action tremor isometric tremor is defined as involuntary oscillations of one or more body regions occurring in situations of isometric muscle contraction against a rigid resistance, e.g. pressing the hand and arm against a heavy table, standing on the feet or hands (orthostatic tremor) or simply holding an object between thumb and other fingers in opposition (Fig. 8.1).

8.3 Diagnostic Pathways and Therapeutic Options in Isometric Tremor

Isometric tremor is typically combined with other subtypes of action tremor but may be the only or predominant tremor variant in a given individual (physiological

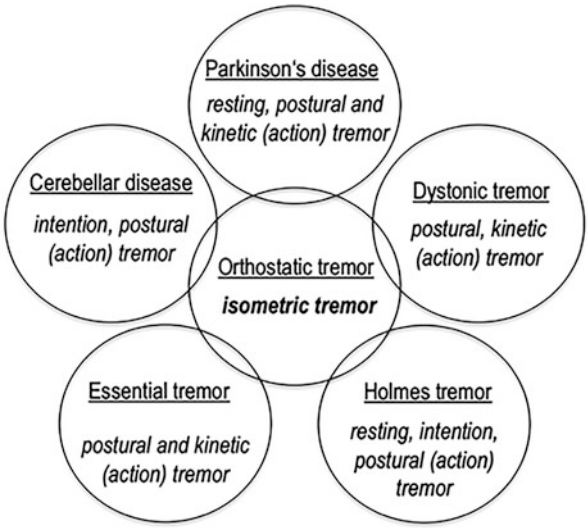

Fig. 8.2 Synopsis of frequent movement disorders exhibiting tremors of different types and sharing the symptom of isometric tremor. In orthostatic tremor, isometric tremor is the only tremor symptom. Isometric tremor may also be a symptom of (normal) physiological tremor, writing tremor and other task-specific tremors, drug-induced tremors and tremors in peripheral neuropathies (all not shown)

tremor, orthostatic tremor). Whereas it can be the only symptom in otherwise healthy individuals ((enhanced) physiological tremor) it is mostly part of the syndrome in a variety of tremor disorders, such as essential tremor (ET) (postural, kinetic and isometric tremor), Parkinson's disease (resting, postural, kinetic and isometric tremor), cerebellar tremor (intention, postural and isometric), dystonic tremor (postural, kinetic and isometric tremor), Holmes tremor (resting, intention, postural and isometric tremor), or functional (psychogenic) tremor (all tremor types and combination of tremor types possible) (Nowak and Fink 2009). Given the fact that isometric tremor may be part of the syndrome in a variety of movement disorders associated with tremor, its presence in an affected individual does not allow direct identification of its aetiology or underlying pathology. There is a broad overlap between movement disorders exhibiting isometric tremor (Fig. 8.2).

In order to diagnose the clinical tremor syndrome, the clinician cannot rely on the identification of isometric tremor alone (with the exception of primary orthostatic tremor where isometric tremor of muscles working against gravity is the major diagnostic clue) but has to screen for additional signs and symptoms, such as akinesia, muscular rigidity, postural abnormalities, dystonia, muscular spasticity, ataxia or signs of peripheral neuropathy to fix the diagnosis in an affected individual. As in other forms of action tremor isometric tremor may occur at different frequencies within the same patient and during the same (isometric) action. In Parkinson's disease, isometric tremor may occur as a *re-emergent postural tremor* at the frequency of the rest tremor of 4–6 Hz (Fig. 8.1) or *kinetic action tremor* with a frequency of $\geq$6 Hz or both. This characteristic is particularly evident when analysing the tremor of grip force when holding or moving a hand-held object (see below). To select appropriate treatment strategies for isometric tremor, it is essential to diagnose the underlying tremor syndrome.

8.3.1 Isometric Tremor in Enhanced Physiological Tremor

Almost every movement is accompanied by usually invisible muscle oscillations, which do not interfere with movement performance or accuracy. The frequency of physiological tremor ranges between 6 and 12 Hz (Deuschl et al. 2007). When this tremor increases in amplitude, becomes visible and starts to affect hand motor performance, it is referred to as an enhanced physiological tremor. Enhanced physiological tremor is usually short lived and often drug induced. It is typically a postural and simple kinetic action tremor. But an isometric component can be a prominent feature. And due to its interference with object manipulation, it may perturb delicate hand motor activity. Longer lasting frequencies below 6 Hz should give rise to suspicion of another pathologic tremor syndrome (Elbe et al. 2005).

8.3.1.1 Pathophysiology

The oscillations of limb segments during movement in physiological tremor result from mechanical amplification of the muscles' effect on limb segments in motion at its resonance frequency (Timmer et al. 1998). Therefore the physiological tremor frequency depends on the stiffness and inertia of the limb segments involved, e.g. physiological tremor frequency is smaller in proximal limb segments, e.g. shoulder and proximal arm, and higher in distal limb segments, e.g. wrist and fingers. Rhythmic activation of muscle spindles induced by the mechanical dynamics of limb movement activates spinal or long-loop (transcortical) reflex mechanisms, which can occasionally enhance the tremor oscillations. In addition, central oscillations may add to the frequency spectrum of physiological tremor. Loading the limb, e.g. placing a weight on the palm of the hand while holding the arm in elevation, usually reduces the frequency in case of mechanical and/or reflex-enhanced mechanical oscillations. In contrast, the frequency of central oscillations in physiological tremor, which are present in up to 30% of healthy subjects, cannot be reduced by loading (Raethjen et al. 2000a). Drugs, e.g. amitriptyline (Raethjen et al. 2001), can increase the amplitude of central oscillations in physiological tremor. Recently, it has been argued that 5-HT availability can influence especially the isometric component of physiologic tremor (Henderson et al. 2022).

8.3.1.2 Therapeutic Strategies

The isometric component of physiological tremor is commonly not disabling and does not need any treatment apart from reassuring the affected individual of the benign nature of the tremor. Also, its transient increase after fatiguing muscle activation (Gandevia 2001) or in stressful situations is a normal and short-lived phenomenon. In case of longer-lasting disabling amplitudes, e.g. enhanced physiological tremor, medical treatment can be considered. Propranolol is often effective but the evidence is scarce (Deuschl et al. 2007). When the tremor is

associated with the intake of a specific drug (valproate, tricyclic antidepressants, lithium, cocaine, alcohol, steroids, thyroid hormones, cytostatics, etc.), cessation of the drug is the therapy of choice.

8.3.2 Isometric Tremor in the Essential Tremor Syndrome

Classic essential tremor is the most common movement disorder. It is a monosymptomatic, bilateral, postural and kinetic (action) tremor with a frequency in the range of 4–12 Hz, which is mostly inherited and slowly progresses over the years (Deuschl et al. 2007). The tremor frequency typically decreases with the duration of the disease and with age (Elble 2000). However, for a given patient at a certain point in time, the tremor frequencies during different activation conditions fall within the same range. Thus, the frequency of isometric tremor in ET usually does not differ from postural or kinetic tremor frequency. Isometric tremor is a common feature in the classic essential tremor syndrome and may enhance disability particularly when it affects isometric muscle contraction of distal muscle segments of the forearm and hand during grasping (Stani et al. 2010).

Primary writing tremor (appearing during writing only, type A or when the hand position used for writing is adopted, type B) is a task-specific tremor. These tremors are not subsumed under the term essential tremor anymore according to the new classification. As holding the pen while writing is an isometric task, these tremors can be partly regarded as isometric tremors. Other task-specific tremors have also been described during other manual tasks, such as playing a musical instrument (piano, guitar, etc.) or handling a sports instrument (golf, tennis, etc.). They have to be separated from dystonic tremor with overt dystonia of the affected body part. In the case of subtle abnormal postures, this differentiation is controversial.

8.3.2.1 Pathophysiology

Classic essential tremor does not significantly change its frequency under different mechanical conditions, which suggests central generators. A network of cortical and subcortical structures is involved in generating the muscle oscillations and there are several independent loops triggering oscillations for each extremity involved (Raethjen et al. 2000b). However, peripheral perturbations (as well as transcranial magnetic stimulation of the primary motor cortex) can reset tremor frequency. So, both peripheral and central mechanisms can influence the centrally generated oscillations in classic essential tremor.

8.3.2.2 Therapeutic Strategies

Isometric tremor in the essential tremor syndrome is most disabling when it affects the hands. About half of subjects with classic essential tremor show at least some

intention tremor during goal-directed hand and grasping movements (Deuschl et al. 2000). Propranolol and primidone as well as topiramate are the treatments of choice (Deuschl et al. 2007). A combination of propranolol and primidone should be tried if a single drug does not allow sufficient symptom relief, the efficacy of combined treatments with topiramate is not known. Deep brain stimulation should be considered for individuals resistant to medical treatment who suffer from profound disability (Limousin et al. 1999). Deep brain stimulation of the nucleus ventralis intermedius of the thalamus at least partially improves isometric tremor in classic essential tremor when grasping and lifting an object (Stani et al. 2010). The response of the isometric tremor component to the new method of focused ultrasound lesions in the VIM has not been looked at specifically. But given the excellent evidence for other action tremor components, it may be considered. Management of task-specific tremors comprises propranolol, local botulinum toxin injections and abstinence from the tremor-producing tasks with consecutive behavioural re-training (Deuschl et al. 2007).

8.3.3 Isometric Tremor in Parkinson's Disease

The majority of subjects with Parkinson's disease present with tremor. The typical tremor in Parkinson's disease is a rest tremor with a frequency of 3–7 Hz, but up to 40% of affected individuals show additional or isolated postural tremor (often re-emergent postural tremor with the same frequency as the rest tremor around 3–6 Hz) and kinetic (action) tremor with a frequency of ≥6 Hz. Postural and kinetic tremor syndromes in Parkinson's disease may be associated with isometric tremor, which is often most disabling at the hands and has an impact on manual dexterity (Forssberg et al. 2000; Nowak and Hermsdörfer 2002; Nowak et al. 2005b; Raethjen et al. 2005; Wenzelburger et al. 2002). Rest tremor hardly influences manual dexterity in Parkinson's disease as it ceases as soon as movement is initiated (Papengut et al. 2013), but it slows movement initiation (Wenzelburger et al. 2002).

Isometric tremor associated with kinetic tremor in Parkinson's disease may interfere with moving an object held between the thumb and other fingers in opposition (Nowak and Hermsdörfer 2002). Remarkably, the isometric kinetic tremor of grip force (representative of distal muscles of the forearm and hand stabilizing the grasp) is not in phase but typically shows a lower frequency, than the kinetic tremor of proximal arm muscles (responsible for moving the object) (Figs. 8.3 and 8.4).

8.3.3.1 Pathophysiology

The pathophysiological substrate of resting tremor in Parkinson's disease is a pathological synchronization of oscillatory activity within a cerebello-thalamo-cortical network (Timmermann et al. 2003; Muthuraman et al. 2018). Within this

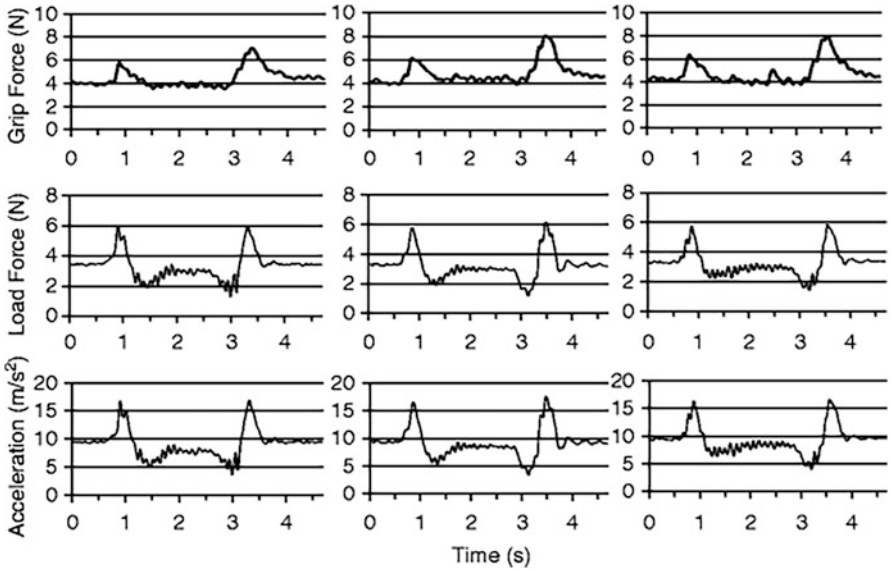

Fig. 8.3 Acceleration in the direction of movement, load force and grip force profiles from consecutive upward and downward movements of a subject with Parkinson's disease on dopaminergic medication during three experimental trials. Acceleration and load force profiles represent the activity of proximal arm muscles, and grip force profiles represent the activity of distal muscles of the forearm and hand holding the object. Oscillations of 8–10 Hz are present in the acceleration and load force profiles towards the end of an upward movement and at the start of a downward movement as well as during the second of stationary holding the object in between the vertical arm movements. These oscillations correspond to kinetic tremor of proximal arm muscles, responsible for moving the object and holding it steady in between each movement. The break in between each movement is too short for a re-emergent postural tremor to be established. Oscillations with a frequency of 5–7 Hz are shown in the grip force profile during and in between each movement. These are representative of an isometric kinetic tremor of the distal muscles of the forearm and hand. (Modified from Nowak and Hermsdörfer (2002))

network, the primary motor cortex plays a major role, which shows a strong frequency coupling with the peripheral muscle oscillations. As in the power spectra of peripheral tremor recordings, tremor activity in the primary motor cortex occurs at double the tremor frequency (8–12 Hz) and the tremor frequency itself (4–6 Hz). The occurrence of tremor activity at harmonic frequencies occurs in other tremors (e.g. ET) as well. But it is strongest in Parkinsonian tremor (Muthuraman et al. 2011) and in contrast to other tremors, its cortical correlate is separated in space and time from the cortical representation of the basic tremor frequency (Raethjen et al. 2009). The pathophysiological basis of this may be the more widespread central pathology in PD with a wide range of pathological oscillatory activities above the tremor frequency (Raethjen et al. 2000a) and might be related to the higher frequency Parkinsonian action tremors encountered in parallel to the classical low frequency resting tremor, e.g. during isometric muscle activation (see

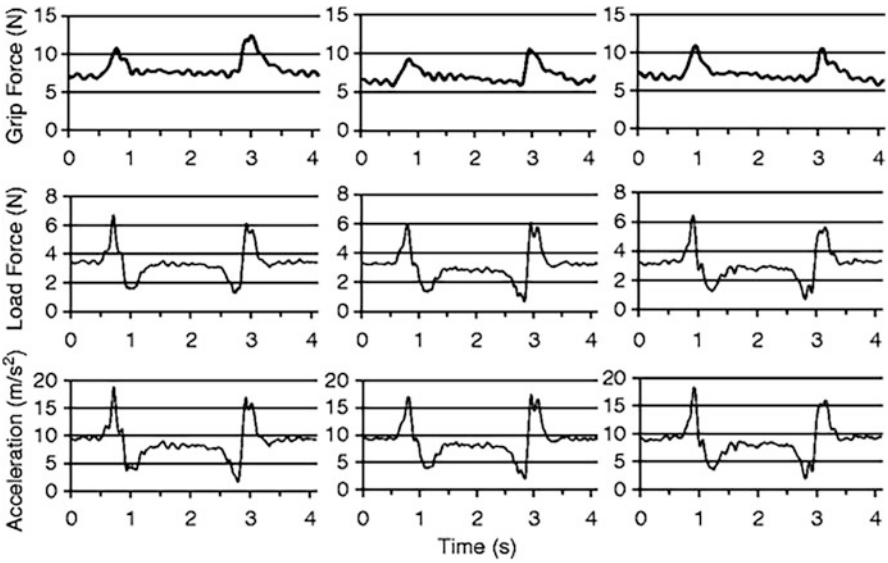

Fig. 8.4 Acceleration, load force and grip force profiles from consecutive vertical movements with a hand-held object performed by a subject with Parkinson's disease under medication during three successive experimental trials. Oscillations with a frequency of 6–7 Hz are illustrated in the acceleration and load force profiles most pronounced towards the end of the upward movement and at the start of the downward movement. These oscillations are attributed to kinetic tremor of proximal arm muscles. Oscillations of 5–6 Hz are present in the grip force profile both during movement and when holding the object in between each movement. These oscillations represent isometric tremor of distal muscles of the forearm and hand grasping the object. (Modified from Nowak and Hermsdörfer (2002))

below). Recent evidence from fMRI studies suggests that the basal ganglia circuit in which the main pathology is located in Parkinson's disease triggers and drives the cerebello-thalamo-cortical loop to produce pathological rest tremor. The basal ganglia interact with the main tremor loop mainly via the motor cortex (Dirkx et al. 2016).

The typical postural tremor in Parkinson's disease is considered to represent re-emergence of the resting tremor once a dynamic movement has ceased and only steady isometric muscle contractions persist (Jankovic et al. 1999;). But an additional kinetic (action) tremor may be present during voluntary movements and isometric contractions in Parkinson's disease (Forssberg et al. 2000; Wenzelburger et al. 2000; Raethjen et al. 2005). Kinetic tremor is observed towards the (acceleration or) deceleration phase of a reaching movement or during movements with a handheld object (Figs. 8.3 and 8.4) and has a higher frequency (6–10 Hz) than the re-emergent postural tremor (4–6 Hz) to be found after the reaching movement has ceased for a while (at least 2–3 s). Thus, action- (including isometric) and re-emergent resting tremors are clearly discernible tremor types in the Parkinsonian tremor syndrome. This independent action and isometric tremors do not respond to

dopaminergic therapy as well as the typical rest and re-emergent tremor (Raethjen et al. 2005) and existing evidence suggests that non-dopamine-responsive Parkinsonian tremors show less correlates in the basal ganglia circuit and seem to mainly originate from the cerebello-thalamo-cortical circuit (van den Berg and Helmich 2021).

8.3.3.2 Therapeutic Strategies

Medical strategies to improve isometric tremor in Parkinson's disease have to take into account that different tremor subtypes may be present. Regarding the effect on isometric re-emergent postural and kinetic tremors in Parkinson's disease, it appears as if L-Dopa develops differential effects. When grasping and lifting an object between the index finger and thumb, both kinetic (lifting the object) and re-emergent postural (holding the object stationary several seconds after lifting it) tremors can be discerned. The low-frequency re-emergent postural tremor when holding the object is significantly ameliorated by L-Dopa (as is resting tremor), while the high-frequency kinetic tremor when lifting the object is not changed by L-Dopa medication (Fig. 8.5).

Deep brain stimulation is an effective therapy in subjects not responding to medical treatment. High-frequency stimulation of the nucleus ventralis intermedius thalami applied bilaterally significantly improves resting tremor, but has no relevant effect on akinesia (Deuschl et al. 2007). Bilateral subthalamic nucleus stimulation improves resting tremor along with akinesia and rigidity (Krack et al. 1998) and is the preferred target for deep brain stimulation. Subthalamic nucleus stimulation improves primarily resting and re-emergent postural tremor when grasping and

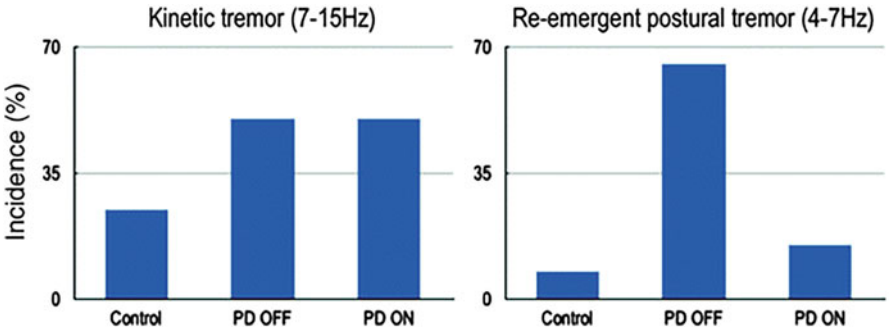

Fig. 8.5 The proportion of subjects with Parkinson's disease ($n = 20$) exhibiting kinetic and re-emergent postural tremors during grasping and lifting an instrumented object between the index finger and thumb. The incidence of each tremor is shown with (ON) and without (OFF) L-Dopa treatment and compared to age-matched controls ($n = 18$). The low-frequency re-emergent postural tremor (4–7 Hz) responds well to L-Dopa, whereas the high-frequency kinetic tremor (7–15 Hz) remains unchanged after L-Dopa administration. (Modified from Raethjen et al. (2005))

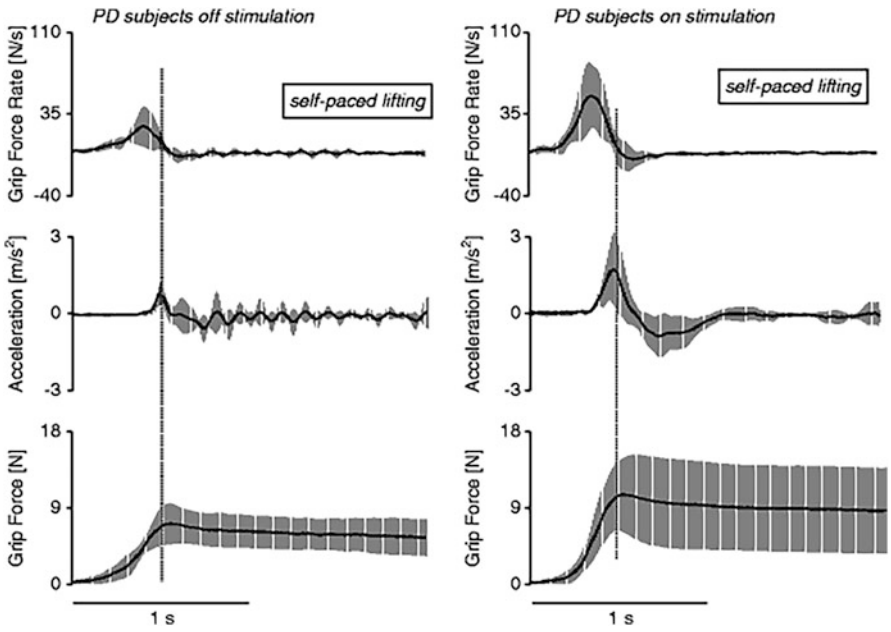

Fig. 8.6 Average profiles (±one standard deviation) of the rate of grip force development, acceleration and grip force obtained from five subjects with Parkinson's disease grasping and lifting an object without dopaminergic medication and subthalamic nucleus stimulation switched either off or on. It is evident that the low amplitude isometric kinetic tremor to be found in the grip force rate (and acceleration) profiles is diminished by stimulation of the contralateral subthalamic nucleus. (Modified from Nowak et al. (2006))

lifting an object between the index finger and thumb in Parkinson's disease (Nowak et al. 2005a, b; Wenzelburger et al. 2002, 2003; Fig. 8.6).

8.3.4 Isometric Tremor in Cerebellar Disorders

Cerebellar tremor is often used synonymously with intention tremor, although all kinds of action tremors have been described in cerebellar disorders (Fahn 1984). The main criterion to diagnose cerebellar tremor is an accompanying cerebellar syndrome (Bhatia et al. 2018). Typical cerebellar tremor is characterized by (1) pure or dominant intention tremor, (2) tremor frequency below 5 Hz and (3) possible postural tremor, but no rest tremor (Deuschl et al. 2007). Disorders most commonly causing intention tremor are multiple sclerosis, brain trauma and hereditary ataxias. Isometric tremor may occur in the cerebellar tremor syndrome (Fig. 8.7).

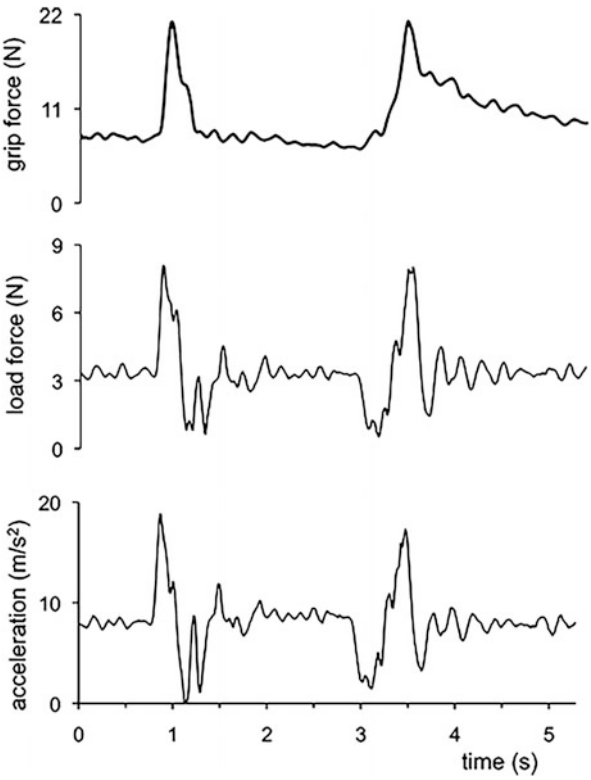

Fig. 8.7 Profiles of grip force, load force and acceleration during single upward and downward movements performed by a subject with cerebellar degeneration with a hand-held object. Six to 7 Hz oscillations in the profiles of acceleration and load force are evident during and in between each movement indicative of intention tremor. As can be seen in the acceleration and load force profile, tremor amplitude decreased following each arm movement. A 5 Hz isometric tremor, which is out of phase with the intention tremor obvious in the acceleration and load force profiles, is evident in the grip force profile during each movement and the phase of stationary holding the object in between each movement

8.3.4.1 Pathophysiology

The cerebellum is generally considered to regulate movement indirectly by adjusting the output of the descending motor system of the brain. Lesions of the cerebellum disrupt the coordination of limb and eye movements, impair balance and decrease muscle tone (Glickstein et al. 2005). The most widely accepted idea is that the cerebellum acts as a comparator that compensates for errors in movement by comparing intended movement with actual performance. Through comparison of internal and external feedback signals, the cerebellum is able to correct ongoing movements when they deviate from the intended course and to modify central motor commands so that subsequent movements are performed with less prediction errors.

The cerebellum receives input from the periphery and from all levels of the central nervous system. Information entering the cerebellum is initially acting on the cerebellar cortex and via collaterals on neurons of the cerebellar nuclei (e.g. the fastigial, interpositus and dentate nuclei) (Colin et al. 2002). Afferent information is processed within the cerebellar cortex. The cerebellar nuclei receive input from the Purkinje cells, the only output cells of the cerebellar cortex. The cerebellar nuclei transmit all output from the cerebellum, primarily to the motor regions of the cerebral cortex and brainstem (Hoover and Strick 1999). Cerebellar (isometric)

tremor is believed to result from abnormal feedforward and feedback mechanisms via long-loop transcortical processing during voluntary movement.

8.3.4.2 Therapeutic Strategies

The treatment of isometric tremor associated with intention tremor is difficult. Carbamazepine can be effective, porpranolol and clonazepam may be tried although results from small studies are conflicting. Cannabis has not been effective in a large controlled study (Koch et al. 2007). Cholinergic drugs (physostigmine) and 5-hydroxytryptophan have been found to be effective in some affected individuals (Deuschl et al. 2007). Also, the loading of the affected extremity can reduce the tremor amplitude for a short period of time, but adaptation to the load increase is frequently observed. Deep brain stimulation of the ventral intermediate thalamic nucleus can significantly reduce intention tremor of $\geq$3 Hz frequency (Lozano 2000).

8.3.5 Isometric Tremor in the Dystonic Tremor Syndrome

Dystonic isometric tremor is defined as a postural/kinetic tremor usually not seen during complete rest, which occurs in an extremity or body part that is affected by dystonia (Deuschl et al. 2007; Bhatia et al. 2018). Usually, dystonic tremor is a focal postural and/or kinetic tremor with irregular amplitudes and variable frequencies (usually less than 7 Hz). Sometimes focal tremors are observed in the absence of overt dystonia. Antagonistic gestures often can reduce tremor frequency and amplitude, e.g. in dystonic head tremor. Postural tremor is the typical clinical presentation of dystonic head tremor. Tremor in task-specific dystonia of the hand, e.g. writer's cramp, is an example of an isometric postural/kinetic tremor. Dystonic tremor and tremor associated with dystonia are different as unspecific postural tremor often at higher frequencies than the dystonic tremor itself may occur in extremities not involved by dystonia. Isometric postural/kinetic dystonic tremor in task-specific focal hand dystonia may hamper manual dexterity during a specific task, e.g. writing, playing a musical instrument or using a sports tool (Nowak et al. 2005a, b).

8.3.5.1 Pathophysiology

The pathophysiology of the dystonic tremor syndrome is unknown. Possibly impaired sensorimotor integration at the level of the basal ganglia with the impaired coupling of feedback and feedforward control mechanisms plays an essential role (Deuschl et al. 2001).

8.3.5.2 Therapeutic Strategies

Medical treatment options for isometric postural/kinetic dystonic limb tremors are widely ineffective (Deuschl et al. 2007). Dystonic head tremor had been found to improve with propranolol. Botulinum toxin is probably the most effective medical treatment option for postural dystonic head tremor and probably also for many cases of isometric postural dystonic hand tremor (Brin et al. 2001). In cases who do not respond, deep brain stimulation of the Globus pallidus internus is meanwhile a well-established advanced treatment option (Mueller et al. 2008).

8.3.6 Isometric Tremor in the Holmes Tremor Syndrome

Holmes tremor (synonyms: rubral tremor, midbrain tremor and Benedikt's syndrome) is caused by a lesion of the central nervous system predominantly the midbrain (Deuschl et al. 1998). Holmes tremor is defined by (1) the presence of both an irregular resting and intention tremor often giving the impression of jerky movements, (2) slow frequency (less than 4.5 Hz) and (3) a delay of 2 weeks to 2 years between the acute lesion and the occurrence of tremor. Holmes tremor is usually unilateral, most frequently affects the arm and hand, and many subjects with Holmes tremor also exhibit a postural tremor. Holmes tremor is the most disabling tremor form as it disturbs rest and all kinds of voluntary and involuntary movements (Deuschl et al. 2007). An isometric kinetic and sometimes postural tremor component may add to the disability of manual dexterity in affected subjects.

8.3.6.1 Pathophysiology

The origin of Holmes tremor is a lesion in the midbrain, cerebellum and/or thalamus (Deuschl et al. 1998; Nowak et al. 2010). However, also lesions of the involved fibre tracts in other regions may cause a similar clinical tremor. The pathophysiology of Holmes tremor is a combined lesion of the cerebello-thalamic and nigro-striatal systems. Central oscillators cause this kind of tremor. In Parkinson's disease, the rhythm of resting tremor is blocked during voluntary movement most likely by the cerebellum. If this cerebellar compensation is absent, a kinetic and even intention tremor component develops.

8.3.6.2 Therapeutic Strategies

Reliable clinical study-based therapeutic recommendations for a successful medical therapy of Holmes tremor do not exist. Dopaminergic substances are effective in many patients, but its specific effect on isometric tremor components is not known.

8.3.7 Isometric Tremor in the Orthostatic Tremor Syndrome

Primary orthostatic tremor is a unique tremor syndrome observed only in subjects older than 40 years of age (Deuschl et al. 2007). Primary orthostatic tremor is characterized by subjective unsteadiness of stance (only in severe cases also of gait). The symptoms disappear in the supine or sitting position. The neurological examination is generally unremarkable. Electromyographic recordings from limb or trunk muscles acting against gravity show a typical 13–18 Hz isometric tremor of agonistic and antagonistic muscles. The tremor oscillations are typically in phase for all limb and trunk muscles when standing. Isometric tremor is the diagnostic clue in primary orthostatic tremor. Other tremor types are not present in orthostatic tremor.

8.3.7.1 Pathophysiology

Because the tremor oscillations in orthostatic tremor are highly coherent in the limbs of both body sides and trunk muscles during standing, a central tremor generator is very likely. However, the anatomical location of this central tremor generator is unknown. Resetting the tremor frequency was possible only after electrical stimulation over the posterior fossa, but not over the cerebral cortex (Wu et al. 2001). This suggests that the tremor generator is sited within the brainstem. But higher regions and even the cortex seem to be involved as well.

8.3.7.2 Therapeutic Strategies

Primary orthostatic tremor has been documented to respond to medical treatment with clonazepam and primidone (Deuschl et al. 2007). Valproate, L-Dopa and propranolol have variable efficiency. Gabapentin has probably the best therapeutic effect to reduce the subjective unsteadiness of stance and electromyographic tremor activity (Evidente et al. 1998). But medical treatment is difficult and ineffective in a large proportion of patients. VIM stimulation in orthostatic tremor has an effect but the response to deep brain stimulation does not seem to be comparable to other tremors.

8.4 Conclusion

Isometric tremor is a subtype of action tremor. Isometric tremor occurs as a result of muscle contraction against a stationary rigid object, e.g. when holding an object between the tips of the thumb and other fingers in opposition. Isometric tremor can occur in isolation, but it is most frequently associated with other types of tremor.

Isometric tremor, a common symptom in a variety of clinical tremor syndromes, varies in frequency and amplitude depending on the underlying condition. Therapy of the underlying clinical condition also improves isometric tremor.

References

Bhatia KP, Bain P, Bajaj N, et al. Consensus statement on the classification of tremors from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33:75–87.

Brin MF, Lyons KE, Doucette J, et al. A randomized, double masked, controlled trial of botulinumtoxin type A in essential hand tremor. Neurology. 2001;56:1523–8.

Colin F, Ris L, Godaux E. Neuroanatomy of the cerebellum. In: Manto M, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press; 2002. p. 6–29.

Deuschl G, Bain P, Brin M, et al. Consensus statement of the Movement Disorder Society on tremor. Mov Disord. 1998;13:2–23.

Deuschl G, Wenzelburger R, Löffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. Brain. 2000;123(Pt 8):1568–80.

Deuschl G, Raethjen J, Lindemann M, et al. The pathophysiology of tremor. Muscle Nerve. 2001;24:716–35.

Deuschl G, Volkmann J, Raethjen J. Tremors: differential diagnosis, pathophysiology, and therapy. In: Jankovic J, Tolosa E, editors. Parkinson's disease and movement disorders. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 298–320.

Dirkx MF, den Ouden H, Aarts E, Timmer M, Bloem BR, Toni I, Helmich R. The cerebral network of Parkinson's tremor: an effective connectivity fMRI study. J Neurosci. 2016;36:5362–72.

Elbe RJ, Higgins C, Elbe S. Electrophysiological transition from physiologic tremor to essential tremor. Mov Disord. 2005;20:1038–42.

Elble RJ. Essential tremor frequency decreases with time. Neurology. 2000;55:1547–51.

Evidente VG, Adler CH, Caviness JN, et al. Effective treatment of orthostatic tremor with gabapentin. Mov Disord. 1998;13:829–31.

Fahn S. Cerebellar tremor: clinical aspects. In: Finley LJ, Capildeo R, editors. Movement disorders: tremor. London: Macmillan; 1984. p. 355–64.

Forssberg H, Ingvarsson PE, Iwasaki N, Johansson RS, Gordon AM. Action tremor during object manipulation in Parkinson's disease. Mov Disord. 2000;15:244–54.

Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev. 2001;81:1725–89.

Glickstein M, Waller J, Baizer JS, Brown B, Timmann D. Cerebellum lesions and finger use. Cerebellum. 2005;4:189–97.

Henderson TT, Thortensen JR, Morrison S, Tucker MG, Kvanagh JJ. Physiological tremor is suppressed and force steadiness is enhanced with increased availability of serotonin regardless of muscle fatigue. J Neurophysiol. 2022;27:27–37.

Hoover J, Strick P. The organization of cerebellar and basal ganglia outputs to primary motor cortex as revealed by retrograde transneural transport of herpes simplex virus type I. J Neurosci. 1999;19:1446–63.

Jankovic J, Schwartz KS, Ondo W. Re-emergent tremor in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;67:646–50.

Koch M, Mostert J, Heersema D, De Kayser J. Tremor in multiple sclerosis. J Neurol. 2007;254:133–45.

Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain. 1998;121:451–7.

Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry. 1999;66:289–96.

Lozano AM. VIM thalamic stimulation for tremor. Adv Med Res. 2000;31:266–9.

Mueller J, Skogseid IM, Benecke R, Kupsch A, Trottenberg T, Poewe W, et al. Pallidal deep brain stimulation improves quality of life in segmental and generalized dystonia: results from a prospective, randomized sham-controlled trial. Mov Disord. 2008;23:131–4.

Muthuraman M, Hossen A, Heute U, Deuschl G, Raethjen J. A new diagnostic test to distinguish advances essential tremor from tremulous Parkinson's disease. Mov Disord. 2011;26(8):1548–52.

Muthuraman M, Raethjen J, Koirala N, Anwar AR, Mideksa KG, Elble R, Groppa S, Deuschl G. Cerebello-cortical network fingerprints differ between essential, parkinsonian and mimicked tremors. Brain. 2018;141:1770–81.

Nowak DA, Fink GR. Psychogenic movement disorders: phenomenology, neuro-anatomical correlates and therapeutic approaches. NeuroImage. 2009;47:1015–25.

Nowak DA, Hermsdörfer J. Coordination of grip and load forces during vertical point-to-point movements with a grasped object in Parkinson's disease. Behav Neurosci. 2002;5:837–50.

Nowak DA, Rosenkranz K, Topka H, Rothwell J. Disturbances of grip force behaviour in focal hand dystonia: evidence for a generalized impairment of sensory-motor integration? J Neurol Neurosurg Psychiatry. 2005a;76:953–9.

Nowak DA, Topka H, Tisch S, Hariz M, Limousin P, Rothwell JC. The beneficial effects of subthalamic nucleus stimulation on manipulative finger force control in Parkinson's disease. Exp Neurol. 2005b;193:427–36.

Nowak DA, Tisch S, Hariz M, Limousin P, Topka H, Rothwell JC. Sensory timing cues improve akinesia of grasping movements in Parkinson's disease: a comparison to the effects of subthalamic nucleus stimulation. Mov Disord. 2006;21:166–72.

Nowak DA, Seidel B, Reiner B. Tremor following ischemic stroke of the posterior thalamus. J Neurol. 2010;257:1934–6.

Papengut F, Raethjen J, Binder A, Deuschl G. Rest tremor suppression may separate essential from parkinsonia rest tremor. Parkinsonism Relat Disord. 2013;19:693–7.

Raethjen J, Lindemann M, Schmaljohann H, Wenzelburger R, Pfister G, Deuschl G. Multiple oscillators are causing parkinsonian and essential tremor. Mov Disord. 2000a;15:84–94.

Raethjen J, Pawlas F, Lindemann M, Wenzelburger R, Deuschl G. Determinants of physiologic tremor in a large normal population. Clin Neurophysiol. 2000b;111:1825–37.

Raethjen J, Lemke MR, Lindemann M, et al. Amitriptyline enhances the central component of physiological tremor. J Neurol Neurosurg Psychiatry. 2001;70:78–82.

Raethjen J, Pohle S, Govindan RB, Morsnowski A, Wenzelburger R, Deuschl G. Parkinsonian action tremor: interference with object manipulation and lacking levodopa response. Exp Neurol. 2005;194:151–60.

Raethjen J, Govindan RB, Muthuraman M, Kopper F, Volkmann J, Deuschl G. Cortical correlates of the basic and first harmonic frequency of Parkinsonian tremor. Clin Neurophysiol. 2009;120:1866–72.

Stani TM, Burchiel KJ, Hart MJ, Lenar DP, Anderson VC. Effects of DBS on precision grip abnormalities in essential tremor. Exp Brain Res. 2010;201:331–18.

Timmer J, Lauk M, Pfleger W, Deuschl G. Cros-spectral analysis of physiological tremor and muscle activity. I. Theory and application to unsynchronised electromyogram. Biol Cybern. 1998;78:349–57.

Timmermann L, Gross J, Dirks M, et al. The cerebral oscillatory network parkinsonian resting tremor. Brain. 2003;126:199–212.

Van den Berg KRE, Helmich RC. The role of the cerebellum in tremor – evidence from neuroimaging. Tremor Other Hyperkinet Mov (N Y). 2021;11:49.

Wenzelburger R, Raethjen J, Loffler K, Stolze H, Illert M, Deuschl G. Kinetic tremor in a reach-to-grasp movement in Parkinson's disease. Mov Disord. 2000;15:1084–94.

Wenzelburger R, Zhang BR, Poepping M, Schrader B, Müller D, Kopper F, Fietzek U, Mehdorn HM, Deuschl G, Krack P. Dyskinesias and grip control in Parkinson's disease are normalized by chronic stimulation of the subthalamic nucleus. Ann Neurol. 2002;52:240–3.

Wenzelburger R, Kopper F, Zhang BR, Witt K, Hamel W, Weinert D, Kuhtz-Buschbeck J, Gölge M, Illert M, Deuschl G, Krack P. Subthalamic nucleus stimulation for Parkinson's disease preferentially improves akinesia of proximal arm movements compared to finger movements. Mov Disord. 2003;18:1162–9.

Wu YR, Ashby P, Lang AE. Orthostatic tremor arises from an oscillator in the posterior fossa. Mov Disord. 2001;16:272–9.

Chapter 9
Essential Tremor and Other Forms of Kinetic Tremor

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Abstract Kinetic tremor is a tremor (i.e., a rhythmic and oscillatory movement) that occurs during guided voluntary movements like writing or touching finger to nose. As such, it is a type of action tremor, that is, tremor that occurs during the voluntary contraction of skeletal muscle. It may be distinguished from rest tremor, which occurs when a limb is fully relaxed, and intention tremor, which is present with visually guided movement and increases in amplitude with the approach of the target. A broad range of kinetic tremors occurs and these may be divided into those that are normal vs. pathological. Physiological or enhanced physiological tremor is the most common form of normal tremor (Elble, Mov Disord 13 Suppl 3:35–39, 1998a; Elble, Mov Disord 13(3):457–464, 1998b; Elble, Clin Neurophysiol 114(4):624–635, 2003; Louis et al., Arch Neurol 55(2):222–227, 1998a; Louis et al., Mov Disord 13(5):803–808, 1998b; Louis et al. Mov Disord 13(1):5–10, 1998c) and essential tremor (ET) is the most common pathological form of tremor (Louis and Ferreira, Mov Disord 25(5):534–541, 2010; Louis and McCreary, Tremor Other Hyperkinet Mov (N Y) 11:28, 2021). Other pathological tremors include dystonic tremor, orthostatic tremor, drug-induced tremor, and several other conditions. The focus of this chapter is the pathological forms of kinetic tremor, and we will begin with ET, which is the most common of these.

Keywords Kinetic · Epidemiology · Genetics · Cerebellum · Purkinje cell · Neurodegeneration

9.1 Kinetic Tremor: An Introduction

Kinetic tremor is a tremor (i.e., a rhythmic and oscillatory movement) that occurs during guided voluntary movements like writing or touching finger to nose. As such, it is a type of action tremor, that is, tremor that occurs during the voluntary

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contraction of skeletal muscle. It may be distinguished from rest tremor, which occurs when a limb is fully relaxed, and intention tremor, which is present with visually guided movement and increases in amplitude with the approach of the target. A broad range of kinetic tremors occurs and these may be divided into those that are normal vs. pathological. Physiological or enhanced physiological tremor is the most common form of normal tremor (Elble 1998a, b, 2003; Louis et al. 1998a, b, c) and essential tremor (ET) is the most common pathological form of tremor (Louis and Ferreira 2010; Louis and McCreary 2021). Other pathological tremors include dystonic tremor, orthostatic tremor, drug-induced tremor, and several other conditions. The focus of this chapter is the pathological forms of kinetic tremor, and we will begin with ET, which is the most common of these.

9.2 Essential Tremor

9.2.1 Essential Tremor or Essential Tremors?

ET is not only the most prevalent abnormal tremor but it is also one of the more prevalent neurological diseases (Louis and Ferreira 2010; Louis and McCreary 2021; Louis et al. 1998a, b, c; Dogu et al. 2003). Patients with ET receive their treatment from a wide range of health professionals aside from neurologists; these include internists, geriatricians, and general practitioners. Although ET is often viewed as a condition that is easy to diagnose, in fact, misdiagnosis is exceedingly common, with an estimated 30–50% of "ET" patients having other diseases (Schrag et al. 1999, 2000; Jain et al. 2006). Thus, in addition to being one of the more prevalent neurological diseases, ET may be one of the most commonly misdiagnosed of these diseases as well.

The traditional paradigm, held for many years, regarded ET as a benign, monosymptomatic condition (Elble 2002)—action tremor. Yet, in recent years, this notion has been challenged (Bermejo-Pareja 2011; Benito-Leon and Louis 2006; Lorenz and Deuschl 2007; Louis 2009). More recent views of ET hold it as a progressive and often disabling neurological disease characterized by a core motor feature, action tremor, yet often accompanied by a number of other motor and nonmotor features (Bermejo-Pareja 2011; Louis and Okun 2011; Louis 2021). Patients often differ with respect to the presence, evolution, and severity of these features, indicating that there is clinical heterogeneity beyond what can be explained by disease stage/duration alone. Furthermore, postmortem studies have identified a range of different structural changes in the brains of ET patients, indicating the presence of some amount of pathological heterogeneity. These parallel observations have appropriately given rise to the question as to whether ET represents a single disease entity or rather a family of diseases (Benito-Leon and Louis 2006; Louis 2009). A nomenclatural issue that naturally follows is whether the more appropriate term is "essential tremor," which has historical primacy (Louis et al. 1998a, b, c)

and whose continued use inertia would favor, or the term "essential tremors," which perhaps better reflects an emerging understanding of the aforementioned clinical and pathological heterogeneity (Louis 2009, 2014a, 2021). For the time being, however, "essential tremor" continues to be the favored term.

9.2.2 Etiology: Epidemiology and Genetics

The rate at which new ET cases arise (i.e., disease incidence) has been estimated in one population-based study, which ascertained cases from central Spain; the adjusted incidence was 619 per 100,000 person-years among persons aged 65 and older (Benito-Leon et al. 2005). Stated in another way, if one were to follow an ET-free cohort of 1000 persons aged 65 and older for 1 year, one would expect that by the end of that year that approximately six individuals would have developed new-onset ET, and following that same cohort for 2 years would yield 12 new ET cases. Although most cases are older adults, it is nevertheless important to note that ET can begin in childhood as well (Louis et al. 2001a, b, c, d, Tan et al. 2006; Ferrara and Jankovic 2009), with the large majority of these young-onset cases being familial (Bain et al. 1994; Louis and Ottman 2006; Louis and Dogu 2007; Louis et al. 2015a).

Although ET is quite common, ironically, establishing a precise prevalence has been challenging; a number of methodological issues have resulted in a wide range of prevalence estimates in the 42 population-based prevalence studies from around the world (Louis and Ferreira 2010; Louis et al. 2011a, b, c, d; Louis and McCreary 2021). These methodological issues include but are not limited to the following: (1) method of case ascertainment, with studies that examine participants rather than relying on self-report (screening questionnaires) yielding higher prevalence estimates, and (2) case definition, with studies that more broadly (i.e., loosely) define ET resulting in higher prevalence estimates (Louis and Ferreira 2010; Louis et al. 1998a, b, c; Louis and McCreary 2021). A population-based study in Mersin, Turkey that did not rely on screening questionnaires (i.e., all study participants were examined regardless of whether they complained of tremor) and that used stringent criteria for ET reported a prevalence of 4.0% among individuals age $\geq$ 40 years (Dogu et al. 2003). In another population-based study in Finland that used a comparable methodology (Rautakorpi et al. 1982), the prevalence in individuals age 40 years and older was 5.6%, and 9.0% among individuals $\geq$60 years of age. In these and numerous other studies, the prevalence of ET increased with advancing age, and ET was highly prevalent in the sixth through eighth decades of life, with prevalence estimates generally in the range of 6–10% (Louis and Ferreira 2010; Louis et al. 1998a, b, c; Dogu et al. 2003; Louis and McCreary 2021), and some data suggest that prevalence continues to rise into advanced age groups (i.e., 90 years and older), where the prevalence may attain values in excess of 20% (Louis and Ferreira 2010; Louis et al. 2009a, b, c, d, e, f; Louis and McCreary 2021).

What predisposes so many people to this disease? Through epidemiological studies, several risk factors for ET have been identified. First, age is clearly a

risk factor, with studies having shown an age-associated rise in both the incidence (Rajput et al. 1984) and prevalence (Louis and Ferreira 2010; Louis et al. 1998a, b, c; Dogu et al. 2003; Louis and McCreary 2021) of ET. Moreover, as with other neurodegenerative diseases, the prevalence increases in a nonlinear, exponential manner with advanced age, with estimates of the prevalence reaching 20% or higher among the oldest old (Louis and Ferreira 2010; Das et al. 2009; Louis et al. 2009a, b, c, d, e, f; Louis and McCreary 2021). Second, there is some evidence that ethnicity may be a risk factor for ET. Studies in the United States have reported differences in the prevalence among whites and African-Americans (Haerer et al. 1982; Louis et al. 1995, 2009a, b, c, d, e, f). A study in Israel reported a very low prevalence of ET in Arabic villagers (Inzelberg et al. 2006) and a study in Singapore (Tan et al. 2005a, b) reported marginally different prevalence estimates for Singaporean Chinese, Malays, and Indians. These ethnic differences could be the result of differences in the presence of genes that increase disease susceptibility. Third, a family history of ET is a strong risk factor for ET, as the disease is in many cases familial (Louis et al. 2001a, b, c, d; Tanner et al. 2001). Canonically, genetic factors have been viewed as important in the etiology of ET, as the disease can aggregate in families, many of which show an autosomal dominant pattern of inheritance (Clark and Louis 2015). Finally, a number of environmental risk factors, and particularly toxicants that can produce tremor (e.g., lead, harmane), are under active investigation as etiological agents in ET (Louis et al. 2003a, b, c, d, 2008a, b, c, d, e, f; Dogu et al. 2007; Louis 2008; Louis et al. 2013a, b; 2020). The etiological roles of both the genetic and environmental factors will be discussed more below.

On an etiological level, ET is often considered to be largely a genetic disorder (Clark and Louis 2015). There are numerous examples of families in which the proband and multiple relatives have ET (Clark and Louis 2015) and in which the pattern of inheritance is most consistent with an autosomal dominant model, although other models of inheritance are highly likely. A detailed review of the genetic risk factors for ET may be found in Siokas et al. 2020.

Environmental factors are likely to contribute to the etiology of ET as well. First, environmental factors are believed to play a substantial role in other progressive and degenerative neurological disorders including Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (Perl 1985; Semchuk et al. 1992; Rybicki et al. 1993; Gorell et al. 1997, 1998, 1999; Ritz and Yu 2000; Racette et al. 2001; Dick 2006; Baldereschi et al. 2008; Morahan et al. 2007; Shcherbatykh and Carpenter 2007, Azar et al. 2021; Ullah et al. 2021), so that by extension, it is conceivable that they could play an etiological role in ET as well. Second, although a common refrain in the ET literature is that "50%" of ET cases have a genetic basis, the precise derivation of this estimate is unclear and its validity is also doubtful (Louis and Ottman 1996). Indeed, some estimates are as low as 17% (Louis and Ottman 1996). There has been one familial aggregation study of ET (Louis et al. 1997a, b), and in that study, 55% of ET cases had no affected first- or second-degree relatives. This observation was consistent with data from numerous other clinical series, among whom the majority of ET cases did not report affected relatives (Critchley 1972; Hornabrook and Nagurney 1976; Aiyesimoju et

al. 1984; Martinelli et al. 1987; Louis and Ottman 1996; Salemi et al. 1998; Dogu et al. 2005; Louis et al. 2015b; Guler et al. 2019). Third, in the ET twin studies (Tanner et al. 2001; Lorenz et al. 2004) concordance in monozygotic twins was far from 100%; it was 60% in one study and 63% in another. Fourth, the well-known existence in ET families of intra-familial differences in age of onset, tremor location, and tremor severity (Larsson and Sjogren 1960; Louis et al. 2001a, b, c, d) also suggests that environmental factors may be serving as modifiers of the putative underlying susceptibility genes in those families. In terms of environmental factors, epidemiological studies (Louis et al. 2002a, b, 2003a, b, c, d, 2008a, b, c, d, e, f; Dogu et al. 2007; Louis 2008; Louis et al. 2013a, b, 2020) have implicated several specific toxicants, namely, β-carboline alkaloids (e.g., harmine and harmane, a group of highly tremorogenic dietary chemicals) and lead, in ET. At least one study has shown that higher levels of baseline ethanol consumption are associated with an increased risk of developing ET, an observation that is interesting in light of the known cerebellar toxicity of ethanol (Louis et al. 2009a, b, c, d, e, f). Studies of several other toxicants (e.g., manganese, pesticides) have failed to demonstrate associations with ET (Louis et al. 2004, 2006a, b, c, d; Louis 2008). Other studies have pointed to a possible protective role of cigarette smoking in ET (Benito-Leon et al. 2008a, b; Louis et al. 2008a, b, c, d, e, f), parallel with the situation that has been observed in Parkinson's disease. In summary, the etiology of ET is likely to be genetic in many instances, environmental in others, and due to the combined influence of these two factors in yet other cases. This is a research area undergoing active investigation.

9.2.3 Pathophysiology

Despite being one of the more common neurological disorders, little progress was made during the nineteenth and most of the twentieth century in terms of advancing the understanding of underlying mechanisms of ET (Louis 2010; Louis and Vonsattel 2007). Curiously, many textbook chapters and review articles on this disease did not include a section devoted to disease pathophysiology. This paralleled the notion that ET was not really a disease per se, but rather, a relatively benign constitutional trait; as such, the loose terms "condition" and "disorder" were often preferred rather than the more definitive term "disease." Discussion of disease mechanisms, although sparse, was also dominated by a focus on tremor physiology (DeLong 1978; Elble 1998a, b; Deuschl and Elble 2000). The existence of a central tremor pacemaker or oscillator was posited, with the main support for this idea being the existence of an animal model of action tremor using the neurotoxin harmaline (similar to harmine and harmane), which induces an acute action tremor in the laboratory animals and postmortem changes in the olivocerebellar pathway in these animals (Llinas and Volkind 1973; Sinton et al. 1989; Handforth and Krahl 2001; Krahl et al. 2004; Martin et al. 2005; Martin and Handforth 2006). Buoyed by this observation, a physiological derangement in the inferior olivary

nucleus, a structure that has inherent oscillatory-pacemaking properties, was viewed as the possible prime mover in ET, although there was very little actual support for this theoretical physiological construct. Indeed, rhythm-generating networks (i.e., pacemakers) are a nonspecific finding, located throughout the mammalian cerebral cortex and brainstem (Li et al. 2010; Buzsaki and Draguhn 2004), and their role in the generation of ET, although widely discussed, has never been empirically demonstrated. Based on corticomuscular coherence studies, other investigators have suggested the existence of several rather than one central pacemaker in ET (i.e., a complex cortical and subcortical network that is responsible for tremor) (Raethjen et al. 2000; Lorenz and Deuschl 2007), although the precise location of these pacers is not clear and furthermore, although these coherence studies indicate that the cortex maybe play some role in tremor oscillations, these data do not necessarily indicate that the cortex is involved in tremor generation (i.e., that the oscillatory activity is transmitted from cortex to muscle) (Raethjen et al. 2007). With regard to the inferior olivary nucleus, positron emission tomography studies, which began to emerge in the 1990s, did not demonstrate the involvement of the inferior olivary nucleus in ET nor did later postmortem studies reveal structural changes in that nucleus (Louis 2010; Wills et al. 1994, 1995), which further casts doubt on this olivary hypothesis. Clinical observations furthermore cast doubt on the olivary model (Ekouzi et al. 2016; Louis et al., 2018a). The many problems with the olivary model are reviewed elsewhere (Lenka and Louis 2017).

The olivary hypothesis regarded ET as a functional dysregulation of an electrophysiological system, that is, no more than a reversible oscillatory disturbance arising from an electrophysiological system gone awry (i.e., similar to epilepsy) (Deuschl and Elble 2009). This stands in contrast to the notion that ET, like Parkinson's disease, Alzheimer's disease, and other neurodegenerative disorders, is more than a manifestation of an abnormality in a central electrophysiological circuit, but represents a clinical–pathological entity that is grounded in a set of molecular and cellular changes, which give rise to a cascade of both microscopic and macroscopic structural changes in the brain as well as altered neuronal function and activity. The olivary hypothesis arose in an environment in which there had been no substantive attempt to search for such structural brain correlates in ET. Indeed, in the 100 year period between 1903 (the first reported postmortem on ET) and 2003, there had only been 15 postmortem examinations (Louis and Vonsattel 2007). Many of these were published in the earlier part of that time period. Most did not use rigorous methodologies, and none used age-matched control brains for comparison (Louis 2010). Hence, the search for a structural brain correlate had not begun with any rigor.

While physiological studies were positing the involvement of the inferior olive, an emerging clinical literature gathered increasing support for the notion that the cerebellum itself might be centrally involved in ET. First, cerebellar-like problems, with abnormalities in tandem gait and balance, have been repeatedly described in ET patients (Louis et al. 2010a, b; Rao et al. 2011; Singer et al. 1994; Hubble et al. 1997; Stolze et al. 2001; Klebe et al. 2005; Parisi et al. 2006; Louis et al. 2013c; Rao and Louis 2019). Intention (i.e., "cerebellar") tremor of the arms (in addition to the more

typical kinetic tremor of ET) occurs in 58% of ET patients (Deuschl et al. 2000; Koster et al. 2002), and in 10% of ET patients, such intention tremor involves the head (Leegwater-Kim et al. 2006). There are a variety of other motor abnormalities that point to what is likely to be a more pervasive underlying abnormality of cerebellar function in ET. These include oculomotor deficits (Helmchen et al. 2003; Gitchel et al. 2013; Wojcik-Pedziwiatr et al. 2016) as well as abnormalities in limb motor behavior in ET (Bares et al. 2010; Farkas et al. 2006; Trillenberg et al. 2006; Avanzino et al. 2009). Second, unilateral cerebellar stroke has been reported to abruptly terminate ipsilateral arm tremor in patients with ET (Dupuis et al. 1989; Rajput et al. 2008) and cerebellar outflow (dentatorubrothalamic) pathways are the target of deep brain stimulation and other surgical therapies for ET, which are highly effective in treating ET (Benabid et al. 1993; Schuurman et al. 2000; Iorio-Morin et al. 2021). Third, a wide array of neuroimaging methods used in a growing number of studies now indicate the presence not only of functional and metabolic abnormalities in the ET cerebellum but also of structural abnormalities in both the cerebellar gray and white matter as well (Pietracupa et al. 2021; van den Berg and Helmich 2021). These studies include functional magnetic resonance imaging (MRI) studies (Bucher et al. 1997), positron emission tomography studies (Colebatch et al. 1990; Jenkins et al. 1993; Wills et al. 1994), [^{1}H] magnetic resonance spectroscopic imaging studies (Louis et al. 2002a, b; Pagan et al. 2003), diffusion tensor imaging studies (Klein et al. 2011; Nicoletti et al. 2010; Shin et al. 2008), voxel-based morphometry studies (Quattrone et al. 2008; Benito-Leon et al. 2009; Galazzo et al. 2020; Agren et al. 2021; Mavroudis et al. 2021), and studies using other automated volumetric methods (Cerasa et al. 2009).

In tandem with the clinical studies, noted above, which were gathering increasing support for the notion that the cerebellum and cerebellar systems seemed to be at the root of ET, a growing postmortem literature was for the first time attempting to quantify microscopic changes in the ET brain and compare these brains to control brains (Louis and Vonsattel 2007). Three ET case series have been published in detail; these comprise 20 cases (Canada, six cases initially published and 14 added later) (Rajput et al. 1991a, b, 2004), 56 cases (Arizona, USA) (Shill et al. 2008; Symanski et al. 2014), and >200 cases (New York, USA, with data from this continually expanding case series reported in a sequence of papers spanning 15 years) (Erickson-Davis et al. 2010; Kuo et al. 2011; Louis et al. 2006a, b, 2007a, b, 2009a, b, 2010a, b; Louis and Vonsattel 2007; Axelrad et al. 2008; Louis et al. 2019; Louis and Faust 2020). In the New York series, which is the largest series, the large majority of ET cases have demonstrated degenerative changes present in and restricted to the cerebellum (Louis et al. 2007a, b), and, based on this simple empiric observation, those brains have been designated as "cerebellar-ET" (Louis et al. 2009a, b, c, d, e, f; Louis et al. 2019; Louis and Faust 2020).

The degenerative changes in ET cases with cerebellar-ET that have been cataloged to date and are numerous (Louis et al. 2019; Louis and Faust 2020). These include (1) a six- to sevenfold increase in the number of swellings of the Purkinje cell axon (i.e., "torpedoes") (Fig. 9.1), (2) changes in numerous other measures of PC axonal morphology (e.g., increase in axonal recurrent collaterals, axonal

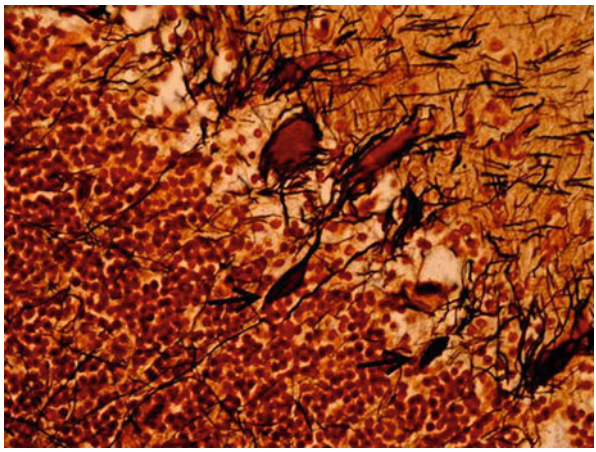

Fig. 9.1 Torpedoes, which are swellings of the proximal portion of the Purkinje cell axon, occur in abundance in patients with cerebellar-ET. Bielschowsky-stained cerebellar cortical section of an ET case (400× magnification) shows two torpedoes (*arrows*)

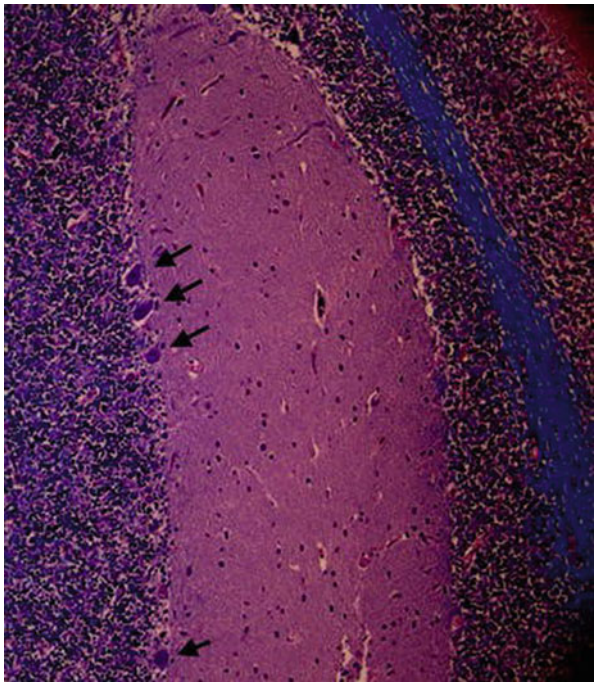

Fig. 9.2 Luxol fast blue/hematoxylin and eosin–stained cerebellar cortical section (100× magnification) in ET showing Purkinje cells (*arrows*, *left*) and segmental loss of Purkinje cells (*right*)

branching, and terminal axonal sprouting) (Babij et al. 2013), (3) changes in the PC dendritic compartment with a 7.3–30 times increase in dendritic swellings as well as significant dendritic pruning, and loss of dendritic spines (Louis et al. 2014; Yu et al. 2012), (4) an approximate 40% reduction in the number of Purkinje cells (Fig. 9.2) and increase in the number of empty basket plexuses (i.e., an indirect marker of PC loss) (Choe et al. 2016; Lee et al. 2019; Louis et al. 2019; Louis and Faust 2020), (5) an increase in the number of heterotopic Purkinje cells (i.e., Purkinje

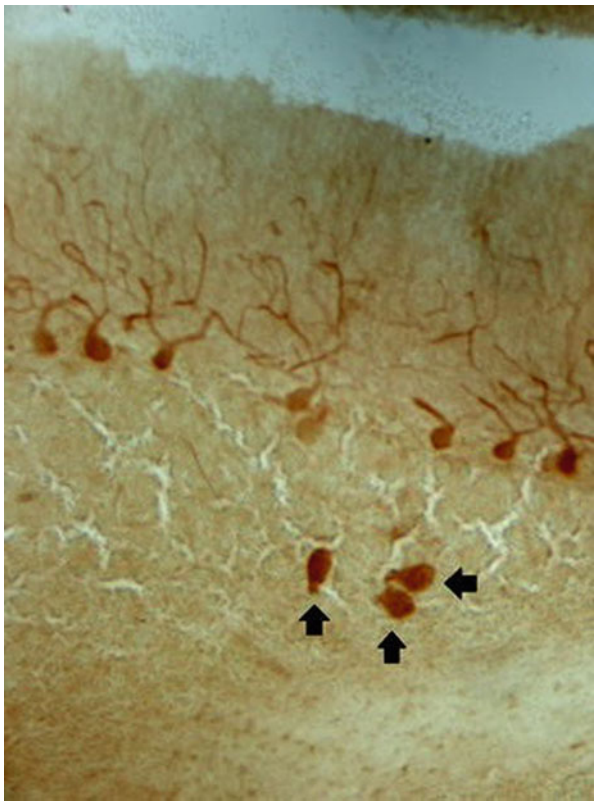

Fig. 9.3 Three heterotopic Purkinje cells in the granular layer (*arrows*). Calbindin-stained cerebellar cortical section of an ET case (100× magnification). Heterotopic Purkinje cells may also be found in the molecular layer in other instances

cells whose cell body lies outside of the Purkinje cell layer) (Fig. 9.3) (Louis et al. 2018b), (6) hypertrophic changes in basket cell axonal processes (Fig. 9.4) (Louis 2010; Louis et al. 2019; Louis and Faust 2020), and (7) changes in the PC-climbing fiber synaptic interface (Lin et al. 2014; Louis et al. 2019; Louis and Faust 2020). It is important to note that each of these changes, noted in the New York study, occurs relative to normal age-matched controls brains as comparators. Although the Canadian study did not examine most of these microscopic changes or attempt to quantify most of them, they did quantify the number of Purkinje cells in a small number of ET cases ($N = 7$), demonstrating between a 5.8 and 23.7% reduction in the number of Purkinje cells, yet they only compared that small number of cases to an even smaller number of controls ($N = 2$) (Rajput et al. 2011), so that the case–control difference could not be effectively assessed due to insufficient study power (Louis et al. 2011a, b, c, d). In a second study, with 12 ET and 6 controls, there was no case-control difference; however, study power was similarly an issue (Rajput et al. 2012) and the data have been called into question (Louis et al. 2012). Investigators in New York also quantified the number of Purkinje cells in five of the Canadian brains with adequate and available tissue and the number was even lower than reported in ET brains in New York (Louis 2010; Louis et al. 2012). The Arizona

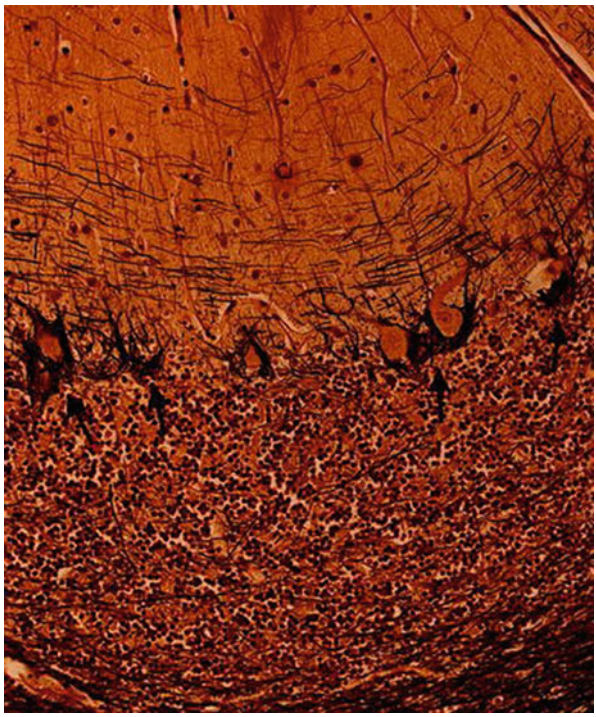

Fig. 9.4
Bielschowsky-stained cerebellar cortical section (200× magnification) in ET. Hypertrophic changes in basket cell axonal processes are shown by *arrows*

series (Symanski et al. 2014) did not attempt to quantify any of the numerous degenerative changes noted above; they did not detect a case-control difference in their PC counts but these results have been questioned on methodological grounds (Louis and Faust 2020). Hence, the most detailed work has come out of the New York cohort. Recent attempts to synthesize the numerous observed changes in ET into a cohesive model—a degenerative cascade—have been published (Louis and Faust 2020).

The above discussion focuses on the degenerative pathology noted in the ET cerebellum. It should also be noted that studies of ET cases have also noted the presence of Lewy bodies in a subset of ET brains. In an initial series in New York, Lewy pathology was present in approximately 25% of ET brains (Louis et al. 2007a, b). Further research is being conducted to determine the cause as well as additional features of this pathology. Another published ET brain points to what appears to be additional heterogeneity of degenerative pathology (Louis et al. 2010a, b). On postmortem examination, there were abundant torpedoes, segmental loss of Purkinje cells, and Bergmann gliosis; in addition, Purkinje cells showed prominent ubiquitinated, nuclear inclusions (Louis et al. 2010a).

In summary, the pathophysiology of ET is far from clear. Dominated for many years by the notion that the disease was the result of brain circuitry gone awry, and that the cerebellum was involved in that circuitry disturbance, more recent studies have been able to identify a set of structural/cellular changes in the ET brain,

most of which are centered on the Purkinje and connected neuronal populations. With evidence of neuronal loss and other degenerative changes in these brains, it is appearing more and more likely that this progressive, age-associated disease is degenerative in nature (Louis and Faust 2020). This then opens the door to further research to identify and elucidate the primary set of molecular events that sets the cascade of degenerative cellular changes in motion.

9.2.4 Clinical Presentation and Natural History

The onset of clinical disease in ET may be at any age, with childhood-onset cases clearly described in the literature (Louis et al. 2001a, b, c, d; Jankovic et al. 2004); however, the majority of ET cases who are seen in clinical settings have an onset that is in the 60s, 70s, and 80s (Brin and Koller 1998). A bimodal distribution of age of onset has been described, with the two peaks in the second and sixth decades of life (Lou and Jankovic 1991; Koller et al. 1994; Brin and Koller 1998), yet that is likely an artifact of ascertainment bias. Thus, one study (Louis and Dogu 2007) assessed the age of onset in ET, comparing cases ascertained from a tertiary referral setting to cases from a population. In the population-based sample, the peak in later life was clearly present but the young-onset peak was barely discernable (Louis and Dogu 2007). By contrast, in the sample from the tertiary referral center, both peaks were clearly present (Louis and Dogu 2007). The young-onset peak is likely due to the preferential referral to tertiary centers of patients with young-onset, familial forms of ET (Bain et al. 1994; Louis and Dogu 2007).

The central, clinical disease-defining feature in patients with ET is a kinetic tremor of the arms. This tremor may be apparent during a variety of common daily activities, including eating, drinking, writing, and typing (Fig. 9.5). ET patients often have a postural tremor as well. This type of tremor is elicited by asking them to hold their arms outstretched in front of their body. The amplitude of the kinetic tremor is generally greater than that of the postural tremor (Brennan et al. 2002; Louis 2013, 2014b, 2016, 2019). The opposite pattern (i.e., postural tremor of greater amplitude than kinetic tremor) may be a clue that the diagnosis is not ET (Louis 2014b, 2016, 2019). The kinetic tremor may also have an intentional component (Louis et al. 2009a, b, c, d, e, f; Louis 2014b, 2016, 2019); thus, during the finger–nose–finger maneuver, the tremor may worsen when the patient approaches his/her own nose or the examiner's finger. Indeed, intention tremor is reported to occur in approximately 44% of ET patients (Deuschl et al. 2000; Louis et al. 2009d). The frequency of the kinetic tremor (generally between 4 and 12 Hz) is inversely related to age, with older patients exhibiting slower tremors and younger patients, faster tremors (Elble et al. 1992, 1994).

Some patients with ET develop a tremor at rest without other features of parkinsonism (Koller and Rubino 1985; Rajput et al. 1993; Cohen et al. 2003). The prevalence of this tremor ranges from 1.9% to 46.4%, depending on the ascertainment of cases, with lower estimates coming from the population and higher

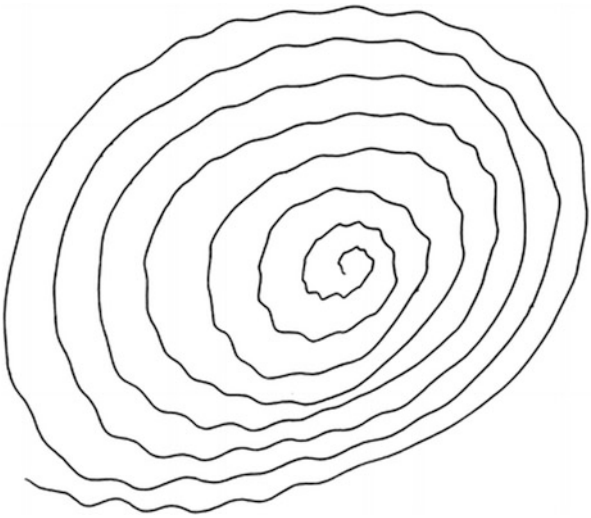

Fig. 9.5 An ET patient's tremor is apparent while they draw an Archimedes spiral with their right hand

estimates from bank cohorts (Louis et al. 2015b). This is an arm rather than a leg tremor. The rest tremor in ET may occur in isolation of other features of parkinsonism (i.e., bradykinesia, rigidity) and, indeed, postmortem studies have repeatedly indicated that ET patients who develop isolated rest tremor do not necessarily have emerging Lewy body pathology in the substantia nigra (Louis et al. 2011a, b, c, d; Rajput et al. 1993, 2004).

While the tremor of ET is most commonly seen in the arms, other body regions may also be involved (Critchley 1949). The most common among these is head (i.e., neck), the prevalence of which varies across study samples, but is generally in the range of 15–55% (Ashenhurst 1973; Lou and Jankovic 1991; Bain et al. 1994; Hubble et al. 1997; Louis et al. 2003a, b, c, d). A characteristic feature of ET is the somatotopic spread of tremors over time. Head tremor typically evolves several years after the onset of arm tremor and the converse pattern (i.e., spread of tremor from the head to the arms) is distinctly unusual (Critchley 1949; Larsson and Sjogren 1960; Louis et al. 2003a, b, c, d; Rajput et al. 2004). The other interesting feature of the head tremor is that it is strongly associated with female gender, with women being several-fold more likely to develop head tremor than men (Hubble et al. 1997; Louis et al. 2003a, b, c, d; Hardesty et al. 2004). Head tremor is not a common finding in children with ET either (Louis et al. 2001a, b, c, d). While the head tremor is a postural tremor that is present while sitting across from the patient, one other feature of the tremor is that it may also have an intentional component. In one study (Leegwater-Kim et al. 2006), approximately 10% of ET cases had a postural head tremor that was exacerbated during goal-oriented movement (e.g., when bending their neck downward while drinking from a cup or spoon). While on the one hand, head tremor may be embarrassing for some patients, one other interesting feature about the head tremor of ET is that patients are often unaware of it, which helps to distinguish it from dystonic head tremor. In one study (Louis

et al. 2008a, b, c, d, e, f), one-third to one-half of ET cases who exhibited a head tremor on examination did not report the presence of head tremor. Indeed, when their tremor was pointed out to them, many of these patients stated that they were unaware of it. A lack of internal feedback about a movement may lessen self-awareness of that movement. Whether, from a proprioceptive vantage point, patients have a subjective experience of head tremor, is not always clear. For example, with some types of oscillatory cranial movements, perceptual stability may be achieved through a reduced sensitivity to the motion or the use of other signals to cancel the effects of the movements (i.e., a spatial constancy feedback loop) (Louis et al. 2008a, b, c, d, e, f). Whether such a mechanism is operative in ET cases is unclear.

Jaw tremor may also occur in patients with ET, with the prevalence estimated to be lowest in population-based studies (7.5%) and highest in referred samples (10.1–18.0%) (Louis et al. 2006a, b, c, d). ET patients with jaw tremor tend to have more clinically severe and more topographically widespread disease. The jaw tremor is predominantly a postural tremor (occurring while the mouth is held slightly open or during sustained phonation) or a kinetic tremor (occurring during speech). A small number of patients may also exhibit mild tremor while their mouth is closed; however, in these, it can be difficult to determine whether the jaw is fully relaxed (Louis et al. 2006a, b, c, d). Jaw tremor differs from the peri-oral tremor of Parkinson's disease, which often manifests as a tremor of the lower lip. Leg tremor also occurs in ET. In one clinical-based study, while mild kinetic leg tremor occurred in nearly one-half of ET cases, moderate kinetic leg tremor occurred in 14.3% of cases, and the severity of leg tremor was correlated modestly with disease duration (i.e., more marked leg tremor occurred in patients with longer disease duration) (Poston et al. 2009). From a functional and clinical-care standpoint, however, kinetic leg tremor is not a major clinical feature of ET (Poston et al. 2009).

Despite the fact that ET is a progressive disorder (Critchley 1949; Louis et al. 2003a, b, c, d), longitudinal studies are scant. In general, the amplitude of the kinetic tremor increases over time (i.e., the tremor in ET progressively worsens) (Critchley 1949; Louis et al. 2003a, b, c, d; Putzke et al. 2006), with recent estimates indicating a median annual increase in tremor severity of approximately 2.0% (Louis et al. 2011a, b, c, d), although patients differ with respect to the rate of change, with some subgroups (e.g., older onset ET) exhibiting more rapid rates of decline (Louis et al. 2000, 2009a, b, c, d, e, f). Both rest tremor (Cohen et al. 2003) and intention tremor (Leegwater-Kim et al. 2006) are associated with disease of longer duration, indicating that both the severity of kinetic tremor and the complexity of tremor phenomenology seem to increase with more longstanding disease.

It is well known that patients with ET can later develop Parkinson's disease (Yahr et al. 2003; Chaudhuri et al. 2005; Shahed and Jankovic 2007; Minen and Louis 2008). Indeed, family studies have shown an increased co-occurrence of the two diseases in the same families above that expected by chance alone (Louis et al. 2003a, b, c, d; Rocca et al. 2007), and case–control studies have shown an increased co-occurrence of the two disorders in the same individuals above that expected by chance alone, with increased odds being at least five times (Tan et al. 2008). A prospective analysis has similarly indicated that patients with ET have a four- to

fivefold increased risk of developing incident Parkinson's disease (Benito-Leon et al. 2008a, b).

The severity of tremor in ET may range from mild and asymptomatic (e.g., cases seen in population settings) to more severe cases seen in treatment settings (Louis et al. 1998a, b, c, 2001a, b, c, d). More than 90% of the patients who come to medical attention report disability (Louis et al. 2001a, b, c, d), and severely affected patients may be unable to feed or dress themselves (Critchley 1949). Between 15% and 25% of patients are forced to retire prematurely, and 60% choose not to apply for a job or promotion because of uncontrollable shaking (Rautakorpi 1978; Bain et al. 1994). Far from being benign, most patients with this disorder must make adjustments in the way they perform their daily activities. Even among community-dwelling patients, the majority (73%) report disability, with most experiencing this in multiple functional domains (Louis et al. 2001a, b, c, d). Moreover, studies have demonstrated that morale is lower in these community-dwelling patients, further underscoring the effect of tremor on their quality of life (Louis et al. 2008a, b, c, d, e, f).

As noted above, while the sine qua non of ET is the kinetic tremor of the arms, tremor phenomenology is quite varied and complex. Kinetic tremor generally worsens over time and layered on top of that tremor patients may experience the progressive addition of tremors that occur under different conditions (e.g., at rest, with intention) and in different bodily regions (e.g., jaw, head) (Louis et al. 2013d). In addition, many other clinical features aside from tremor are now appreciated (Louis 2005a, b; Benito-Leon and Louis 2006, 2007). These features may be subdivided into motor features vs. nonmotor features.

A number of motor features aside from tremor have been described in ET patients. Thus, in a growing number of studies (Louis et al. 2010a, b; Rao et al. 2011; Singer et al. 1994; Deuschl et al. 2000; Stolze et al. 2001; Kronenbuerger et al. 2009; Rao et al. 2014; Rao and Louis 2019) postural instability and mild to moderate ataxic gait, beyond that seen in normal aging, have been demonstrated in patients with ET. In some patients, this may reach moderate levels of severity (Louis et al. 2013c). Lower balance confidence and increased falls may be functional accompaniers (Rao et al. 2014). In addition, subtle eye movement abnormalities have also been observed in patients with ET (Helmchen et al. 2003; Gitchel et al. 2013; Wojcik-Pedziwiatr et al. 2016). These types of studies further support the notion that there is cerebellar dysfunction in this disease.

The presence of a variety of nonmotor features, including specific personality traits (Chatterjee et al. 2004; Lorenz et al. 2006; Thenganatt and Louis 2012), anxiety (Tan et al. 2005a, b), depressive symptoms (Louis et al. 2001a, b, c, d, 2007a, b; Dogu et al. 2005; Miller et al. 2007) and social phobia (Schneier et al. 2001), has gained widespread recognition (Findley 2004; Louis 2005a, b; Lee et al. 2015). In one study (Louis et al. 2007a, b), depressive symptoms were more common in ET cases than controls, and these symptoms preceded the onset of the motor manifestations, suggesting that they could be a primary manifestation of the disease. ET is also associated with cognitive features, which can vary in severity (Louis and Cosentino 2019). Mild cognitive changes (esp. executive dysfunction) have been

documented in many studies (Gasparini et al. 2001; Lombardi et al. 2001; Vermilion et al. 2001; Duane and Vermilion 2002; Lacritz et al. 2002; Benito-Leon et al. 2006a, b), and increased odds or risk of dementia has been demonstrated in two population-based studies (Benito-Leon et al. 2006a, b; Bermejo-Pareja et al. 2007). These data suggest that, as in several other progressive movement disorders (Parkinson's disease and Huntington's disease), cognitive-neuropsychological features are a part of this disease in addition to involuntary movements. The mechanistic basis for these cognitive disturbances in ET is not clear, although the cerebellum has been implicated in the milder deficits (Troster et al. 2002; Louis and Cosentino 2019). The associated dementia in ET is likely the result of other degenerative pathologies (e.g., Alzheimer's type or other) (Louis and Cosentino 2019; Kim et al. 2021). There is a sizable literature demonstrating that neurodegenerative diseases may be associated with one another, with the notion being that the development of one such disorder is a marker of a biological propensity/vulnerability for the development of others (Louis and Okun 2011). For example, the co-occurrence of amyotrophic lateral sclerosis with frontotemporal dementia within individuals and within families is well documented (Zago et al. 2011), and it is well established that a high proportion of Parkinson's disease patients with dementia have concurrent AD (Shi et al. 2010).

In summary, the traditional clinical view of ET as no more than an isolated nonspecific action tremor is being challenged by a view of ET as a disease entity in which the tremor phenomenology on the one hand is manifold (i.e., kinetic tremor, postural tremor, intention tremor, rest tremor, arm tremor, leg tremor, cranial tremors) but on the other hand follows certain distinctive, definable patterns (e.g., rest tremor tends to occur as a late feature, women are more likely to develop head tremor, later age of onset is associated with more rapidly progression). Along with the tremors, gait abnormalities and other signs of cerebellar dysfunction as well cognitive-psychiatric features characterize this disease as well. The disease itself increases the likelihood of developing other degenerative diseases of the central nervous system, including Parkinson's and Alzheimer's disease, so that ET itself may be viewed on some level as a risk factor for these other conditions.

9.2.5 Diagnosis

The diagnostic approach to patients with ET should begin with a medical history and a physical examination. In select situations, laboratory tests may also be ordered (Louis 2001a, b, 2016).

The diagnosis of ET is still made by history and physical examination. Thus, there is no test to validate a clinical diagnosis of ET. To aid in the diagnosis, several clinical criteria have been proposed, including those by the Consensus Statement on Tremor by the Movement Disorder Society (Deuschl et al. 1998), which were modified slightly by the Tremor Research Group (Elble 2000) and modified more recently by a revised Consensus Statement (Bhatia et al. 2018). The Washington Heights-Inwood Genetic Study of ET criteria is similarly useful, particularly for

genetic and epidemiological studies, in which the distinction between ET and enhanced physiological tremor is essential (Louis et al. 1997a, b).

During the history, the clinician should collect information on the localization of tremor, the age of onset, and the progression of tremor over time. Caffeinated beverages, cigarettes, and numerous medications (e.g., bronchodilators, lithium, methylphenidate, prednisone, pseudoephedrine, theophylline, and valproic acid) can exacerbate enhanced physiological tremor, which can resemble ET. Thus, taking a complete inventory of current medications and use of caffeine and tobacco products is suggested. Patients with tremor due to other disorders such as hyperthyroidism, Parkinson's disease, or Wilson's disease frequently have concomitant symptoms that lead the clinician to these diagnoses (Louis 2001a, b, 2005a, b; Benito-Leon and Louis 2007). For example, patients with hyperthyroidism may complain of palpitations, hyperactivity, increased sweating, heat hypersensitivity, fatigue, increased appetite, weight loss, insomnia, weakness, frequent bowel movements, or hypomenorrhea (Nayak and Hodak 2007; Nygaard 2007). Patients with Parkinson's disease often complain of limb stiffness and rest tremor. Psychiatric manifestations often accompany Wilson's disease; these may include psychosis or more subtle signs, such as difficulties with school work or job performance, personality changes, emotionality, loss of sexual inhibition, insomnia, and aggressiveness (Pfeiffer 2007; Mak and Lam 2008).

During the neurological examination, the clinician should carefully evaluate the characteristics of the movements. To begin, the clinician should determine that the movement is indeed a tremor and not some other type of involuntary movement. Tremor, by definition, is a rhythmic and oscillatory movement. "Rhythmic" indicates that it is regularly recurrent and "oscillatory" means that the movement alternates around a central plane. Signs of systemic diseases should also be noted. For example, patients with hyperthyroidism may have warm, moist skin, tachycardia, widened pulse pressure, and atrial fibrillation (Louis 2001a, b, 2011).

It is important to distinguish ET patients from those with Parkinson's disease. While patients with Parkinson's disease often manifest a mild to moderate postural tremor or kinetic tremor (Koller et al. 1989; Jankovic et al. 1999), rest tremor is also present in approximately 85% (Louis et al. 1997a, b) of patients with autopsy-proven Parkinson's disease. While rest tremor can accompany ET, it usually occurs in the setting of severe kinetic tremor of long duration and generally involves the arm and not the leg. While mild cogwheeling can occur in ET, it does not occur in the setting of increased tone, as is seen in Parkinson's disease. Other features of Parkinson's disease that generally do not occur in patients with ET are hemi-body involvement (e.g., ipsilateral arm and leg tremor) and bradykinesia. The postural tremor of ET also tends to involve wrist flexion and extension whereas in Parkinson's disease, wrist rotation often occurs (Louis 2011; Sternberg et al. 2013).

It is also important to distinguish ET from enhanced physiological tremor. Enhanced physiological tremor is an 8–12 Hz postural and kinetic tremor that may occur in the limbs and voice (but not the head) and may be further exacerbated by emotion and by medications (Elble 2003). While the amplitude of kinetic tremor in ET is generally higher and the frequency lower than that of enhanced physiological

tremor, mild ET and severe enhanced physiological tremor may have similar tremor amplitudes (Elble 2003). In this setting, quantitative computerized tremor analysis, with accelerometers attached to the arms, which is available at some tertiary care centers, may guide the clinician; inertial loading of the limbs leads to a reduction in tremor frequency in ET tremor but not in the predominant, peripherally generated component of enhanced physiological tremor (Louis 2011).

Patients with dystonic tremor are often misdiagnosed as having ET (Jain et al. 2006). Dystonic tremor may occur in the limbs or neck. Dystonic neck tremor is often neither rhythmic nor oscillatory and it may be accompanied by dystonic posturing of the neck and hypertrophy of neck muscles (esp. the sternocleidomastoid). Also, it tends to continue when the patient is supine, in contrast to the head tremor of ET, which generally resolves in the supine position. Dystonic hand tremor is similarly often neither rhythmic nor oscillatory and it may be accompanied by dystonic posturing of the hands. This is often best evidenced by asking the patient to hold their arms extended in front of their body for 30–60 s. In this setting, dystonic thumb flexion and other dystonic postures (flexion of the wrist with hyperextension of the fingers [i.e., "spooning"]) may be evident (Louis 2011). This being said, there is considerable recognition now that patients with ET may manifest some degree of dystonic features on neurological examination (Bhatia et al. 2018).

The final step in the evaluation of the patient who is suspected of having ET is the laboratory evaluation. Thus, if symptoms or signs of hyperthyroidism are present, then thyroid function tests should be performed. In younger patients (i.e., under 40 years old) with no family history of ET or dystonia, the possibility of Wilson disease should be explored with a serum ceruloplasmin, which may be reduced; this is usually not an issue in older patients. Striatal dopamine transporter imaging may be useful in distinguishing patients with ET from Parkinson's disease. Values in Parkinson's disease patients are lower than those of controls; while some ET patients may have reduced values, in general, their values are similar to those of controls (Antonini et al. 2001), but such testing is not often necessary as the diagnosis of Parkinson's disease can generally be made with a careful history and physical examination (Louis 2011).

9.3 Other Kinetic Tremors

As noted above, ET is the most common pathological form of kinetic tremor. Other kinetic tremors include dystonic tremor and orthostatic tremor, both of which are the topics of separate chapters in this book. Hence, the remainder of this discussion will focus on those forms of kinetic tremor that are not covered in separate chapters. These include drug-induced kinetic tremor, the kinetic tremors that may be associated with various disease entities (Wilson's disease, fragile X tremor ataxia syndrome, peripheral neuropathy, Parkinson's disease), primary writing tremor, and rubral tremor.

9.3.1 Drug-Induced Kinetic Tremor

As noted above, a variety of medications may produce kinetic tremor, which can range in severity from mild to marked (Deuschl et al. 1998; Morgan and Sethi 2005). These medications include but are not limited to bronchodilators, lithium, methylphenidate, prednisone, pseudoephedrine, theophylline, valproic acid, tricyclic antidepressants, and calcineurin inhibitors (e.g., tacrolimus). Among the more commonly reported of these tremors is lithium-induced kinetic tremor (Gelenberg and Jefferson 1995; Morgan and Sethi 2005).

The mechanism for drug-induced kinetic tremor is not fully established, although it is believed to be a form of enhanced physiological tremor (Deuschl et al. 1998). Thus, an increase in the gain of the muscle receptors and spinal reflex loops is thought to lead to an enhancement of oscillations in peripheral physiological tremor (Foley et al. 1967; Homberg et al. 1987; Raethjen et al. 2001). Yet there is also some evidence that some forms of drug-induced kinetic tremor may also be mediated through central mechanisms (Raethjen et al. 2001; Morgan et al. 2017). Lithium salts may have a genuine cerebellar toxicity (Grignon and Bruguereolle 1996).

The following features help to distinguish drug-induced kinetic tremor from other forms of tremor (1) By history, there should be a link between the onset of the tremor and the use of a medication that is presumed to be causing the tremor, with the onset of tremor following the use of the medication. The onset may not be immediate, but may occur gradually over several months. (2) There may be a dose–response relation such that higher doses of medication are associated with increased tremor amplitude. (3) Discontinuing the medication should result in the complete resolution of tremor. (4) While limb tremor may be present, head tremor should not be a feature of drug-induced action tremor. (5) The tremor should not progressively worsen, in contrast to the tremor of ET or Parkinson's disease (Morgan and Sethi 2005).

9.3.2 Kinetic Tremor of Wilson's Disease

Patients with Wilson's disease may present with a wide range of movement disorders, and tremor is among these (Lorincz 2010; Oder et al. 1991; Stremmel et al. 1991; Walshe and Yealland 1992; Frucht et al. 1998; Brewer 2005; Machado et al. 2006; Soltanzadeh et al. 2007), ranking among the eight major complaints reported by neurological patients with this disease (Walshe and Yealland 1992). These tremors are usually associated with other neurological signs, although there are rare reports of isolated tremor and even rarer reports of isolated action tremor (Frucht et al. 1998; Soltanzadeh et al. 2007). Most of the large case series focus on the broad panoply of neurological signs, and a focused and detailed characterization of the tremor phenomenology is generally lacking. Furthermore, the phenomenology does seem to be considerably varied. Thus, across patients, a wide range of tremors

may accompany Wilson's disease, and these may include kinetic tremor as well as resting tremor, postural and intention tremors, tremors that are either symmetric or asymmetric, those that are low amplitude and high amplitude, and those that are intermittent and progressive (Lorincz 2010; Starosta-Rubinstein et al. 1987). Within patients, a variety of different tremors may be present as well (Lorincz 2010; Soltanzadeh et al. 2007). According to one series, 32% of patients exhibited tremor at the time of their first neurological evaluation at a tertiary care center (Starosta-Rubinstein et al. 1987), although other data suggest that this proportion is higher (55%) (Samanci et al. 2021); in another retrospective review of patients seen in a tertiary referral center, 60% of patients exhibited tremor at some point (Machado et al. 2006). Tremor most commonly occurs in the hands, with 82% of patients having hand tremor according to one report (Saito 1987). Although postural tremor has been reported to be the most common type of tremor (Oder et al. 1991; Machado et al. 2006; Czlonkowska et al. 2018), the classic wing-beat tremor, present on abduction of the shoulder and flexion of the elbow, is well described, although it is not the most commonly observed type of tremor (Lorincz 2010; Starosta-Rubinstein et al. 1987). Most patients present well before the age of 40, and the laboratory work-up may reveal low serum ceruloplasmin, abnormal brain MRI (lesions in the basal ganglia), high 24 h urine copper, abnormal slit lamp examination (Kayser Fleischer rings), elevated liver function tests, or abnormal liver biopsy (Walshe and Yealland 1992).

9.3.3 Kinetic Tremor of Fragile X Tremor Ataxia Syndrome

Fragile X-associated tremor/ataxia syndrome (FXTAS) is an inherited degenerative disorder that primarily affects older men and is associated with an array of neurological symptoms and signs (Leehey 2009; Salcedo-Arellano et al. 2020). The syndrome is caused by a CGG repeat expansion in the premutation range (i.e., 55–200 repeats) in the 5′ noncoding region of the fragile X mental retardation 1 (*FMR1*) gene. Classically, FXTAS patients are men in their 60s who develop intention tremor, progressive cerebellar ataxia, parkinsonism, and cognitive decline (Leehey 2009). Almost all affected persons develop problematic cerebellar gait ataxia as the disorder progresses (Leehey 2009).

Tremor is one of the earliest signs (Leehey et al. 2007), and in one series, 70% of FXTAS patients developed intention tremor and 10% had isolated rest tremor (Leehey 2009). In a series of 50 patients, there was tremor in 70% (Juncos et al. 2011). The tremor phenomenology in FXTAS has variably been described as "action" or "intention" tremor (Berry-Kravis et al. 2007; Loesch et al. 2007; Aguilar et al. 2008; Leehey 2009; Juncos et al. 2011; Salcedo-Arellano et al. 2020) and many patients likely have mixed phenomenology (i.e., kinetic tremor with an intentional component) (Berry-Kravis et al. 2007;). Other authors have described the presence of postural tremor in these patients (Berry-Kravis et al. 2007; Davous et al. 2007; Loesch et al. 2007), again pointing to what is likely a mixed tremor that varies

with position (Jacquemont et al. 2004). Voice tremor has been described as well (Juncos et al. 2011). The tremor may vary in severity from mild and asymptomatic to severe and disabling (Leehey 2009); one retrospective cohort study reported that tremor becomes considerably disabling within 13 years of onset of motor symptoms (Leehey et al. 2007). It has been noted that affected persons usually have definite tremor reduction with the use of medications that are commonly prescribed in the treatment of ET (Leehey 2009), and an occasional patient will have isolated action tremor that resembles that seen in patients with ET (Peters et al. 2006; Leehey 2009), although as noted above, most patients have a constellation of neurological signs in addition to tremor.

9.3.4 Kinetic Tremor in Patients with Peripheral Neuropathy

Several types of acquired and familial neuropathies may be associated with postural and kinetic tremors of the arms (Kamei et al. 1993; Pedersen et al. 1997; Saverino et al. 2001; Budak et al. 2005; Alonso-Navarro et al. 2008) and in the case of some neuropathies (e.g., IgM demyelinating paraproteinemic neuropathy), up to 90% of patients are reported to have such tremor (Bain et al. 1996). Neuropathic tremor can generally be diagnosed based on history and physical examination. By history, patients with this type of tremor have a coexisting peripheral neuropathy of the same limbs that are tremulous (i.e., the tremor occurs in limbs that are affected by the neuropathy). Also, by history, the neuropathy and the tremor should be temporally linked, with tremor accompanying or following the neuropathy. On examination, a peripheral neuropathy characterized by sensory deficits, weakness, and/or diminished/absent deep tendon reflexes is readily apparent in the tremulous limb(s) (Said et al. 1982; Barbieri et al. 1984; Dalakas et al. 1984; Cardoso and Jankovic 1993; Bain et al. 1996; Budak et al. 2005); some data suggest that the severity of the weakness does not correlate with the severity of the tremor (Dalakas et al. 1984). The tremor is often asymmetric (Saverino et al. 2001; Budak et al. 2005). Tremor may disappear if weakness becomes so severe that the muscle is no longer contracting or conversely if muscle strength returns to normal. As the etiologies of neuropathic tremor are diverse, the underlying mechanisms are likely to be equally diverse. Even within the category of tremors associated with demyelinating peripheral neuropathy, data indicate that one group of patients has tremor that is modified by inertial weighting while other patients have tremor that is less affected by such weighting (Pedersen et al. 1997). The latter suggests that there may be a central component that underlies these demyelinating peripheral neuropathic tremors, and some have suggested that this involves an abnormal afferent sensory input from the periphery to the thalamus followed by changes in cerebellar output. Support for this notion comes from the observation that some patients with such neuropathies respond to deep brain stimulation surgery (Ruzicka et al. 2003; Bayreuther et al. 2009; Breit et al. 2009; McMaster et al. 2009).

9.3.5 Kinetic Tremor in Parkinson's Disease

Although rest tremor is one of the hallmark features of Parkinson's disease, a large proportion of patients also have postural and/or kinetic tremors of the arms (Lance et al. 1963; Hoehn and Yahr 1967; Koller et al. 1989; Rajput et al. 1991a, b; Brooks et al. 1992; Louis et al. 1997a, b, 2001a, b, c, d; Jankovic et al. 1999; Forssberg et al. 2000), with prevalence in some studies >90% (Mailankody et al. 2007). The kinetic tremor is often but not always more severe on the side with more severe parkinsonism, and may range from mild to severe. Sometimes the postural and kinetic tremor have a re-emergent quality; this so-called "re-emergent tremor" surfaces after a latency of one or several seconds, has a frequency that is similar to that of the rest tremor in Parkinson's disease, and often attains amplitudes greater than that seen in patients with ET (Jankovic et al. 1999). The tremor is often asymmetric and tends to increase in severity (i.e., crescendo) with sustained posture or during the course of repetitive movements during which much of the limb is immobile (e.g., while pouring water between two cups, during which much of the movement is proximal rather than distal). Re-emergent tremor may at times occur in patients who do not have rest tremor (Louis et al. 2008a, b, c, d, e, f).

9.3.6 Primary Writing Tremor

This is a hand tremor that occurs primarily or only during writing but not initially during other tasks that involve the active hand (Bain et al. 1995; Deuschl et al. 1998). The tremor may involve other activities with the passage of time (e.g., eating and drinking, brushing teeth, shaving) (Ondo and Satija 2012). The tremor has a similar frequency to that seen in patients with ET (i.e., between 4 and 8 Hz) and in 30–50% of cases is relieved by ethanol consumption (Bain et al. 1995). In one study, patients were subdivided into those having type A and type B primary writing tremor, depending on whether tremor appeared during writing (i.e., type A or "task induced tremor") or while adopting the hand position used in writing (i.e., type B or "positionally sensitive tremor") (Bain et al. 1995). The mechanisms that underlie primary writing tremor are unclear and it is debated whether it represents a variant of ET or a variant of dystonia (Bain 2011; Kachi et al. 1985; Koller and Martyn 1986; Cohen et al. 1987; Elble et al. 1990; Deuschl et al. 1998; Datta et al. 2021), and in some families, all three conditions may be present (Cohen et al. 1987).

9.3.7 Rubral Tremor

This type of tremor has also been referred to as "Holmes' tremor" or "midbrain tremor" (Kiriyama et al. 2011; Deuschl et al. 1998; Yang et al. 2005; Liou and

Shih 2006). When occurring in the setting of a stroke, the tremor may arise after a latency of months to years; the tremor may occur in a variety of other settings (e.g., in the setting of a brain tumor or slowly expanding vascular lesion). The tremor is generally unilateral and has three components: rest, postural, and kinetic/intentional with the severity being such that kinetic > postural > rest. The tremor is usually severe and disabling, often rendering the affected limb functionally useless. Patients may also have other neurological signs (e.g., dystonia, ataxia). On brain imaging, a lesion is often but not always present in the pontine-midbrain region, affecting cerebellar outflow tracts and dopaminergic nigrostriatal fibers (Samie et al. 1990; Goto and Yamada 2004). There are reports of lesions occurring elsewhere (e.g., thalamus) (Mossuto-Agatiello et al. 1993; Tan et al. 2001), which is one of the motivations for referring to the tremor as "Holmes' tremor" rather than "rubral tremor" (Deuschl et al. 1998).

9.4 Kinetic Tremor: Conclusions

Kinetic tremors are extremely common. Indeed, physiological or enhanced physiological tremor is the most common form of normal tremor (Elble 1998a, b, 2003; Louis et al. 1998a, b, c) present in most normal individuals, and ET, the most common pathological form of kinetic tremor, occurs in 4% of individuals over the age of 40 and as many as 20% of the oldest old (Louis and Ferreira 2010; Louis and McCreary 2021). A wide range of other forms of kinetic tremor were discussed in this chapter. Hence, these tremors are commonly seen in a variety of clinical practice settings. A basic understanding of their underlying mechanisms and a detailed understanding of their clinical features will aid in the diagnosis and treatment of these disorders.

References

Agren R, Awad A, et al. Voxel-based morphometry of cerebellar lobules in essential tremor. Front Aging Neurosci. 2021;13:667854.

Aguilar D, Sigford KE, et al. A quantitative assessment of tremor and ataxia in FMR1 premutation carriers using CATSYS. Am J Med Genet A. 2008;146A(5):629–35.

Aiyesimoju AB, Osuntokun BO, et al. Hereditary neurodegenerative disorders in Nigerian Africans. Neurology. 1984;34(3):361–2.

Alonso-Navarro H, Fernandez-Diaz A, et al. Tremor associated with chronic inflammatory demyelinating peripheral neuropathy: treatment with pregabalin. Clin Neuropharmacol. 2008;31(4):241–4.

Antonini A, Moresco RM, et al. The status of dopamine nerve terminals in Parkinson's disease and essential tremor: a PET study with the tracer [11-C]FE-CIT. Neurol Sci. 2001;22(1):47–8.

Ashenhurst EM. The nature of essential tremor. Can Med Assoc J. 1973;109(9):876–8.

Avanzino L, Bove M, et al. Cerebellar involvement in timing accuracy of rhythmic finger movements in essential tremor. Eur J Neurosci. 2009;30(10):1971–9.

Axelrad JE, Louis ED, et al. Reduced purkinje cell number in essential tremor: a postmortem study. Arch Neurol. 2008;65(1):101–7.
Azar J, Yousef MH, et al. Mercury and Alzheimer's disease: a look at the links and evidence. Metab Brain Dis. 2021;36:3610374.
Babij R, Lee M, et al. Purkinje cell axonal anatomy: quantifying morphometric changes in essential tremor versus control brains. Brain. 2013;136:3051–61.
Bain PG. Task-specific tremor. Handb Clin Neurol. 2011;100:711–8.
Bain PG, Findley LJ, et al. A study of hereditary essential tremor. Brain. 1994;117(Pt 4):805–24.
Bain PG, Findley LJ, et al. Primary writing tremor. Brain. 1995;118(Pt 6):1461–72.
Bain PG, Britton TC, et al. Tremor associated with benign IgM paraproteinaemic neuropathy. Brain. 1996;119(Pt 3):789–99.
Baldereschi M, Inzitari M, et al. Pesticide exposure might be a strong risk factor for Parkinson's disease. Ann Neurol. 2008;63(1):128.
Barbieri F, Filla A, et al. Evidence that Charcot-Marie-tooth disease with tremor coincides with the Roussy-Levy syndrome. Can J Neurol Sci. 1984;11(4 Suppl):534–40.
Bares M, Lungu OV, et al. Predictive motor timing performance dissociates between early diseases of the cerebellum and Parkinson's disease. Cerebellum. 2010;9(1):124–35.
Bayreuther C, Delmont E, et al. Deep brain stimulation of the ventral intermediate thalamic nucleus for severe tremor in anti-MAG neuropathy. Mov Disord. 2009;24(14):2157–8.
Benabid AL, Pollak P, et al. Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. Acta Neurochir Suppl (Wien). 1993;58:39–44.
Benito-Leon J, Louis ED. Essential tremor: emerging views of a common disorder. Nat Clin Pract Neurol. 2006;2(12):666–78.
Benito-Leon J, Louis ED. Clinical update: diagnosis and treatment of essential tremor. Lancet. 2007;369(9568):1152–4.
Benito-Leon J, Bermejo-Pareja F, et al. Incidence of essential tremor in three elderly populations of Central Spain. Neurology. 2005;64(10):1721–5.
Benito-Leon J, Louis ED, et al. Elderly-onset essential tremor is associated with dementia. Neurology. 2006a;66(10):1500–5.
Benito-Leon J, Louis ED, et al. Population-based case-control study of cognitive function in essential tremor. Neurology. 2006b;66(1):69–74.
Benito-Leon J, Louis ED, Bermejo-Pareja F. Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population-based study. Neurology. 2008a;70 Suppl 1:A191.
Benito-Leon J, Louis ED, et al. Population-based case-control study of cigarette smoking and essential tremor. Mov Disord. 2008b;23(2):246–52.
Benito-Leon J, Alvarez-Linera J, et al. Brain structural changes in essential tremor: voxel-based morphometry at 3-tesla. J Neurol Sci. 2009;287(1–2):138–42.
Bermejo-Pareja F. Essential tremor–a neurodegenerative disorder associated with cognitive defects? Nat Rev Neurol. 2011;7(5):273–82.
Bermejo-Pareja F, Louis ED, et al. Risk of incident dementia in essential tremor: a population-based study. Mov Disord. 2007;22(11):1573–80.
Berry-Kravis E, Abrams L, et al. Fragile X-associated tremor/ataxia syndrome: clinical features, genetics, and testing guidelines. Mov Disord. 2007;22(14):2018–30. Quiz 2140
Bhatia KP, Bain P, et al. Consensus statement on the classification of tremors. From the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33:75–87.
Breit S, Wachter T, et al. Effective thalamic deep brain stimulation for neuropathic tremor in a patient with severe demyelinating neuropathy. J Neurol Neurosurg Psychiatry. 2009;80(2):235–6.
Brennan KC, Jurewicz EC, et al. Is essential tremor predominantly a kinetic or a postural tremor? A clinical and electrophysiological study. Mov Disord. 2002;17(2):313–6.
Brewer GJ. Neurologically presenting Wilson's disease: epidemiology, pathophysiology and treatment. CNS Drugs. 2005;19(3):185–92.

Brin MF, Koller W. Epidemiology and genetics of essential tremor. Mov Disord. 1998;13 Suppl 3:55–63.
Brooks DJ, Playford ED, et al. Isolated tremor and disruption of the nigrostriatal dopaminergic system: an 18 F-dopa PET study. Neurology. 1992;42(8):1554–60.
Bucher SF, Seelos KC, et al. Activation mapping in essential tremor with functional magnetic resonance imaging. Ann Neurol. 1997;41(1):32–40.
Budak F, Alemdar M, et al. Tremor in idiopathic distal acquired demyelinating symmetric neuropathy. Mov Disord. 2005;20(11):1529–30.
Buzsaki G, Draguhn A. Neuronal oscillations in cortical networks. Science. 2004;304(5679):1926–9.
Cardoso FE, Jankovic J. Hereditary motor-sensory neuropathy and movement disorders. Muscle Nerve. 1993;16(9):904–10.
Cerasa A, Messina D, et al. Cerebellar atrophy in essential tremor using an automated segmentation method. AJNR Am J Neuroradiol. 2009;30(6):1240–3.
Chatterjee A, Jurewicz EC, et al. Personality in essential tremor: further evidence of non-motor manifestations of the disease. J Neurol Neurosurg Psychiatry. 2004;75(7):958–61.
Chaudhuri KR, Buxton-Thomas M, et al. Long duration asymmetrical postural tremor is likely to predict development of Parkinson's disease and not essential tremor: clinical follow up study of 13 cases. J Neurol Neurosurg Psychiatry. 2005;76(1):115–7.
Choe M, Cortes E, et al. Purkinje cell loss in essential tremor: random sampling quantification and nearest neighbor analysis. Mov Disord. 2016;31:393–401.
Clark LN, Louis ED. Challenges in essential tremor genetics. Rev Neurol. 2015;171:466–74.
Cohen LG, Hallett M, et al. A single family with writer's cramp, essential tremor, and primary writing tremor. Mov Disord. 1987;2(2):109–16.
Cohen O, Pullman S, et al. Rest tremor in patients with essential tremor: prevalence, clinical correlates, and electrophysiologic characteristics. Arch Neurol. 2003;60(3):405–10.
Colebatch JG, Findley LJ, et al. Preliminary report: activation of the cerebellum in essential tremor. Lancet. 1990;336(8722):1028–30.
Critchley M. Observations of essential (heredofamilial) tremor. Brain. 1949;72:113–39.
Critchley E. Clinical manifestations of essential tremor. J Neurol Neurosurg Psychiatry. 1972;35(3):365–72.
Czlonkowska A, Litwin T, et al. Characteristics of a newly diagnosed polish cohort of patients with neurological manifestatios of Wilson disease evaluated with the united Wilson's disease rating scale. BMC Neurol. 2018;18:34.
Dalakas MC, Teravainen H, et al. Tremor as a feature of chronic relapsing and dysgammaglobulinemic polyneuropathies. Incidence and management. Arch Neurol. 1984;41(7):711–4.
Das SK, Banerjee TK, et al. Prevalence of essential tremor in the city of Kolkata, India: a house-to-house survey. Eur J Neurol. 2009;16(7):801–7.
Datta A, Batra N, Pandey S. Primary writing tremor. Ann Indian Acad Neurol. 2021;24:319–26.
Davous P, Juntas Morales R, et al. Fragile X premutation presenting as postural tremor and ataxia (FXTAS syndrome). Rev Neurol (Paris). 2007;163(11):1091–5.
DeLong MR. Possible involvement of central pacemakers in clinical disorders of movement. Fed Proc. 1978;37(8):2171–5.
Deuschl G, Elble RJ. The pathophysiology of essential tremor. Neurology. 2000;54(11 Suppl 4):S14–20.
Deuschl G, Elble R. Essential tremor – neurodegenerative or nondegenerative disease towards a working definition of ET. Mov Disord. 2009;24(14):2033–41.
Deuschl G, Bain P, et al. Consensus statement of the Movement Disorder Society on tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13 Suppl 3:2–23.
Deuschl G, Wenzelburger R, et al. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. Brain. 2000;123(Pt 8):1568–80.
Dick FD. Parkinson's disease and pesticide exposures. Br Med Bull. 2006;79–80:219–31.
Dogu O, Sevim S, et al. Prevalence of essential tremor: door-to-door neurologic exams in Mersin Province, Turkey. Neurology. 2003;61(12):1804–6.

Dogu O, Louis ED, et al. Clinical characteristics of essential tremor in Mersin, Turkey–a population-based door-to-door study. J Neurol. 2005;252(5):570–4.
Dogu O, Louis ED, et al. Elevated blood lead concentrations in essential tremor: a case-control study in Mersin, Turkey. Environ Health Perspect. 2007;115(11):1564–8.
Duane DD, Vermilion KJ. Cognitive deficits in patients with essential tremor. Neurology. 2002;58(11):1706. author reply 1706
Dupuis MJ, Delwaide PJ, et al. Homolateral disappearance of essential tremor after cerebellar stroke. Mov Disord. 1989;4(2):183–7.
Ekouzi A, Kattah JC, et al. Hypertrophic olivary degeneration does not reduce essential tremor. Mov Disord Clin Pract. 2016;3:209–2011.
Elble RJ. Animal models of action tremor. Mov Disord. 1998a;13 Suppl 3:35–9.
Elble RJ. Tremor in ostensibly normal elderly people. Mov Disord. 1998b;13(3):457–64.
Elble RJ. Diagnostic criteria for essential tremor and differential diagnosis. Neurology. 2000;54(11 Suppl 4):S2–6.
Elble RJ. Essential tremor is a monosymptomatic disorder. Mov Disord. 2002;17(4):633–7.
Elble RJ. Characteristics of physiologic tremor in young and elderly adults. Clin Neurophysiol. 2003;114(4):624–35.
Elble RJ, Moody C, et al. Primary writing tremor. A form of focal dystonia? Mov Disord. 1990;5(2):118–26.
Elble RJ, Higgins C, et al. Longitudinal study of essential tremor. Neurology. 1992;42(2):441–3.
Elble RJ, Higgins C, et al. Factors influencing the amplitude and frequency of essential tremor. Mov Disord. 1994;9(6):589–96.
Erickson-Davis CR, Faust PL, et al. "Hairy baskets" associated with degenerative Purkinje cell changes in essential tremor. J Neuropathol Exp Neurol. 2010;69(3):262–71.
Farkas Z, Szirmai I, et al. Impaired rhythm generation in essential tremor. Mov Disord. 2006;21(8):1196–9.
Ferrara J, Jankovic J. Epidemiology and management of essential tremor in children. Paediatr Drugs. 2009;11(5):293–307.
Findley LJ. Expanding clinical dimensions of essential tremor. J Neurol Neurosurg Psychiatry. 2004;75(7):948–9.
Foley TH, Marsden CD, et al. Evidence for a direct peripheral effect of adrenaline on physiological tremor in man. J Physiol. 1967;189(2):65P–6P.
Forssberg H, Ingvarsson PE, et al. Action tremor during object manipulation in Parkinson's disease. Mov Disord. 2000;15(2):244–54.
Frucht S, Sun D, et al. Arm tremor secondary to Wilson's disease. Mov Disord. 1998;13(2):351–3.
Galazzo IB, Magrinelli F. Voxel-based morphometry and task functional magnetic resonance imaging in essential tremor: evidence for a disrupted brain network. Sci Rep. 2020;10(1):15061.
Gasparini M, Bonifati V, et al. Frontal lobe dysfunction in essential tremor: a preliminary study. J Neurol. 2001;248(5):399–402.
Gelenberg AJ, Jefferson JW. Lithium tremor. J Clin Psychiatry. 1995;56(7):283–7.
Gitchel GT, Wetzel PA, et al. Slowed saccades and increased square wave jerks in essential tremor. Tremor Other Hyperkinet Mov (N Y). 2013;3.
Gorell JM, Johnson CC, et al. Occupational exposures to metals as risk factors for Parkinson's disease. Neurology. 1997;48(3):650–8.
Gorell JM, Johnson CC, et al. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology. 1998;50(5):1346–50.
Gorell JM, Johnson CC, et al. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. Neurotoxicology. 1999;20(2–3):239–47.
Goto S, Yamada K. Combination of thalamic Vim stimulation and GPi pallidotomy synergistically abolishes Holmes' tremor. J Neurol Neurosurg Psychiatry. 2004;75(8):1203–4.
Grignon S, Bruguereolle B. Cerebellar lithium toxicity: a review of recent literature and tentative pathophysiology. Therapie. 1996;51:101–6.
Guler S, Caylan A, et al. The prevalence of essential tremor in Edirne and its counties accompanied comorbid conditions. Neurol Res. 2019;41:847–56.

Haerer AF, Anderson DW, et al. Prevalence of essential tremor. Results from the Copiah County study. Arch Neurol. 1982;39(12):750–1.
Handforth A, Krahl SE. Suppression of harmaline-induced tremor in rats by vagus nerve stimulation. Mov Disord. 2001;16(1):84–8.
Hardesty DE, Maraganore DM, et al. Increased risk of head tremor in women with essential tremor: longitudinal data from the Rochester Epidemiology Project. Mov Disord. 2004;19(5):529–33.
Helmchen C, Hagenow A, et al. Eye movement abnormalities in essential tremor may indicate cerebellar dysfunction. Brain. 2003;126(Pt 6):1319–32.
Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967;17(5):427–42.
Homberg V, Hefter H, et al. Differential effects of changes in mechanical limb properties on physiological and pathological tremor. J Neurol Neurosurg Psychiatry. 1987;50(5):568–79.
Hornabrook RW, Nagurney JT. Essential tremor in Papua, New Guinea. Brain. 1976;99(4):659–72.
Hubble JP, Busenbark KL, et al. Clinical expression of essential tremor: effects of gender and age. Mov Disord. 1997;12(6):969–72.
Inzelberg R, Mazarib A, et al. Essential tremor prevalence is low in Arabic villages in Israel: door-to-door neurological examinations. J Neurol. 2006;253(12):1557–60.
Iorio-Morin YK, et al. Bilateral focused ultrasound thalamotomy for essential tremor (BEST-FUS Phase 2 trial). Mov Disord. 2021;36:2653–62.
Jacquemont S, Farzin F, et al. Aging in individuals with the FMR1 mutation. Am J Ment Retard. 2004;109:154–64.
Jain S, Lo SE, et al. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? Arch Neurol. 2006;63(8):1100–4.
Jankovic J, Schwartz KS, et al. Re-emergent tremor of Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;67(5):646–50.
Jankovic J, Madisetty J, et al. Essential tremor among children. Pediatrics. 2004;114(5):1203–5.
Jenkins IH, Bain PG, et al. A positron emission tomography study of essential tremor: evidence for overactivity of cerebellar connections. Ann Neurol. 1993;34(1):82–90.
Juncos JL, Lazarus JT, et al. New clinical findings in the fragile X-associated tremor ataxia syndrome (FXTAS). Neurogenetics. 2011;12:123–35.
Kachi T, Rothwell JC, et al. Writing tremor: its relationship to benign essential tremor. J Neurol Neurosurg Psychiatry. 1985;48(6):545–50.
Kamei H, Nishimaru K, et al. A case of hereditary motor and sensory neuropathy (HMSN type 2) with bilateral recurrent nerve palsy. Rinsho Shinkeigaku. 1993;33(9):957–60.
Kim SH, Farrell K, et al. Tau isoform profile in essential tremor diverges from other tauopathies. J Neuropathol Exp Neurol. 2021;80:835–43.
Kiriyama T, Hirano M, et al. A case of chemotherapy-responsive paraneoplastic rubral tremor. Clin Neurol Neurosurg. 2011;113(8):693–5.
Klebe S, Stolze H, et al. Influence of alcohol on gait in patients with essential tremor. Neurology. 2005;65(1):96–101.
Klein JC, Lorenz B, et al. Diffusion tensor imaging of white matter involvement in essential tremor. Hum Brain Mapp. 2011;32(6):896–904.
Koller WC, Martyn B. Writing tremor: its relationship to essential tremor. J Neurol Neurosurg Psychiatry. 1986;49(2):220.
Koller WC, Rubino FA. Combined resting-postural tremors. Arch Neurol. 1985;42(7):683–4.
Koller WC, Vetere-Overfield B, et al. Tremors in early Parkinson's disease. Clin Neuropharmacol. 1989;12(4):293–7.
Koller WC, Busenbark K, et al. The relationship of essential tremor to other movement disorders: report on 678 patients. Essential Tremor Study Group. Ann Neurol. 1994;35(6):717–23.
Koster B, Deuschl G, et al. Essential tremor and cerebellar dysfunction: abnormal ballistic movements. J Neurol Neurosurg Psychiatry. 2002;73(4):400–5.
Krahl SE, Martin FC, et al. Vagus nerve stimulation inhibits harmaline-induced tremor. Brain Res. 2004;1011(1):135–8.

Kronenbuerger M, Konczak J, et al. Balance and motor speech impairment in essential tremor. Cerebellum. 2009;8(3):389–98.
Kuo SH, Erickson-Davis C, et al. Increased number of heterotopic Purkinje cells in essential tremor. J Neurol Neurosurg Psychiatry. 2011;82(9):1038–40.
Lacritz LH, Dewey R Jr, et al. Cognitive functioning in individuals with "benign" essential tremor. J Int Neuropsychol Soc. 2002;8(1):125–9.
Lance JW, Schwab RS, et al. Action tremor and the cogwheel phenomenon in Parkinson's disease. Brain. 1963;86:95–110.
Larsson T, Sjogren T. Essential tremor: a clinical and genetic population study. Acta Psychiatr Scand Suppl. 1960;36(144):1–176.
Lee S-M, Kim M, et al. Nonmotor symptoms in essential tremor: comparison with Parkinson's disease and normal control. J Neurol Sci. 2015;349:168–73.
Lee PJ, Kerridge CA, et al. A quantitative study of empty baskets in essential tremor and other motor neurodegenerative diseases. J Neuropathol Exp Neurol. 2019;78:113–22.
Leegwater-Kim J, Louis ED, et al. Intention tremor of the head in patients with essential tremor. Mov Disord. 2006;21(11):2001–5.
Leehey MA. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. J Investig Med. 2009;57(8):830–6.
Leehey MA, Berry-Kravis E, et al. Progression of tremor and ataxia in male carriers of the FMR1 premutation. Mov Disord. 2007;22(2):203–6.
Li WC, Roberts A, et al. Specific brainstem neurons switch each other into pacemaker mode to drive movement by activating NMDA receptors. J Neurosci. 2010;30(49):16609–20.
Lin CY, et al. Abnormal climbing fibre-Purkinje cell synaptic connections in the essential tremor cerebellum. Brain. 2014;137:3149–59.
Liou LM, Shih PY. Successful treatment of rubral tremor by high-dose trihexyphenidyl: a case report. Kaohsiung J Med Sci. 2006;22(3):149–53.
Llinas R, Volkind RA. The olivo-cerebellar system: functional properties as revealed by harmaline-induced tremor. Exp Brain Res. 1973;18(1):69–87.
Loesch DZ, Litewka L, et al. Tremor/ataxia syndrome and fragile X premutation: diagnostic caveats. J Clin Neurosci. 2007;14(3):245–8.
Lombardi WJ, Woolston DJ, et al. Cognitive deficits in patients with essential tremor. Neurology. 2001;57(5):785–90.
Lorenz D, Deuschl G. Update on pathogenesis and treatment of essential tremor. Curr Opin Neurol. 2007;20(4):447–52.
Lorenz D, Frederiksen H, et al. High concordance for essential tremor in monozygotic twins of old age. Neurology. 2004;62(2):208–11.
Lorenz D, Schwieger D, et al. Quality of life and personality in essential tremor patients. Mov Disord. 2006;21(8):1114–8.
Lorincz MT. Neurologic Wilson's disease. Ann N Y Acad Sci. 2010;1184:173–87.
Lou JS, Jankovic J. Essential tremor: clinical correlates in 350 patients. Neurology. 1991; 41(2 Pt 1):234–8.
Louis ED. Clinical practice. Essential tremor. N Engl J Med. 2001a;345(12):887–91.
Louis ED. Etiology of essential tremor: should we be searching for environmental causes? Mov Disord. 2001b;16(5):822–9.
Louis ED. Behavioral symptoms associated with essential tremor. Adv Neurol. 2005a;96:284–90.
Louis ED. Essential tremor. Lancet Neurol. 2005b;4(2):100–10.
Louis ED. Environmental epidemiology of essential tremor. Neuroepidemiology. 2008;31(3):139–49.
Louis ED. Essential tremors: a family of neurodegenerative disorders? Arch Neurol. 2009;66(10):1202–8.
Louis ED. Essential tremor: evolving clinicopathological concepts in an era of intensive post-mortem enquiry. Lancet Neurol. 2010;9(6):613–22.
Louis ED. Essential tremor. Handb Clin Neurol. 2011;100:433–48.

Louis ED. The primary type of tremor in essential tremor is kinetic rather than postural: cross-sectional observation of tremor phenomenology in 369 cases. Eur J Neurol. 2013;20:725–7.
Louis ED. “Essential tremor” or “the essential tremors”: is this one disease of a family of diseases? Neuroepidemiology. 2014a;42:81–9.
Louis ED. Twelve clinical pearls to help distinguish essential from other tremors. Expert Rev Neurother. 2014b;14:1057–65.
Louis ED. Diagnosis and management of tremor. Continuum. 2016;222:1143–58.
Louis ED. Essential tremor: a nuanced approach to the clinical features. Pract Neurol. 2019;19:389–98.
Louis ED. The essential tremors: evolving concepts of a family of diseases. Front Neurol. 2021;12:650601.
Louis ED, Cosentino S. Mind the gaps: what we don’t know about cognitive impairment in essential tremor. Parkinsonism Relat Disord. 2019;63:10–9.
Louis ED, Dogu O. Does age of onset in essential tremor have a bimodal distribution? Data from a tertiary referral setting and a population-based study. Neuroepidemiology. 2007;29(3–4):208–12.
Louis ED, Faust PL. Essential tremor pathology: neurodegeneration and reorganization of neuronal connections. Nat Rev Neurol. 2020;16:69–83.
Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010;25(5):534–41.
Louis ED, Lenka A. The olivary hypothesis of essential tremor: time to lay this model to rest? Tremor Other Hyperkinet Mov (N Y). 2017;7:473.
Louis ED, McCreary M. How common is essential tremor? Update on the worldwide prevalence of essential tremor. Tremor Other Hyperkinet Mov (N Y). 2021;11:28.
Louis ED, Okun MS. It is time to remove the ‘benign’ from the essential tremor label. Parkinsonism Relat Disord. 2011;17(7):516–20.
Louis ED, Ottman R. How familial is familial tremor? The genetic epidemiology of essential tremor. Neurology. 1996;46(5):1200–5.
Louis ED, Ottman R. Study of possible factors associated with age of onset in essential tremor. Mov Disord. 2006;21(11):1980–6.
Louis ED, Vonsattel JP. The emerging neuropathology of essential tremor. Mov Disord. 2007;23(2):174–82.
Louis ED, Marder K, et al. Differences in the prevalence of essential tremor among elderly African Americans, whites, and Hispanics in northern Manhattan, NY. Arch Neurol. 1995;52(12):1201–5.
Louis ED, Klatka LA, et al. Comparison of extrapyramidal features in 31 pathologically confirmed cases of diffuse Lewy body disease and 34 pathologically confirmed cases of Parkinson’s disease. Neurology. 1997a;48(2):376–80.
Louis ED, Ottman R, et al. The Washington Heights-Inwood genetic study of essential tremor: methodologic issues in essential-tremor research. Neuroepidemiology. 1997b;16(3):124–33.
Louis ED, Ford B, et al. How normal is ‘normal’? Mild tremor in a multiethnic cohort of normal subjects. Arch Neurol. 1998a;55(2):222–7.
Louis ED, Ford B, et al. Clinical characteristics of essential tremor: data from a community-based study. Mov Disord. 1998b;13(5):803–8.
Louis ED, Ottman R, et al. How common is the most common adult movement disorder? Estimates of the prevalence of essential tremor throughout the world. Mov Disord. 1998c;13(1):5–10.
Louis ED, Ford B, et al. Clinical subtypes of essential tremor. Arch Neurol. 2000;57(8):1194–8.
Louis ED, Barnes L, et al. Correlates of functional disability in essential tremor. Mov Disord. 2001a;16(5):914–20.
Louis ED, Dure LS, et al. Essential tremor in childhood: a series of nineteen cases. Mov Disord. 2001b;16(5):921–3.
Louis ED, Ford B, et al. Risk of tremor and impairment from tremor in relatives of patients with essential tremor: a community-based family study. Ann Neurol. 2001c;49(6):761–9.

Louis ED, Levy G, et al. Clinical correlates of action tremor in Parkinson disease. Arch Neurol. 2001d;58(10):1630–4.
Louis ED, Shungu DC, et al. Metabolic abnormality in the cerebellum in patients with essential tremor: a proton magnetic resonance spectroscopic imaging study. Neurosci Lett. 2002a;333(1):17–20.
Louis ED, Zheng W, et al. Elevation of blood beta-carboline alkaloids in essential tremor. Neurology. 2002b;59(12):1940–4.
Louis ED, Ford B, et al. Factors associated with increased risk of head tremor in essential tremor: a community-based study in northern Manhattan. Mov Disord. 2003a;18(4):432–6.
Louis ED, Jurewicz EC, et al. Association between essential tremor and blood lead concentration. Environ Health Perspect. 2003b;111(14):1707–11.
Louis ED, Jurewicz EC, et al. Community-based data on associations of disease duration and age with severity of essential tremor: implications for disease pathophysiology. Mov Disord. 2003c;18(1):90–3.
Louis ED, Levy G, et al. Risk of action tremor in relatives of tremor-dominant and postural instability gait disorder PD. Neurology. 2003d;61(7):931–6.
Louis ED, Applegate LM, et al. Essential tremor: occupational exposures to manganese and organic solvents. Neurology. 2004;63(11):2162–4.
Louis ED, Honig LS, et al. Essential tremor associated with focal nonnigral Lewy bodies: a clinicopathologic study. Arch Neurol. 2005;62(6):1004–7.
Louis ED, Factor-Litvak P, et al. Organochlorine pesticide exposure in essential tremor: a case-control study using biological and occupational exposure assessments. Neurotoxicology. 2006a;27(4):579–86.
Louis ED, Rios E, et al. Jaw tremor: prevalence and clinical correlates in three essential tremor case samples. Mov Disord. 2006b;21(11):1872–8.
Louis ED, Vonsattel JP, et al. Essential tremor associated with pathologic changes in the cerebellum. Arch Neurol. 2006c;63(8):1189–93.
Louis ED, Vonsattel JP, et al. Neuropathologic findings in essential tremor. Neurology. 2006d;66(11):1756–9.
Louis ED, Benito-Leon J, et al. Self-reported depression and anti-depressant medication use in essential tremor: cross-sectional and prospective analyses in a population-based study. Eur J Neurol. 2007a;14(10):1138–46.
Louis ED, Faust PL, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain. 2007b;130(Pt 12):3297–307.
Louis ED, Benito-Leon J, et al. Philadelphia geriatric morale scale in essential tremor: a population-based study in three Spanish communities. Mov Disord. 2008a;23(10):1435–40.
Louis ED, Benito-Leon J, et al. Population-based prospective study of cigarette smoking and risk of incident essential tremor. Neurology. 2008b;70(19):1682–7.
Louis ED, Broussolle E, et al. Historical underpinnings of the term essential tremor in the late 19th century. Neurology. 2008c;71(11):856–9.
Louis ED, Jiang W, et al. Elevated blood harmane (1-methyl-9 H-pyrido[3,4-b]indole) concentrations in essential tremor. Neurotoxicology. 2008d;29(2):294–300.
Louis ED, Pellegrino KM, et al. Unawareness of head tremor in essential tremor: a study of three samples of essential tremor patients. Mov Disord. 2008e;23(16):2423–4.
Louis ED, Pullman SL, et al. Re-emergent tremor without accompanying rest tremor in Parkinson's disease. Can J Neurol Sci. 2008f;35(4):513–5.
Louis ED, Benito-Leon J, et al. Population-based study of baseline ethanol consumption and risk of incident essential tremor. J Neurol Neurosurg Psychiatry. 2009a;80(5):494–7.
Louis ED, Faust PL, et al. Older onset essential tremor: more rapid progression and more degenerative pathology. Mov Disord. 2009b;24(11):1606–12.
Louis ED, Faust PL, et al. Torpedoes in Parkinson's disease, Alzheimer's disease, essential tremor, and control brains. Mov Disord. 2009c;24(11):1600–5.
Louis ED, Frucht SJ, et al. Intention tremor in essential tremor: prevalence and association with disease duration. Mov Disord. 2009d;24(4):626–7.

Louis ED, Thawani SP, et al. Prevalence of essential tremor in a multiethnic, community-based study in northern Manhattan, New York, NY. Neuroepidemiology. 2009e;32(3):208–14.
Louis ED, Yi H, et al. Structural study of Purkinje cell axonal torpedoes in essential tremor. Neurosci Lett. 2009f;450(3):287–91.
Louis ED, Erickson-Davis C, et al. Essential tremor with ubiquitinated Purkinje cell intranuclear inclusions. Acta Neuropathol. 2010a;119(3):375–7.
Louis ED, Rios E, et al. Tandem gait performance in essential tremor: clinical correlates and association with midline tremors. Mov Disord. 2010b;25(11):1633–8.
Louis ED, Agnew A, Gillman A, Gerbin M, Viner AS. Estimating annual rate of decline: prospective, longitudinal data on arm tremor severity in two groups of essential tremor cases. J Neurol Neurosurg Psychiatry. 2011a;82(7):761–5.
Louis ED, Asabere N, et al. Rest tremor in advanced essential tremor: a post-mortem study of nine cases. J Neurol Neurosurg Psychiatry. 2011b;82(3):261–5.
Louis ED, Faust PL, et al. Purkinje cell loss is a characteristic of essential tremor. Parkinsonism Relat Disord. 2011c;17(6):406–9.
Louis ED, Hafeman D, et al. Prevalence of essential tremor in Araihazar, Bangladesh: a population-based study. Neuroepidemiology. 2011d;36(2):71–6.
Louis ED, Faust PL, Vonsattel JPG. Purkinje cell loss is a characteristic of essential tremor: towards a more mature understanding of pathogenesis. Parkinsonism Relat Disord. 2012;18:1003–4.
Louis ED, Benito-Leon J, et al. Blood harmane (1-methyl-9H-pyrido[3,4-b]indole) concentration in essential tremor cases in Spain. Neurotoxicology. 2013a;34:264–8.
Louis ED, Factor-Litvak P, et al. Elevated brain harmane (1-methyl-9H-pyrido[3,4-b]indole) in essential tremor cases vs controls. Neuroepidemiology. 2013b;38:131–5.
Louis ED, Galecki M, et al. Four essential tremor cases with moderately impaired gait: how impaired can gait be in this disease? Tremor Other Hyperkinet Mov (N Y). 2013c;3.
Louis ED, Gerbin M, et al. Essential tremor 10, 20, 30, 40: clinical snapshots of the disease by decade of duration. Eur J Neurol. 2013d;20:949–54.
Louis ED, Lee M, et al. Reduced Purkinje cell dendritic arborization and loss of dendritic spines in essential tremor. Brain. 2014;137:3142–8.
Louis ED, Clark LN, et al. Familial versus sporadic essential tremor: what patterns can one decipher in age of onset? Neuroepidemiology. 2015a;44:166–72.
Louis ED, Hernandez N, et al. Prevalence and correlates of rest tremor in essential tremor: cross-sectional survey of 831 patients across four distinct cohorts. Eur J Neurol. 2015b;22:927–032.
Louis ED, Diaz DT, et al. Inferior olivary nucleus degeneration does not lessen tremor in essential tremor. Cerebellum Ataxias. 2018a;5:1.
Louis ED, Kuo SH, et al. Heterotopic Purkinje cells: a comparative postmortem study of essential tremor and spinocerebellar ataxias 1, 2, 3, and 6. Cerebellum. 2018b;17:104–10.
Louis ED, Kerridge CA, et al. Contextualizing the pathology in the essential tremor cerebellar cortex: a pathology-omics approach. Acta Neuropathol. 2019;138:859–76.
Louis ED, Eliasen EH, et al. Blood harmane (1-methyl-9H-pyrido[3,4-b]indole) and mercury in essential tremor: a population-based, environmental epidemiology study in The Faroe Islands. Neuroepidemiology. 2020;54:272–80.
Machado A, Chien HF, et al. Neurological manifestations in Wilson's disease: report of 119 cases. Mov Disord. 2006;21(12):2192–6.
Mailankody P, Netrvathia M, Pal PK. Review of tremor in Parkinson's disease and atypical parkinsonian disorders. Neurol India. 2007;65:1083–90.
Mak CM, Lam CW. Diagnosis of Wilson's disease: a comprehensive review. Crit Rev Clin Lab Sci. 2008;45(3):263–90.
Martin FC, Handforth A. Carbenoxolone and mefloquine suppress tremor in the harmaline mouse model of essential tremor. Mov Disord. 2006;21(10):1641–9.
Martin FC, Le Thu A, et al. Harmaline-induced tremor as a potential preclinical screening method for essential tremor medications. Mov Disord. 2005;20(3):298–305.
Martinelli P, Gabellini AS, et al. Different clinical features of essential tremor: a 200-patient study. Acta Neurol Scand. 1987;75(2):106–11.

Mavroudis I, Petrides F, et al. A voxel-wise-meta-analysis on the cerebellum in essential tremor. Medicina. 2021;57:264.
McMaster J, Gibson G, et al. Neurosurgical treatment of tremor in anti-myelin-associated glycoprotein neuropathy. Neurology. 2009;73(20):1707–8.
Miller KM, Okun MS, et al. Depression symptoms in movement disorders: comparing Parkinson's disease, dystonia, and essential tremor. Mov Disord. 2007;22(5):666–72.
Minen MT, Louis ED. Emergence of Parkinson's disease in essential tremor: a study of the clinical correlates in 53 patients. Mov Disord. 2008;23(11):1602–5.
Morahan JM, Yu B, et al. Genetic susceptibility to environmental toxicants in ALS. Am J Med Genet B Neuropsychiatr Genet. 2007;144(7):885–90.
Morgan JC, Sethi KD. Drug-induced tremors. Lancet Neurol. 2005;4(12):866–76.
Morgan JC, Kurek JA, et al. Insights into pathophysiology from medication-induced tremor. Tremor Other Hyperkinet Mov (N Y). 2017;7:442.
Mossuto-Agatiello L, Puccetti G, et al. 'Rubral' tremor after thalamic haemorrhage. J Neurol. 1993;241(1):27–30.
Nayak B, Hodak SP. Hyperthyroidism. Endocrinol Metab Clin N Am. 2007;36(3):617–56.
Nicoletti G, Manners D, et al. Diffusion tensor MRI changes in cerebellar structures of patients with familial essential tremor. Neurology. 2010;74(12):988–94.
Nygaard B. Hyperthyroidism. Am Fam Physician. 2007;76(7):1014–6.
Oder W, Grimm G, et al. Neurological and neuropsychiatric spectrum of Wilson's disease: a prospective study of 45 cases. J Neurol. 1991;238(5):281–7.
Ondo WG, Satija P. Task-specific writing tremor: clinical phenotypes, progression, treatment, outcomes, and proposed nomenclature. Int J Neurosci. 2012;122:88–91.
Pagan FL, Butman JA, et al. Evaluation of essential tremor with multi-voxel magnetic resonance spectroscopy. Neurology. 2003;60(8):1344–7.
Parisi SL, Heroux ME, et al. Functional mobility and postural control in essential tremor. Arch Phys Med Rehabil. 2006;87(10):1357–64.
Pedersen SF, Pullman SL, et al. Physiological tremor analysis of patients with anti-myelin-associated glycoprotein associated neuropathy and tremor. Muscle Nerve. 1997;20(1):38–44.
Perl DP. Relationship of aluminum to Alzheimer's disease. Environ Health Perspect. 1985;63:149–53.
Peters N, Kamm C, et al. Intrafamilial variability in fragile X-associated tremor/ataxia syndrome. Mov Disord. 2006;21(1):98–102.
Pfeiffer RF. Wilson's disease. Semin Neurol. 2007;27(2):123–32.
Pietracupa S, Bologna M, et al. The contribution of neuroimaging to the understanding of essential tremor pathophysiology: a systematic review. Cerebellum. 2021;21(6):1029–51.
Poston KL, Rios E, et al. Action tremor of the legs in essential tremor: prevalence, clinical correlates, and comparison with age-matched controls. Parkinsonism Relat Disord. 2009;15(8):602–5.
Putzke JD, Whaley NR, et al. Essential tremor: predictors of disease progression in a clinical cohort. J Neurol Neurosurg Psychiatry. 2006;77(11):1235–7.
Quattrone A, Cerasa A, et al. Essential head tremor is associated with cerebellar vermis atrophy: a volumetric and voxel-based morphometry MR imaging study. AJNR Am J Neuroradiol. 2008;29(9):1692–7.
Racette BA, McGee-Minnich L, et al. Welding-related parkinsonism: clinical features, treatment, and pathophysiology. Neurology. 2001;56(1):8–13.
Raethjen J, Lindemann M, et al. Multiple oscillators are causing parkinsonian and essential tremor. Mov Disord. 2000;15(1):84–94.
Raethjen J, Lemke MR, et al. Amitriptyline enhances the central component of physiological tremor. J Neurol Neurosurg Psychiatry. 2001;70(1):78–82.
Raethjen J, Govindan RB, et al. Cortical involvement in the generation of essential tremor. J Neurophysiol. 2007;97(5):3219–28.
Rajput AH, Offord KP, et al. Epidemiology of parkinsonism: incidence, classification, and mortality. Ann Neurol. 1984;16(3):278–82.

Rajput AH, Rozdilsky B, et al. Occurrence of resting tremor in Parkinson's disease. Neurology. 1991a;41(8):1298–9.
Rajput AH, Rozdilsky B, et al. Clinicopathologic observations in essential tremor: report of six cases. Neurology. 1991b;41(9):1422–4.
Rajput AH, Rozdilsky B, et al. Significance of parkinsonian manifestations in essential tremor. Can J Neurol Sci. 1993;20(2):114–7.
Rajput A, Robinson CA, et al. Essential tremor course and disability: a clinicopathologic study of 20 cases. Neurology. 2004;62(6):932–6.
Rajput AH, Maxood K, et al. Classic essential tremor changes following cerebellar hemorrhage. Neurology. 2008;71(21):1739–40.
Rajput AH, Robinson CA, et al. Cerebellar Purkinje cell loss is not pathognomonic of essential tremor. Parkinsonism Relat Disord. 2011;17(1):16–21.
Rajput AH, Robinson CA, et al. Essential tremor is not dependent upon cerebellar Purkinje cell loss. Parkinsonism Relat Disord. 2012;18:626–8.
Rao AK, Louis ED. Ataxic gait in essential tremor: A disease-associated feature? Tremor Other Hyperkinet Mov (N Y). 2019;9.
Rao AK, Gillman A, Louis ED. Quantitative gait analysis in essential tremor reveals impairments that are maintained into advanced age. Gait Posture. 2011;34(1):65–70.
Rao AK, Gilman A, et al. Balance confidence and falls in nondemented essential tremor patients: the role of cognition. Arch Phys Med Rehab. 2014;95:1832–7.
Rautakorpi I. Essential tremor. An epidemiological, clinical and genetic study. Turku: Academic Dissertation University of Turku; 1978.
Rautakorpi I, Takala J, et al. Essential tremor in a Finnish population. Acta Neurol Scand. 1982;66(1):58–67.
Ritz B, Yu F. Parkinson's disease mortality and pesticide exposure in California 1984-1994. Int J Epidemiol. 2000;29(2):323–9.
Rocca WA, Bower JH, et al. Increased risk of essential tremor in first-degree relatives of patients with Parkinson's disease. Mov Disord. 2007;22(11):1607–14.
Ruzicka E, Jech R, et al. VIM thalamic stimulation for tremor in a patient with IgM paraproteinaemic demyelinating neuropathy. Mov Disord. 2003;18(10):1192–5.
Rybicki BA, Johnson CC, et al. Parkinson's disease mortality and the industrial use of heavy metals in Michigan. Mov Disord. 1993;8(1):87–92.
Said G, Bathien N, et al. Peripheral neuropathies and tremor. Neurology. 1982;32(5):480–5.
Saito T. Presenting symptoms and natural history of Wilson disease. Eur J Pediatr. 1987;146(3):261–5.
Salcedo-Arellano MJ, Dufour B, et al. Fragile X syndrome and associated disorders: clinical aspects and pathology. Neurobiol Dis. 2020;136:104740.
Salemi G, Aridon P, et al. Population-based case-control study of essential tremor. Ital J Neurol Sci. 1998;19(5):301–5.
Samanci B, Sahin E, et al. Neurological features and outcomes of Wilson's disease: a single center experience. Neurol Sci. 2021;42:3829–34.
Samie MR, Selhorst JB, et al. Post-traumatic midbrain tremors. Neurology. 1990;40(1):62–6.
Saverino A, Solaro C, et al. Tremor associated with benign IgM paraproteinaemic neuropathy successfully treated with gabapentin. Mov Disord. 2001;16(5):967–8.
Schneier FR, Barnes LF, et al. Characteristics of social phobia among persons with essential tremor. J Clin Psychiatry. 2001;62(5):367–72.
Schrag A, Muenchau A, et al. Overdiagnosis of essential tremor. Lancet. 1999;353(9163):1498–9.
Schrag A, Munchau A, et al. Essential tremor: an overdiagnosed condition? J Neurol. 2000;247(12):955–9.
Schuurman PR, Bosch DA, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med. 2000;342(7):461–8.
Semchuk KM, Love EJ, et al. Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology. 1992;42(7):1328–35.

Shahed J, Jankovic J. Exploring the relationship between essential tremor and Parkinson's disease. Parkinsonism Relat Disord. 2007;13(2):67–76.
Shcherbatykh I, Carpenter DO. The role of metals in the etiology of Alzheimer's disease. J Alzheimers Dis. 2007;11(2):191–205.
Shi M, Huber BR, et al. Biomarkers for cognitive impairment in Parkinson disease. Brain Pathol. 2010;20(3):660–71.
Shill HA, Adler CH, et al. Pathologic findings in prospectively ascertained essential tremor subjects. Neurology. 2008;70(16 Pt 2):1452–5.
Shin DH, Han BS, et al. Diffusion tensor imaging in patients with essential tremor. AJNR Am J Neuroradiol. 2008;29(1):151–3.
Singer C, Sanchez-Ramos J, et al. Gait abnormality in essential tremor. Mov Disord. 1994;9(2):193–6.
Sinton CM, Krosser BI, et al. The effectiveness of different isomers of octanol as blockers of harmaline-induced tremor. Pflugers Arch. 1989;414(1):31–6.
Siokas V, Aloizou A-M, et al. Genetic risk factors for essential tremor: a review. Tremor Other Hyperkinet Mov (N Y). 2020;10:4.
Soltanzadeh A, Soltanzadeh P, et al. Wilson's disease: a great masquerader. Eur Neurol. 2007;57(2):80–5.
Starosta-Rubinstein S, Young AB, et al. Clinical assessment of 31 patients with Wilson's disease. Correlations with structural changes on magnetic resonance imaging. Arch Neurol. 1987;44(4):365–70.
Sternberg EJ, Alcalay RN, et al. Postural and intention tremors: a detailed clinical study of essential tremor vs. Parkinson's disease. Front Neurol. 2013;4:51.
Stolze H, Petersen G, et al. The gait disorder of advanced essential tremor. Brain. 2001;124(Pt 11):2278–86.
Stremmel W, Meyerrose KW, et al. Wilson disease: clinical presentation, treatment, and survival. Ann Intern Med. 1991;115(9):720–6.
Symanski C, Shill HA, et al. Essential tremor is not associated with cerebellar Purkinje cell loss. Mov Disord. 2014;29:496–500.
Tan H, Turanli G, et al. Rubral tremor after thalamic infarction in childhood. Pediatr Neurol. 2001;25(5):409–12.
Tan EK, Fook-Chong S, et al. Non-motor manifestations in essential tremor: use of a validated instrument to evaluate a wide spectrum of symptoms. Parkinsonism Relat Disord. 2005a;11(6):375–80.
Tan LC, Venketasubramanian N, et al. Prevalence of essential tremor in Singapore: a study on three races in an Asian country. Parkinsonism Relat Disord. 2005b;11(4):233–9.
Tan EK, Lum SY, et al. Clinical features of childhood onset essential tremor. Eur J Neurol. 2006;13(12):1302–5.
Tan EK, Lee SS, et al. Evidence of increased odds of essential tremor in Parkinson's disease. Mov Disord. 2008;23(7):993–7.
Tanner CM. Essential tremor in twins. Neurology. 2001;57:1389–91. https://doi.org/10.1212/wnl.57.8.1389.
Thenganatt MA, Louis ED. Personality profile in essential tremor: a case-control study. Parkinsonism Relat Disord. 2012;18:1042–4.
Trillenberg P, Fuhrer J, et al. Eye-hand coordination in essential tremor. Mov Disord. 2006;21(3):373–9.
Troster AI, Woods SP, et al. Neuropsychological deficits in essential tremor: an expression of cerebello-thalamo-cortical pathophysiology? Eur J Neurol. 2002;9(2):143–51.
Ullah I, Zhao L, et al. Metal elements and pesticides as risk factors for Parkinson's disease – a review. Toxicol Rep. 2021;8:607–16.
Van den Berg KRE, Helmich RC. The role of the cerebellum in tremor – Evidence from neuroimaging. Tremor Other Hyperkinet Mov (N Y). 2021;11:49.
Vermilion K, Stone A, et al. Cognition and affect in idiopathic essential tremor. Mov Disord. 2001;16:S30.

Walshe JM, Yealland M. Wilson's disease: the problem of delayed diagnosis. J Neurol Neurosurg Psychiatry. 1992;55(8):692–6.
Wills AJ, Jenkins IH, et al. Red nuclear and cerebellar but no olivary activation associated with essential tremor: a positron emission tomographic study. Ann Neurol. 1994;36(4):636–42.
Wills AJ, Jenkins IH, et al. A positron emission tomography study of cerebral activation associated with essential and writing tremor. Arch Neurol. 1995;52(3):299–305.
Wojcik-Pedziwiatr M, Plinta K, et al. Eye movement abnormalities in essential tremor. J Hum Kinet. 2016;52:53–64.
Yahr MD, Orosz D, et al. Co-occurrence of essential tremor and Parkinson's disease: clinical study of a large kindred with autopsy findings. Parkinsonism Relat Disord. 2003;9(4):225–31.
Yang YW, Chang FC, et al. Clinical and magnetic resonance imaging manifestations of Holmes tremor. Acta Neurol Taiwanica. 2005;14(1):9–15.
Yu M, Ma K, et al. Increased number of Purkinje cell dendritic swellings in essential tremor. Eur J Neurol. 2012;19:625–30.
Zago S, Poletti B, et al. Amyotrophic lateral sclerosis and frontotemporal dementia (ALS-FTD). Arch Ital Biol. 2011;149(1):39–56.

Chapter 10
Dystonic Tremor

Stefania Lalli and Alberto Albanese

Abstract We review here the development and usage of the expression "dystonic tremor" and put it into perspective with controversies in the clinical setting. The term was introduced by Fahn to indicate patients who had dystonia with a tremulous phenomenology and underline a difference from essential tremor. Terminology usage and clinical challenges have since then kept these two expressions in close alternative, up to the recent definition of the "essential tremor plus" syndrome, to highlight cases where the clinical features are so intermixed as to raise significant uncertainty. As diagnostic criteria for dystonia and tremor get more refined, usage of the expression dystonic tremor will become less necessary.

Keywords Dystonia · tremor · torticollis

Abbreviations

DT Dystonic tremor
ET Essential tremor
PD Parkinson disease
TAWD Tremor associated with dystonia

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10.1 Introduction

Tremor is a very common movement disorder in adults described also in ancient literature (Albanese 2018). Patients with tremor may exhibit a broad phenomenology under a range of different circumstances. Tremor is usually easy to observe, although tremors with very low amplitude may remain undetected by visual observation. Tremor is defined as an involuntary, rhythmic, and oscillatory movement, which may involve one or several body parts (Bhatia et al. 2018). This definition emphasizes the oscillatory nature of tremors without dictating a specific waveform shape. It is ideally expected to observe sinusoidal oscillations by accelerometric or kinematic measures, although in practice any to-and-fro oscillation fits into the current definition of tremor.

Phenomenologically, tremor is a physical sign to be recognized during a physical examination (Albanese and Sorbo 2016). Visual recognition identifies rhythmicity and the oscillatory nature of tremors observed in a body part (Bhatia et al. 2018). Even visually, however, some irregularities can be perceived: jerky, arrhythmic, irregular tremors have been described. These require differentiation from irregular involuntary movements, such as myoclonus or chorea, or suggest overlap of irregular features, such as dystonic movements and postures. Strictly speaking, an involuntary movement that is oscillatory but not strictly rhythmic, would not be considered tremor. However, rhythmicity is difficult to assess visually and requires instrumented analysis. In dystonia, for example, tremulous dystonic movements may be generated by tonic contractions with sustained EMG activity that break up the oscillations, thus generating an occasionally non-rhythmic tremor-like movement.

Not surprisingly, the tremor quality is occasionally described with qualifiers, such as "irregular" or "jerky," to indicate noncoincidence with a typical sinusoidal oscillation. Irregular tremors can vary in frequencies (Jedynak et al. 1991). Occasionally, tremor needs to be distinguished from myoclonus, particularly when myoclonus is regular or rhythmic. The recognition of subtypes of tremor and myoclonus can be challenging in some patients (Apartis 2013). Myoclonic jerks are usually repetitive and can be rhythmic or arrhythmic. However, they do not have a torsional character as observed in dystonia. The term "dystonic tremor" (DT) is a bridging expression that is widely used with different meanings, occasionally as a synonym of jerky tremor (Shimazaki et al. 2022; Gonzalez-Herrero et al. 2023). However, terminology usage is variable and clearly inconsistent.

In the field of movement disorders, three main qualifiers for tremor are of common use: essential tremor (ET), parkinsonian tremor, and dystonic tremor. The best-defined qualifier is parkinsonian tremor, whose classical description has not changed over time (Deuschl et al. 2012). Rest tremor occurs when there is no voluntary muscle contraction in a body part. It is enhanced by cognitive tasks (e.g., counting backward) and movement of another body part (e.g., contralateral arm) (Saifee 2019). Rest tremor in the upper or lower extremities is a very specific feature of Parkinson's disease (PD), and for many patients and physicians, it is a disease-defining symptom (Elble 2009). The frequency is 3–5 Hz or occasionally a little

faster. Tremor at rest is a common initial motor symptom of PD, found in 50% of patients at the time of diagnosis, and is diagnostically specific (Fishman 2008). The most typical appearance of parkinsonian tremor is a pill-rolling tremor, a type of resting tremor characterized by simultaneous rubbing movements of thumb and index fingers against each other. However, resting tremor does not necessarily have a pill-rolling appearance, can involve the wrist, or even more proximal joints.

In most cases, tremor is perceived by patients as a symptom and reported to the neurologist. When perceived subjectively while not visible, it is often described as an "internal tremor." This tremor type is reported by 32.6% of PD patients, 36% of multiple sclerosis patients, and 55% of ET patients (Cochrane et al. 2015). Upon physical examination, tremor can be diagnosed by visual inspection as well as perceived by palpation of the shaking body part. Furthermore, the physical characteristics of tremor can be measured with dedicated instruments, including lab-based tools, hand-held devices, and even smartphones. In these studies, PD patients were often compared to ET patients, without considering patients with dystonia and tremor (van Brummelen et al. 2020). It is advisable, therefore, to consider the phenomenology and context of tremor before performing instrumented assessments.

Specific tremor syndromes are diagnosed based on their clinical features. The main variables to consider are motor condition of the trembling body part and the frequency of tremor. For example, resting tremor, position tremor, action tremor, and intention tremor orientate toward different diagnoses and different pathophysiology. Low frequency ($\leq$4 Hz) orientates toward cerebellar tremor; whereas parkinsonian tremor has usually a frequency of $\leq$4 Hz, and ET of 6–8 Hz (Deuschl et al. 1998).

10.2 Classification of Tremors

The most recent consensus on the classification of tremor disorders was published in 2018 (Bhatia et al. 2018). The aim was to provide a systematic approach to tremors using the two-axis system originally developed in dystonia. Axis I emphasizes the clinical features, history, and tremor characteristics; Axis II lists the etiology of tremor. ET is classified under Axis I as a syndrome of isolated action tremor. The new category of ET plus was created for those patients fulfilling the criteria for ET, but also exhibiting additional "soft signs" that do not suffice to make an alternative diagnosis. This intermediate category clearly is the expression of a compromise and shed shades over the definition of ET as well (Espay et al. 2017; Fasano et al. 2018). In the same tremor classification, there is a definition of DT as a syndrome combining tremor and dystonia as the leading neurological signs (Bhatia et al. 2018).

In the current classification, ET is a syndrome characterized by bilateral upper limb action tremor with at least 3 years of duration (Bhatia et al. 2018). This observational time is considered sufficient to allow the development of additional features of dystonia or parkinsonism that would exclude a classification of ET. Therefore, ET stands as the quintessential syndrome of isolated tremor in the upper

limbs without any appreciable additional feature. ET plus is a gray box where the characteristics of ET are enriched by a variety of 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 is also classified as ET plus.

10.2.1 Dystonia and Tremor

The coexistence of tremor and dystonia has been regarded differently when observed from the clinical or the neurophysiological perspectives. Stanley Fahn observed that a significant proportion of dystonia patients had repetitive, rhythmic, dystonic movements with a tremor-like appearance and indicated criteria to differentiate these from nondystonic ET (Fahn 1984). He introduced the term "dystonic tremor" to highlight his observation that tremor is part of the spectrum of dystonia. It was later widely acknowledged that tremor is a feature observed in dystonia (Albanese et al. 2013, 2019), but uncertainty still exists whether these tremulous movements should be considered dystonic in nature, as originally proposed by Fahn, or a coexisting tremor (Bhatia et al. 2018; Elble 2013a; Shaikh et al. 2021; Panyakaew et al. 2022). Whatever the pathophysiological interpretation, it is now widely accepted that tremor is a phenomenological feature observed in patients with dystonia.

Neurophysiologists traditionally considered instead tremor and dystonia as two separate and distinct movement disorders. To accommodate this belief, the first classification of tremors introduced the expression "tremor associated with dystonia" (TAWD) to indicate tremor observed in a body part where there are no features of dystonia, while the patient has dystonia in a different body part (Deuschl et al. 1998). The same classification redefined DT as a tremor affecting a body part where dystonia co-occurs.

Although dystonia and tremor may be viewed as distinct conditions, there is ample evidence that they coexist. Individuals diagnosed with dystonia frequently have tremor, with reported prevalence rates of 14–90% (Pandey and Sarma 2016). Conversely, many individuals diagnosed with tremor disorders also have dystonia, with prevalence rates of 1–27% (Shaikh et al. 2021). However, there are significant clinical and etiologic heterogeneities among cohorts, as well as differences on how dystonia and tremor were assessed. In addition, it must be admitted that the two conditions can sometimes be difficult to separate on clinical grounds.

The dilemma on the coexistence of tremor and dystonia can be solved by considering that tremor is a single physical sign, while dystonia is a collection of different physical signs, which include postures, movements, alleviating maneuvers, overflow, and mirroring (Albanese et al. 2019). Therefore, the coexistence of tremor and dystonia may be accommodated in two ways: (1) tremor is a phenomenology of dystonic movements, (2) tremor is a separate physical sign observed in dystonia (Fig. 10.1).

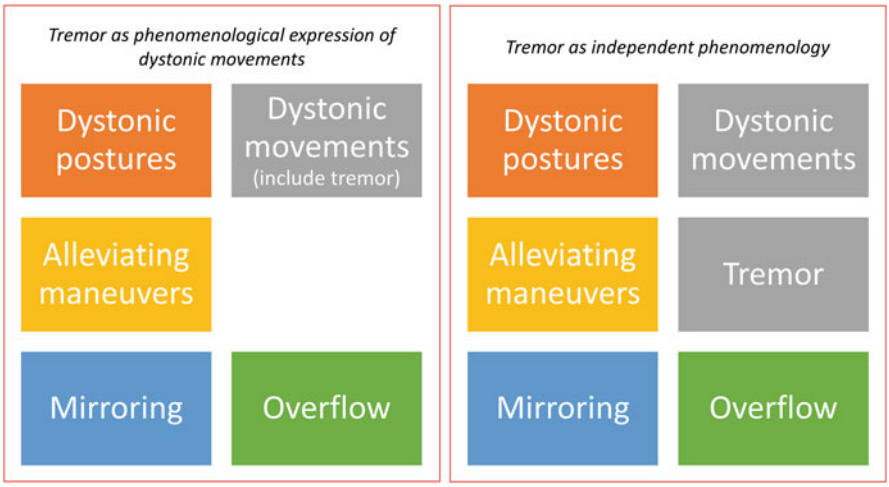

Fig. 10.1 There are two different views about tremor in dystonia. A first view (shown on the left) considers tremor part of the phenomenology of dystonic movements, according to the original definition of dystonic tremor (Fahn 1984). Another view (shown on the right) considers tremor a separate phenomenology observed in patients with dystonia (Bhatia et al. 2018; Deuschl et al. 1998). The first vision, mainly supported by dystonia experts, implies that the phenomenology of dystonia consists of five main features (Albanese et al. 2019); the second vision, supported mainly by neurophysiologists expert on tremor, implies that the phenomenology of dystonia consists of six main features

Tremor can be studied by accelerometry, EMG, or kinematic analysis and its diagnosis is reliable either clinically or instrumentally. By contrast, the diagnosis of dystonia is only based on clinical observation and cannot be supported by laboratory or biomarker data. The clinical recognition of dystonia is facilitated by the observation of a full phenomenology, more difficult when dystonic movements occur in isolation, such as in the case of isolated head tremor (Albanese et al. 2023). Although the discussion whether tremor is a phenomenology of dystonic movements or a separate feature observed in patients with dystonia remains unsettled, there is no doubt that tremor is commonly observed in patients with dystonia (Albanese et al. 2013). It is also widely accepted that isolated tremor can be a presenting feature (i.e., a soft sign or *forme fruste*) of dystonia. For example, the longitudinal evaluation of a cohort of patients with isolated head tremors showed that 75% had developed over cervical dystonia after 5 years (Ferrazzano et al. 2022). Isolated tremor syndromes commonly raise suspicion of a coexisting dystonia, particularly if mild dystonic features are observed (Albanese and Sorbo 2016; Albanese et al. 2019; Albanese and Lalli 2009). Tremor in dystonia is mostly seen during postural holding and reaching tasks; but resting tremor can be seen in elderly patients with dystonia (Gigante et al. 2016). The body regions affected by tremor and the temporal relationship between the onset of tremor and dystonia are variable.

In summary, dystonia and tremor may coexist or, instead, occur independently in patients who have dystonia syndromes without tremor or tremor syndromes without dystonia. Dystonia has been variably reported in cohorts of patients with a diagnosis of ET, most commonly as blepharospasm, cervical or upper limb dystonia (Pandey and Sarma 2016; Lou and Jankovic 1991). The current classification scheme would label many of these cases as having "ET plus," a diagnostic category not endorsed by several dystonia experts (Fasano et al. 2018; Pandey and Bhattad 2019). This category appears to many as a compromise solution to accommodate an ongoing process of changing the definition of ET, which was initially considered a disease with a rich phenomenology (Critchley 1972) and is now limited to an isolated upper limb tremor syndrome (Bhatia et al. 2018). In the individual patient, it is practically impossible to predict whether an isolated tremor is an expression of underlying dystonia and whether it will remain isolated or instead evolve into a full picture of dystonia (Albanese and Sorbo 2016; Ferrazzano et al. 2022; Rivest and Marsden 1990).

10.2.1.1 Historical Development of the Term

Following the observation that patients with dystonia sometimes presented with rhythmic movements, particularly in the arms and neck, manifesting as tremor (Jankovic and Fahn 1980), the expression "dystonic tremor" was introduced by Fahn to distinguish these cases from those of "essential tremor" (Fahn 1984). ET was then considered a nosologic entity; therefore, this distinction was key to distinguish two different nosologic conditions. Fahn noted (Fahn 1984):

> Repetitive and rhythmic dystonic movements result from the regular grouping of action potentials frequently on voluntary contractions. This can result in the appearance of a tremor that I call "dystonic tremor." Typically, this tremor pattern occurs when the patient voluntarily attempts to move in the direction apposite to the direction forced by the dystonia. Thus if the dystonic movements tend to induce a posture of pronation of the forearm, and the patient tries to supinate this limb, rhythmic contractions usually develop. It is helpful to ask the patient not to fight the pulling of the muscles, but to let them go where they want to go. One will usually see sustained posturing and loss of the tremor pattern. This maneuver helps establish the diagnosis that the tremor was dystonic in nature and not some other type of associated tremor, such as essential tremor, cerebellar tremor, or parkinsonian tremor.

Yanagisawa and Goto performed multichannel EMG analysis of muscle activity and found that phasic contractions were commonly observed in dystonia (Yanagisawa and Goto 1971). Rhythmic 5–11 Hz bursts were seen during voluntary contractions, whereas rhythmic and irregular bursts at 1–6.5 Hz occurred during involuntary dystonic movements. Involuntary muscle contractions occurred in the recumbent posture, on standing, in response to passive stretch and to isometric voluntary contraction in the neck, trunk, and limbs. Their observations were summarized as follows: (1) tonic nonreciprocal, involuntary activity appeared in agonists and antagonists, directly stimulated by postural effort, such as attempted sitting or standing, or by attempted voluntary movement; regular or irregular grouping

of action potentials appeared in the EMG in most cases in which synchronous activity among different muscles was characteristic. They debated whether some of these phasic muscle contractions were sufficiently rhythmic to be called tremor and reported that tremor in dystonic contractions was irregular in rhythm and amplitude.

A consensus panel later defined dystonic tremors according to three features: an associated dystonic posture, irregular amplitudes and frequency (usually 7 Hz), and postural/intentional tremor rather than resting tremor (Deuschl et al. 1998). This consensus considered that dystonic tremor indicates a coexistence of tremor and other dystonia features in the same body part and suggested using the expression "tremor associated with dystonia" for tremor observed in a body part not affected by dystonia. This complex terminology is currently used, although a number of incongruencies have been reported (Hvizdosova et al. 2020). Neurological follow-up is required for patients with isolated upper limb action tremor to detect whether dystonia may develop at a later stage (Deuschl 2003). This clinical exercise is based solely on phenomenology and clinical skills.

The more recent consensus on DT requires observing obvious twisting movements or postures in the same body region with tremor (Bhatia et al. 2018). Whether tremor is regular, irregular, or jerky is considered irrelevant. Hence, the expression "dystonic tremor" currently refers simply to the clinical observation of the coexistence of a tremor with dystonia in the same body region. However, many neurologists still use the expression to refer instead to a tremor with atypical neurophysiological features. Appreciation of soft signs of dystonia also marks a difference. A subtle tilting of the head or subtle hyperextension of one finger could be considered evidence of dystonia by some or, alternatively, variants of normal motor behavior by others. The new term "ET plus" to encompass a quite heterogeneous collection of cases where there is the occurrence of ET with 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 alternative syndromic diagnosis (Bhatia et al. 2018). This category includes also such conditions where dystonic features are too mild to allow firmly establishing the occurrence of dystonia. Unfortunately, there are no operational criteria for the definition of soft signs of dystonia and their interpretation is, per consensus, subjective and left to the investigator. It has been recently shown that the soft signs differently contribute to modulating the probability that a patient does not have ET and that multiple soft signs are not always addictive for the purpose of specifying the diagnosis (Erro et al. 2022a). Therefore, ET plus represents a source of ambiguity and syndromic overlap that demands reconsideration, particularly in the interface between dystonia and tremor.

In fact, there is no contraposition between dystonia and tremor, for the simple reason that tremor is a feature observed in dystonia and can be the only feature observed in some patients, at least during an initial period. Tremor can be a presenting feature of dystonia and phenomenologically can be considered a particular expression of dystonic movements or—alternatively—an individual physical sign within the dystonia spectrum. Whichever the interpretation, tremor in dystonia can

present as regular, rhythmic oscillations, or as a jerky phenomenon. The latter feature was recognized as a common characteristic of tremor observed in dystonia (Deuschl et al. 1998). The expression DT has been subject to evolutionary changes in usage and there is no homogeneity in its current application to neurological examination. In our team, we pragmatically use the expression DT to indicate that tremor and dystonia coexist and to underline a distinction with ET. This usage adapts particularly to patients with upper limb or head tremor and conveys the practical message that patients with DT have dystonia with a prevalence of tremor, ruling out a diagnosis of ET. In our team, we rarely use the expression ET plus, that is too generic; we rather tend to clarify as much as possible the subtle motor features observed in those patients who belong to this category.

10.2.2 Epidemiology

Given the varied usage of the expression DT over time and across centers, epidemiological data are poorly consistent.

Tremor has been reported in 14–87% of the patients diagnosed with dystonia (Pandey and Sarma 2016). A recent reassessment showed that approximately half of all patients with dystonia have tremor (Shaikh et al. 2021). The prevalence of tremor in dystonia depends on the body regions affected by dystonia, on disease duration and the severity of dystonia, as well as on how tremor is evaluated. When DT is defined as a jerky and irregular movement, regardless of any coexisting dystonic posturing, its overall prevalence was reckoned to be 36.9% (Shaikh et al. 2021). The prevalence of regular/sinusoidal tremors was instead 21.2%, regardless of whether dystonia occurred in the same body part as tremor. A small portion of patients (1.9%) had a combination of irregular/jerky and regular/sinusoidal tremors among those who had both tremor types, 71.1% had both tremors simultaneously in the same body part, while 28.9% had irregular/jerky tremor in one body region combined with regular/sinusoidal tremor in another body region. When dystonic tremor was instead defined by the co-occurrence of tremor and overt dystonia, regardless of any irregular or jerky quality, its overall prevalence among all 2362 participants was 48.4% (Shaikh et al. 2021). Among these participants, 26.0% had a strict concordance of tremor with dystonia, while 22.4% had concurrent tremor and dystonia, with tremor affecting a body region that was not dystonic. Only 4.3% of patients had tremor in a nondystonic body region without a concurrent tremor in the dystonic body region (Shaikh et al. 2021).

Rest tremor in dystonia has also been reported, with a variable frequency (1.81–12.05%), most commonly in the arms, where it tends to be asymmetric (Gupta and Pandey 2020). Most patients with rest tremor have multifocal or segmental dystonia. Rest tremor should be distinguished from pseudo-rest tremor that is observed when a limb is not fully relaxed, for example in a patient who maintains a baseline contraction while walking or resting. Pseudo-rest tremors can lead to a differential

diagnosis of Parkinson's disease (Albanese and Lalli 2010). Rest tremor is a late-onset phenomenon associated with increased severity and spread of dystonia (Gupta and Pandey 2020).

Recently, a large tremor registry reported that rest tremor was the commonest additional feature observed in patients with a diagnosis of ET plus (about 50% of cases), followed by questionable dystonia (about 11%), and undetermined slowing (about 9% of cases) (Erro et al. 2022b).

The observation of tremor in patients with inherited dystonia raised the question whether a same pathophysiology may cause both phenomena. Dystonia associated with variants in the *ANO3* gene is known to cause an autosomal dominant cranio-cervical dystonia. These patients may initially present only with action tremor of the upper extremities (Stamelou et al. 2014). Tremor in *ANO3* dystonia commonly involves both the upper extremities and the head; tremor in the extremities is usually asymmetric. Dystonia associated with variants in the *THAP1* gene has reduced penetrance. Some independent studies recently reported that upon detailed clinical examination, nonmanifesting siblings or children from manifesting probands also had tremor (Zittel et al. 2010; LeDoux et al. 2012).

10.2.3 Neurophysiological Assessment

Using surface electromyography combined with an accelerometry, it has been shown that dystonic tremor is frequently more irregular than ET (Deuschl et al. 1997). Studies of the blink reflex recovery curve have shown increased R2 in dystonic tremor compared to ET (Nistico et al. 2012). The repetitive movements of DT were viewed as being irregular in both oscillatory cycle frequency and amplitude with fluctuations in each patient. It was hypothesized that the irregularity in the oscillatory train differs from more common tremors, which are more regular. Second, the waveform shape of DT was reported to have a jerky quality (i.e., waveform shape domain), caused by a rapid movement in one direction followed by a slower movement in the opposite direction. This jerkiness contrasts with the waveform of classic tremors, which are typically sinusoidal (Elble 2013b).

Tremor in dystonia mostly occurs while holding a posture or during voluntary movements, similar to tremor observed in ET (Pandey and Sarma 2016). Using a 3-axis accelerometer to compare tremor in patients with cervical dystonia and arm tremor and patients with ET, it was also found that tremor is more irregular in cervical dystonia than in ET (Shaikh et al. 2008).

It has been reported that, compared with ET, DT, and TAWD had smaller magnitudes and were more irregular in amplitude and frequency (Jedynak et al. 1991). Recent neurophysiological studies confirmed that DT has higher variability and increased instability compared to ET and TAWD (Panyakaew et al. 2020). TAWD had more characteristics in common with ET compared to DT. However, ET and TAWD varied in the interaction between voluntary movements and tremor oscillators during a simple kinetic task.

Studies with the coherence entrainment test, which quantifies entrainment on the accelerometer or surface EMG signals, showed that DT bursts varied widely in duration, reflecting jerkiness (McAuley and Rothwell 2004). The term "jerk" has a double usage. Clinically, it is considered jerky a sudden, brief, irregular, involuntary movement. On the other hand, there is no unique neurophysiological definition for jerkiness: arms or neck movements recording may generate waveform patterns that may vary forming a continuous spectrum ranging from pure sinusoidal shape to jerky (saw-tooth) shape in the others. The coherence test also showed that dystonic tremor decreases in frequency with mechanical loading, suggesting a role for mechanical inertia in setting up the oscillations.

The current consensus on tremors considers neurophysiological tests under Axis I aside from other laboratory measures (Bhatia et al. 2018). The listing of electrophysiological tests includes surface EMG to document the presence of tremor, to measure tremor frequency, and perform EMG burst analysis (including burst morphology and rhythmicity). Other measures include Fourier analysis of accelerometric and EMG recordings, with and without weight loading, to identify mechanical reflex and central neurogenic tremors. In the clinical setting, electrophysiological tests may be difficult to perform and are not ubiquitously available. Furthermore, there are no validated tests for differentiating dystonic from other tremors (van der Veen et al. 2021). Motion transducers or EMG may help measuring rhythm variability and elucidating the cause of jerkiness (e.g., differentiating fast dystonic movements from myoclonus) (van der Veen et al. 2022). No form of tremor is perfectly rhythmic or sinusoidal, and the cycle-to-cycle variability (i.e., regularity) of the tremor frequency varies with tremor amplitude. A higher tremor amplitude is probably caused by greater entrainment of motor pathways, which is likely to increase the rhythmicity. It therefore seems unlikely that ET can be distinguished from other forms of tremor simply based on rhythm variability (i.e., regularity). Tremor amplitude must be controlled when comparing different types of tremors based on rhythm regularity.

Reciprocal inhibition is a neurophysiological tool potentially useful for this purpose, although interindividual variability makes this approach inconclusive in the single patient. In a study using this technique, presynaptic inhibition was normal in six patients with ET, but absent in seven patients with cervical dystonia and upper limb tremor (Munchau et al. 2001). Patients whose EMG recording disclosed abnormally reduced presynaptic reciprocal H reflex inhibition and had larger agonist-antagonist forearm muscle co-contraction typically had early-onset arm tremor (before 20 years) and developed cervical dystonia later than patients who had normal presynaptic inhibition and late-onset arm tremor. Further research is needed to confirm whether reduced descending control over spinal circuitry in patients with early-onset arm tremor may be an underlying trait of dystonia.

Patients with DT have increased somatosensory temporal discrimination thresholds, which is instead normal in ET and in healthy controls (Govert et al. 2020). In summary, some abnormalities have been described in patients with dystonia and tremor, including reduced reciprocal inhibition in the spinal cord (in tremor associated with dystonia), increased excitability in the brainstem interneuronal

Table 10.1 Descriptions related to the expression dystonic tremor

Year	Description
1976	Dystonia and tremor in spasmodic torticollis patients (Couch 1976)
1976	Benign essential tremor in combination with idiopathic torsion dystonia (Marsden 1976)
1984	Repetitive and rhythmic dystonic movements result from the regular grouping of action potentials frequently on voluntary contractions (Fahn 1984)
1988	Focal tremor and focal dystonia related to generalized essential tremor and generalized dystonia (Rosenbaum and Jankovic 1988)
1989	The "yips" is an involuntary motor disturbance affecting golfers described most frequently as jerks, tremors, and spasms affecting the preferred arm distally and primarily during putting (McDaniel et al. 1989)
1990	Patients presenting with isolated tremors of the trunk or neck are described eventually developed cervical dystonia, sometimes with arm dystonia (Rivest and Marsden 1990)
1990	Patients with reflex sympathetic dystrophy manifested abnormalities of movement, including focal dystonia, weakness, spasms, tremor, difficulty initiating movement, and increased tone and reflexes (Schwartzman and Kerrigan 1990)
1991	Patients with early-onset ET were more likely to have hand involvement and associated dystonia than patients with late-onset ET; dystonia was more frequently associated with mild ET than with severe ET (Lou and Jankovic 1991)
1991	Dystonic tremor in idiopathic dystonia described to be postural, localized, and irregular in amplitude and periodicity, absent during muscle relaxation, exacerbated by smooth muscle contraction (Jedynak et al. 1991)
1996	Cases of focal tremors induced by different specific tasks, without overt dystonia, but considered forms of focal dystonia rather than manifestation of essential tremor (Soland et al. 1996)
1998	Definition of dystonic tremor and of tremor associated with dystonia (Deuschl et al. 1998)
2013	Introduction of the expression "primary tremor" (Elble 2013a)
2018	Definition of dystonic tremor as a syndrome (Bhatia et al. 2018)

circuits underlying the brainstem reflex (in DT), and abnormalities in sensory function (in TAWD). These abnormalities resemble those observed in patients with different focal or generalized dystonia syndromes, pointing at the lack of inhibitory mechanisms at multiple levels (spinal, brainstem, basal ganglia, and cortical), a potential electrophysiologic hallmark for dystonia. Patients with ET do not have these abnormalities (Defazio et al. 2015) (Table 10.1).

10.3 Treatment

Therapeutic options available for tremor in dystonia include drugs, botulinum toxin, deep brain stimulation (DBS), MRI-guided focused ultrasound (MRgFUS), and other procedures such as transcutaneous electrical nerve stimulation. No

Table 10.2 Treatment options for dystonic tremor

Treatment	Modalities	Efficacy
Trihexyphenidyl	Oral route: 4–10 mg/day	Mild to moderate improvement of tremor
Clonazepam	Oral route: 0.5–3 mg/day	Mild to moderate improvement of tremor, occasionally complete abolishment
Botulinum toxin	Intramuscular injection: site-dependent dose	Improvement of tremor
Deep brain stimulation	Stereotactic surgery: bentrointermediate (Vim) nucleus of thalamus, globus pallidus internus (GPi)	Improvement of tremor (Vim) and of dystonia (GPi)
MRI-guided focus ultrasound	Stereotactic noncraniotomic surgery: Vim	Improvement of contralateral tremor

randomized trials on drug efficacy on DT are available. Therefore, the treatment algorithms are based on case reports and expert consensus. Oral drugs available for treatment include trihexyphenidyl, clonazepam, propranolol, and occasionally tetrabenazine (Table 10.2).

Tremor in dystonia may have a good response to botulinum toxin, especially when involving the head, jaw, and vocal cords (Fasano et al. 2014). Botulinum toxin has also proven useful in primary writing tremor (Papapetropoulos and Singer 2006). A comparative study of patients with cervical dystonia found better response with botulinum toxin in those who also had tremor (Godeiro-Junior et al. 2008). DBS is an important modality of treatment in tremor in dystonia, especially in cases that are not responsive to conservative measures. It involves electrical stimulation of specific regions of the brain through electrodes with a subcutaneously placed pulse generator. Different sites have been targeted, such as the ventrointermediate (Vim) nucleus of the thalamus, the globus pallidus internus (GPi), and the zona incerta. A retrospective study evaluating the outcome of DBS in 10 patients found the best tremor control with Vim stimulation, although with persisting mild dystonia, whereas those with GPi stimulation had marked improvement in dystonia and around 50% improvement in tremor (Fasano et al. 2014).

MRgFUS is a novel, incision-free ablative technique used successfully in patients with essential tremor. Encouraging results with this technique have been reported in dystonic tremor as well. It was recently published that unilateral thalamotomy in the Vim nucleus of the dominant hemisphere with MRgFUS improved contralateral dystonic tremor (Fasano et al. 2016).

Although there are no clear-cut guidelines for the treatment of tremor in dystonia, it is suggested that a patient with arm tremor may be first treated with oral agents, whereas patients with jaw, head, and vocal cord tremor may be treated with botulinum toxin. Response failure with these approaches should warrant a consideration for DBS (Table 10.2).

10.4 Conclusion and Outlook

The field of dystonia and tremor is evolving quickly. Diagnostic criteria for different dystonia syndromes are being developed and tremor holds a specific place in many of these descriptions (Albanese et al. 2023). Furthermore, the classification of dystonia is under review 10 years after its initial publication. Traditional expressions, such as ET and DT, are expected to gradually disappear, leaving the place to more clear phenomenological (and neurophysiological) descriptions. For the time being, these terms remain in use mainly to describe what it is not, rather than what it is, as per the original introduction of the expression DT. Therapeutic trials require more solid clinical criteria in order to address the treatment algorithm for this condition.

References

Albanese A. Classifying tremor: language matters. Mov Disord. 2018;33(1):3–4.
Albanese A, Lalli S. Is this dystonia? Mov Disord. 2009;24(12):1725–31.
Albanese A, Lalli S. Distinguishing scan without evidence of dopaminergic depletion patients with asymmetric resting tremor from Parkinson's disease: a clinical diagnosis of dystonia is required. Mov Disord. 2010;25(16):2899.
Albanese A, Sorbo FD. Dystonia and tremor: the clinical syndromes with isolated tremor. Tremor Other Hyperkinet Mov (N Y). 2016;6:319.
Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863–73.
Albanese A, Di Giovanni M, Lalli S. Dystonia: diagnosis and management. Eur J Neurol. 2019;26(1):5–17.
Albanese A, Bhatia KP, Cardoso F, Comella C, Defazio G, Fung VSC, et al. Isolated cervical dystonia: diagnosis and classification. Mov Disord. 2023.
Apartis E. Clinical neurophysiology in movement disorders. Handb Clin Neurol. 2013;111:87–92.
Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. From the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33(1):75–87.
Cochrane GD, Rizvi S, Abrantes A, Crabtree B, Cahill J, Friedman JH. Internal tremor in Parkinson's disease, multiple sclerosis, and essential tremor. Parkinsonism Relat Disord. 2015;21(10):1145–7.
Couch JR. Dystonia and tremor in spasmodic torticollis. Adv Neurol. 1976;14:245–58.
Critchley E. Clinical manifestations of essential tremor. J Neurol Neurosurg Psychiatry. 1972;35(3):365–72.
Defazio G, Conte A, Gigante AF, Fabbrini G, Berardelli A. Is tremor in dystonia a phenotypic feature of dystonia? Neurology. 2015;84(10):1053–9.
Deuschl G. Dystonic tremor. Rev Neurol (Paris). 2003;159(10 Pt 1):900–5.
Deuschl G, Heinen F, Guschlbauer B, Schneider S, Glocker FX, Lucking CH. Hand tremor in patients with spasmodic torticollis. Mov Disord. 1997;12(4):547–52.
Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13 Suppl 3(Suppl. 3):2–23.
Deuschl G, Papengut F, Hellriegel H. The phenomenology of parkinsonian tremor. Parkinsonism Relat Disord. 2012;18 Suppl 1(Suppl 1):S87–9.

Elble RJ. Tremor: clinical features, pathophysiology, and treatment. Neurol Clin. 2009;27(3):679–95. v-vi

Elble RJ. Defining dystonic tremor. Curr Neuropharmacol. 2013a;11(1):48–52.

Elble RJ. Tremor disorders. Curr Opin Neurol. 2013b;26(4):413–9.

Erro R, Pilotto A, Magistrelli L, Olivola E, Nicoletti A, Di Fonzo A, et al. A Bayesian approach to essential tremor plus: a preliminary analysis of the TITAN cohort. Parkinsonism Relat Disord. 2022a;103:73–6.

Erro R, Pilotto A, Esposito M, Olivola E, Nicoletti A, Lazzeri G, et al. The Italian tremor network (TITAN): rationale, design and preliminary findings. Neurol Sci. 2022b;43(9):5369–76.

Espay AJ, Lang AE, Erro R, Merola A, Fasano A, Berardelli A, et al. Essential pitfalls in "essential" tremor. Mov Disord. 2017;32(3):325–31.

Fahn S. The varied clinical expressions of dystonia. Neurol Clin. 1984;2(3):541–54.

Fasano A, Bove F, Lang AE. The treatment of dystonic tremor: a systematic review. J Neurol Neurosurg Psychiatry. 2014;85(7):759–69.

Fasano A, Sammartino F, Llinas M, Lozano AM. MRI-guided focused ultrasound thalamotomy in fragile X-associated tremor/ataxia syndrome. Neurology. 2016;87(7):736–8.

Fasano A, Lang AE, Espay AJ. What is "essential" about essential tremor? A diagnostic placeholder. Mov Disord. 2018;33(1):58–61.

Ferrazzano G, Belvisi D, De Bartolo MI, Baione V, Costanzo M, Fabbrini G, et al. Longitudinal evaluation of patients with isolated head tremor. Parkinsonism Relat Disord. 2022;94:10–2.

Fishman PS. Paradoxical aspects of parkinsonian tremor. Mov Disord. 2008;23(2):168–73.

Gigante AF, Berardelli A, Defazio G. Rest tremor in idiopathic adult-onset dystonia. Eur J Neurol. 2016;23(5):935–9.

Godeiro-Junior C, Felicio AC, Aguiar PC, Borges V, Silva SM, Ferraz HB. Head tremor in patients with cervical dystonia: different outcome? Arq Neuropsiquiatr. 2008;66(4):805–8.

Gonzalez-Herrero B, Di Vico IA, Pereira E, Edwards M, Morgante F. Treatment of dystonic tremor of the upper limbs: a single-center retrospective study. J Clin Med. 2023;12(4):1427.

Govert F, Becktepe J, Balint B, Rocchi L, Brugger F, Garrido A, et al. Temporal discrimination is altered in patients with isolated asymmetric and jerky upper limb tremor. Mov Disord. 2020;35(2):306–15.

Gupta N, Pandey S. Rest tremor in dystonia: epidemiology, differential diagnosis, and pathophysiology. Neurol Sci. 2020;41(9):2377–88.

Hvizdosova L, Nevrly M, Otruba P, Hlustik P, Kanovsky P, Zapletalova J. The prevalence of dystonic tremor and tremor associated with dystonia in patients with cervical dystonia. Sci Rep. 2020;10(1):1436.

Jankovic J, Fahn S. Physiologic and pathologic tremors. Diagnosis, mechanism, and management. Ann Intern Med. 1980;93(3):460–5.

Jedynak CP, Bonnet AM, Agid Y. Tremor and idiopathic dystonia. Mov Disord. 1991;6(3):230–6.

LeDoux MS, Xiao J, Rudzinska M, Bastian RW, Wszolek ZK, Van Gerpen JA, et al. Genotype-phenotype correlations in THAP1 dystonia: molecular foundations and description of new cases. Parkinsonism Relat Disord. 2012;18(5):414–25.

Lou JS, Jankovic J. Essential tremor: clinical correlates in 350 patients. Neurology. 1991;41(2 (Pt 1)):234–8.

Marsden CD. Dystonia: the spectrum of the disease. Res Publ Assoc Res Nerv Ment Dis. 1976;55:351–67.

McAuley J, Rothwell J. Identification of psychogenic, dystonic, and other organic tremors by a coherence entrainment test. Mov Disord. 2004;19(3):253–67.

McDaniel KD, Cummings JL, Shain S. The "yips": a focal dystonia of golfers. Neurology. 1989;39(2 Pt 1):192–5.

Munchau A, Schrag A, Chuang C, MacKinnon CD, Bhatia KP, Quinn NP, et al. Arm tremor in cervical dystonia differs from essential tremor and can be classified by onset age and spread of symptoms. Brain. 2001;124(Pt 9):1765–76.

Nistico R, Pirritano D, Salsone M, Valentino P, Novellino F, Condino F, et al. Blink reflex recovery cycle in patients with dystonic tremor: a cross-sectional study. Neurology. 2012;78(17):1363–5.

Pandey S, Bhattad S. Questionable dystonia in essential tremor plus: a video-based assessment of 19 patients. Mov Disord Clin Pract. 2019;6(8):722–3.
Pandey S, Sarma N. Tremor in dystonia. Parkinsonism Relat Disord. 2016;29:3–9.
Panyakaew P, Cho HJ, Lee SW, Wu T, Hallett M. The pathophysiology of dystonic tremors and comparison with essential tremor. J Neurosci. 2020;40(48):9317–26.
Panyakaew P, Jinnah HA, Shaikh AG. Clinical features, pathophysiology, treatment, and controversies of tremor in dystonia. J Neurol Sci. 2022;435:120199.
Papapetropoulos S, Singer C. Treatment of primary writing tremor with botulinum toxin type a injections: report of a case series. Clin Neuropharmacol. 2006;29(6):364–7.
Rivest J, Marsden CD. Trunk and head tremor as isolated manifestations of dystonia. Mov Disord. 1990;5(1):60–5.
Rosenbaum F, Jankovic J. Focal task-specific tremor and dystonia: categorization of occupational movement disorders. Neurology. 1988;38(4):522–7.
Saifee TA. Tremor. Br Med Bull. 2019;130(1):51–63.
Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. Neurology. 1990;40(1):57–61.
Shaikh AG, Jinnah HA, Tripp RM, Optican LM, Ramat S, Lenz FA, et al. Irregularity distinguishes limb tremor in cervical dystonia from essential tremor. J Neurol Neurosurg Psychiatry. 2008;79(2):187–9.
Shaikh AG, Beylergil SB, Scorr L, Kilic-Berkmen G, Freeman A, Klein C, et al. Dystonia and tremor: a cross-sectional study of the dystonia coalition cohort. Neurology. 2021;96(4):e563–e74.
Shimazaki R, Ikezawa J, Okiyama R, Azuma K, Akagawa H, Takahashi K. Dystonic tremor in adult-onset DYT-KMT2B. Intern Med. 2022;61(15):2357–60.
Soland VL, Bhatia KP, Volonte MA, Marsden CD. Focal task-specific tremors. Mov Disord. 1996;11(6):665–70.
Stamelou M, Charlesworth G, Cordivari C, Schneider SA, Kagi G, Sheerin UM, et al. The phenotypic spectrum of DYT24 due to ANO3 mutations. Mov Disord. 2014;29(7):928–34.
van Brummelen EMJ, Ziagkos D, de Boon WMI, Hart EP, Doll RJ, Huttunen T, et al. Quantification of tremor using consumer product accelerometry is feasible in patients with essential tremor and Parkinson's disease: a comparative study. J Clin Mov Disord. 2020;7:4.
van der Veen S, Klamer MR, Elting JWJ, Koelman J, van der Stouwe AMM, Tijssen MAJ. The diagnostic value of clinical neurophysiology in hyperkinetic movement disorders: a systematic review. Parkinsonism Relat Disord. 2021;89:176–85.
van der Veen S, Caviness JN, Dreissen YEM, Ganos C, Ibrahim A, Koelman J, et al. Myoclonus and other jerky movement disorders. Clin Neurophysiol Pract. 2022;7:285–316.
Yanagisawa N, Goto A. Dystonia musculorum deformans. Analysis with electromyography. J Neurol Sci. 1971;13(1):39–65.
Zittel S, Moll CK, Bruggemann N, Tadic V, Hamel W, Kasten M, et al. Clinical neuroimaging and electrophysiological assessment of three DYT6 dystonia families. Mov Disord. 2010;25(14):2405–12.

Chapter 11
Cerebellar Lesions and Tremor

Andrea Kovács and Anita Kamondi

Abstract The cerebellum, among others, has key functions in organising fine, goal-oriented limb movements. The most frequent clinical symptoms of cerebellar dysfunction are tremor and dysmetria. The features of tremor induced by structural or functional lesions of the cerebellum are in many cases overlapping with other tremor syndromes; however, there are important characteristics that might help the differentiation. Although some patients show a tremor with marked amplitude, in most of the cases cerebellar tremor can be identified only by quantitative assessment because due to its small amplitude and low frequency, it might be overlooked at bedside clinical examination. The pathomechanism of cerebellar tremor is not fully understood. Neither the size nor the localisation of the cerebellar lesion predicts the appearance of pathological tremor or its quantitative characteristics. The cerebellar tremor caused by acute ischemic stroke usually recovers after 3–6 weeks. Tremors caused by chronic disorders involving the cerebellar pathways cause progressive tremor. The treatment options for cerebellar tremor are limited.

Keywords Cerebellar tremor · Quantitative tremor parameters · Recovery of tremor · Lesion-tremor mapping

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11.1 Introduction

Tremor in cerebellar lesions (*cerebellar tremor*) is traditionally considered a distinct tremor entity. In the 1998 Consensus Statement on Tremor, cerebellar tremor was defined as a symptomatic, uni- or bilateral *intention tremor* of cerebellar origin with a frequency below 5 Hz, which might also appear in postural position, but never at rest (Deuschl et al. 1998). In the 2018 Consensus Statement on Tremor, the *intention tremor syndrome* has replaced the definition of the previous cerebellar tremor. It has been stated that intention tremor syndrome is a rarely isolated tremor syndrome, with a frequency below 5 Hz, presenting with or without other localising signs (Bhatia et al. 2018). According to a recent systemic study, cerebellar tremor, which is tremor in cerebellar lesions, is a pathological postural and intentional tremor with low frequency (lower than 3 Hz) and usually with low amplitude. Co-occurrent brainstem involvement is often present, due to the partially common blood supply of the cerebellum and brainstem (Kovács et al. 2019). This description of cerebellar tremor is in accordance with Gordon Holmes' observations. In cases with cerebellar lesions, he reported intention tremor ('when reaching a target'), postural tremor ('static tremor') and a third type of tremor involving the head and the trunk (Holmes 1922). Lenka and Louis draw attention that the interchangeable use of *intention tremor* and *cerebellar tremor* is an incorrect oversimplification since the cerebellum is involved in various tremor forms like postural tremor, kinetic tremor (this term remains widely used), rest tremor and orthostatic tremor, which extend far beyond intention tremor. Similarly, tremor occurs in various chronic and acute neurological diseases linked to the cerebellum, like spinocerebellar ataxias, cerebellar tumours and cerebellar strokes (Lenka and Louis 2019).

The aim of this chapter is to present recent data on cerebellar tremor, focusing on tremor caused by focal lesions of the cerebellum.

11.2 Epidemiologic Data

Cerebellar tremor is known as a cardinal sign of focal cerebellar lesions. However, there has been no systemic investigation into its prevalence for many years. The majority of related publications were case reports. The first systemic study involved 68 patients with focal cerebellar lesions: acute and chronic vascular lesions, malignant primary CNS tumours, secondary CNS tumours (metastases), meningiomas and other lesions (MS, abscess, cavernoma) (Kovács et al. 2019). This study showed a 47% prevalence (32 out of 68 patients) of pathological tremor in focal cerebellar lesions. The remaining 35 patients had physiologic tremor. Physiologic tremor was found in meningiomas and chronic vascular lesions. The occurrence of pathological tremor in cerebellar lesions is summarised in Table 11.1.

Table 11.1 Prevalence of pathological tremor in focal cerebellar lesions of various origins

Nature of lesion		Number of patients	Number of patients with pathological tremor (%)
Acute vascular lesion		28	18 (64.28%)
Chronic vascular lesion		6	0 (0%)
Primary malignant CNS tumours	adults	3	3 (100%)
	children	6	3 (50%)
Metastases		11	5 (45.45%)
Meningiomas		9	1 (11.11%)
Other lesions (MS, abscess, cavernoma)		5	2 (40%)

11.3 Pathophysiological Basis of Cerebellar Tremor

11.3.1 Anatomy of the Cerebellum

The cerebellum is composed of anterior (lobules I–V), and posterior lobes (lobules VI–IX) – separated by the primary fissure – and the flocculo-nodular lobe (lobule X). The midline structure of the cerebellum, the vermis, separates the two cerebellar hemispheres. The cerebellar grey matter is organised into three layers of the cerebellar cortex (molecular, Purkinje cells and granular layers) and the deep nuclei of the cerebellum, which are (in latero-medial direction) the dentate, the interposed (globose nucleus + emboliform nucleus) and the fastigial nuclei (Lai 2010). Three functional structures of the cerebellum are identified (Lawrenson et al. 2018): (1) Microzones: the cerebellum is composed of microzones, each containing about 1000 Purkinje cells, all having a somatotopic receptive field. Purkinje cells are organised in narrow strips, being perpendicular to the surface of the cerebellar cortex (Cerminara et al. 2013). (2) Modules: the cerebellum is organised into modules. A module is composed of several non-adjacent parasagittal bands of Purkinje cells projecting to specific areas of cerebellar nuclei and gating segregated projections from the inferior olive (D'Angelo and Casali 2013). (3) Segregated loops: there are segregated loops between the cerebellum and the prefrontal, parietal, paralimbic cortices and the superior temporal sulcus (Schmahmann 2013). Both corticopontine motor projections and association cortex projections are somatotopically organised (Lawrenson et al. 2018). Three somatotopic maps were identified in the cerebellum: one is located in the anterior lobe (in lobules I–V), the other is located in lobule VIII (Stoodley and Schmahmann 2018; Grodd et al. 2001) and the third one is located in lobules VI–VII (Schlerf et al. 2010). The anterior lobe and lobule VIII get dense spinocerebellar afferent fibres (Oscarsson 1965; Voogd and Feirabend 2012). On the contrary, lobules VI and VII do not get somatosensory fibres and are therefore not directly connected with the spinal cord. They are in reciprocal connection with the prefrontal and association cortices (Schmahmann

2013), being responsible for cognitive performance, including concentration tasks during complex movements. According to the above presented functional anatomy, the anterior lobe is called the motor cerebellum, while the posterior lobe is called the cognitive cerebellum. Classification of cerebellar symptoms echoes the same logic: motor cerebellar symptoms, cognitive cerebellar symptoms and vestibulo-cerebellar symptoms (Lawrenson et al. 2018).

11.3.2 Role of the Cerebellum in Motor Learning

The redundant structure of the cerebellum is ideal for motor learning (Marr 1969). The aim of motor learning is to adjust planned movements that imply predictive mechanisms. According to the current theory, the cerebellum anticipates the consequences of actions driven by the cortex and adjusts the execution to achieve the goal of the action (Lawrenson et al. 2018). Two models take part in this theory: the forward model and the inverse model (Popa et al. 2013, 2017). The forward model predicts the consequence of the action based on information about the present state. The inverse model transforms a desired achievement into the necessary commands to reach it. The cerebellum stores internal models and makes a comparison between the actual sensation and the predicted sensation (Molinari et al. 2009). If there is a match, the known pattern is maintained. If there is a mismatch, the cerebellum starts to recalibrate/repair the pattern (Gruol et al. 2016). Impairment of motor learning results in dysmetria, ataxia and tremor (Lawrenson et al. 2018).

11.3.3 Role of the Cerebellum in Various Tremor Syndromes

The cerebellum is involved in the pathogenesis of all tremor syndromes as it is the hub of a network for motor regulation (Elble 2000).

Clinical, neurophysiological, imaging and neuropathological data prove that the cerebellum is involved in the pathogenesis of essential tremor (ET). Clinical and objective assessments showed that a group of ET patients presents with mild (sub)clinical cerebellar signs. A new term of *ET plus syndrome* was introduced in the 2018 Tremor Consensus Statement for this patient group (Bhatia et al. 2018). Slight dysarthria (Kronenbuerger et al. 2009), subclinical eye movement disorders (Helmchen et al. 2003) and impaired tandem gait (Rao et al. 2011) are part of the syndrome. Repetitive transcranial magnetic stimulation of the cerebellum transiently decreased the amplitude of essential tremor (Gironell et al. 2015). PET studies proved bilaterally enhanced metabolism in both cerebellar hemispheres of ET patients (Colebatch et al. 1990). Diffusion tensor imaging MRI studies showed decreased fractional anisotropy in the superior cerebellar peduncle and in the dentate nucleus of ET patients (Nicoletti et al. 2010). Neuropathological examinations found the cerebellum as the most affected structure: loss of Purkinje

cells, axon degeneration, abnormal branching of dendrites, an increase of the climbing fibre/Purkinje cell ratio and loss of GABA receptors in the dentate nuclei (Louis 2016). Recent studies raised the possibility that essential tremor may not be caused by increased cerebellar drive, but by cerebellar dysfunction especially at the level of the Purkinje neuron (cerebellar decoupling hypothesis). This is proved by the significantly decreased dentate nucleus functional connectivity with cortical, subcortical and cerebellar areas in essential tremor patients. The cerebello-thalamic connections showed a negative correlation with tremor amplitude (Madelein van der Stouwe et al. 2020).

The pathogenesis of Parkinson's disease (PD) is linked to the thalamus and basal ganglia. However, some evidence suggests that the cerebellum is also involved. A SPECT and functional MRI study showed that both the basal ganglia and the cerebellum show increased activity at the onset of rest tremor episodes. However, only the cerebellar activity correlated with the amplitude of the tremor. This finding is the basis of the 'dimmer-switch' theory: the cerebellum regulates tremor amplitude, whereas the basal ganglia define the onset and end of a rest tremor episode (Helmich et al. 2012). Moreover, increased connectivity was found between the cerebello-thalamo-cortical pathways and the basal ganglia. This might explain the effectiveness of both STN-GPi and VLp as deep brain stimulation (DBS) targets in PD. At the same time, it raises the possibility that the hyperactivity of the cerebellum is a result of a compensatory mechanism to overcome the hypoactivity of basal ganglia in PD (Wu and Hallett 2013).

The cerebellum is involved in many other degenerative diseases like multisystem atrophy (Dash et al. 2019), spinocerebellar ataxias (Adanyeguh et al. 2018) and fragile X tremor ataxia syndrome (Wang et al. 2017). Focal cerebellar lesions might cause tremor as well. Cerebellar tremor represents a distinct entity among tremor syndromes.

11.3.4 Animal Experiments on Cerebellar Tremor

In 1894, Ferrier and Turner carried out experiments on 26 monkeys by lesioning various cerebellar structures. They observed action tremor and upper limb clumsiness accompanying various lesions. Action tremor emerged always ipsilateral to the side of the lesion (Ferrier 1894). These observations showed that focal structural damage of the cerebellum might induce tremor. Nearly 70 years later, Larochelle et al. could not provoke tremor by cooling the dentate nucleus and by damaging the superior cerebellar peduncle, only when intramuscular harmaline, which increases the effect of brainstem monoaminergic substances, was co-administered (Larochelle et al. 1970). This finding suggested the importance of the brainstem in evoking tremor. Later experiments found that the inferior olive could act as a pacemaker in tremor genesis (Park et al. 2010). Flament and Hore demonstrated that cooling of the dentate nucleus provoked low frequency tremor. Moreover, they showed that tremor frequency was influenced by isometric and isotonic muscle contractions

(Flament and Hore 1988). This finding raised the suspicion that central components of cerebellar tremor might be modulated by peripheral components.

11.3.5 Theories on Cerebellar Lesion Location and Tremor Genesis

It has been generally accepted that cerebellar tremor is a consequence of lesion of the dentato-rubro-thalamic tract (DRT) or the Guillain-Mollaret triangle (Elble 2000). Cerebellar tremor might develop without cerebellar lesion if the DRT is damaged (Marek et al. 2015). The DRT is involved in most tremor syndromes, which makes it an ideal DBS target (Coenen et al. 2014). Earlier theories suggested that the cerebellum and basal ganglia worked as separate entities. Newer studies showed that these functional systems are interconnected at the subcortical level by disynaptic projections from the subthalamic nucleus (in the basal ganglia) to the cerebellar cortex and from the dentate nucleus (in the cerebellum) to the striatum, respectively. Based on these observations, the basal ganglia, the cerebellum and the cerebral cortex work as an integrated network in tremor genesis. Synaptic dysfunctions or pathological activity of one or the other node of the network might induce network-wide effects (Bostan and Strick 2018). Tremor, including cerebellar tremor, is most probably a result of network impairment.

11.4 Neurophysiological Examination of Tremor

Neurophysiological examination of tremor provides objective information about tremor characteristics and it helps to differentiate between pathological and physiologic tremor and between central and peripheral tremor and it supports the identification of different forms of pathological tremors. Furthermore, objective tremor measurements help to assess disease progression and treatment efficacy.

11.4.1 Development of Quantitative Tremor Recording Devices: A Historical Overview

Objective tremor recording began with graphical recording devices like tambours, which were modified from instruments developed for other purposes (Eshner 1897). Electricity enabled new tremor recording methods. Early myographs and electrophysiological examination methods were unable to store data (Grimaldi and Mario 2013). Potentiometer-like sensors and electrodes in combination with oscilloscopes were used for many years. Since then, several new methods have been

introduced for tremor registration, but according to the 1998 Consensus Statement of Tremor, electromyography (EMG) still remains the most reliable method of confirming or excluding negative myoclonus, high frequency, irregular tremors and the only method of detecting the agonist and antagonist muscles' firing pattern (Deuschl et al. 1998). Long-term EMG is an objective method to differentiate between parkinsonian tremor and essential tremor (Breit et al. 2008). Since the 1990s, concomitant EMG and other electrophysiological recordings (e.g. EEG) have enabled non-invasive and invasive corticomuscular coherence investigations (Conway et al. 1995). These detect tremorogenic neuronal assemblies of certain subcortical areas (thalamus, globus pallidus internus, subthalamic nucleus) by making a correlation between the firing pattern of 'tremor cells' and the tremor of the limbs of parkinsonian patients (Lenz et al. 1994).

Over time, sensors have become more sophisticated, and digital signal processing has significantly improved data processing and storage (Grimaldi and Mario 2013). Nowadays, EMG is often replaced by accelerometry as it is cheaper, lighter and easier to use. Accelerometric tremor recordings have been performed since the 1950s but it became a reliable method only later on. Accelerometers measure linear acceleration and limb orientation with respect to gravity. Uni-, bi- and triaxial accelerometers have been developed. There is still no validated method to distinguish between data due to acceleration and gravity. Low-pass filtering is commonly used. Gyroscopes have been used since 1975 and quickly became very popular. Gyroscopes measure rotational acceleration and they have no gravitational artefact in contrast to accelerometers (Agate et al. 1956). Gyroscopes are considered as presenting long-term stability, eliminating the need for periodic recalibration. However, a disadvantage is the presence of a low frequency bias, mainly due to temperature effects (Grimaldi and Manto 2010). Inertial measurement units often combine accelerometers and gyroscopes (sometimes also magnetometers) to get even more precise motion analysis. Some classical methods like drawing Archimedes spirals gained new potentials due to digitalisation since 1998 (Pullman 1998). It is a figure-copying test, which provides visual information about macrography, micrography, loop-to-loop width tightness, variation, etc. At the same time, it may quantify signs of bradykinesia (Aly et al. 2007).

Today's core challenge in modern motion analysis is patients' long-term monitoring in home settings. However, we do not know yet if continuous recordings do better detection of clinical change than rating scales. Long-term monitoring requires wireless sensors described for the first time in 2009. Portable systems contain a combination of different sensors like accelerometer, gyroscope and magnetic motion sensor (Barrantes et al. 2017; Lukšys et al. 2018; Shawen et al. 2020; McNames et al. 2019). Physicians are able to give therapeutic advice after online data analysis. The most recent methods use accelerometers placed into smartphones. They have been validated since 2013 for registration as well as for data analysis (McNames et al. 2019; van Brummelen et al. 2020).

Based on the above, there has been a significant technological development in the objective assessment of tremor. The development is expected to continue,

driven by more and more sophisticated technologies and the expectation to provide personalised and timely treatment for patients (Ciuti et al. 2015).

11.4.2 Tremor Quantifying Parameters

The acquired data (by various sensors) are time series showing changes in voltage over time (in the case of EMG) or acceleration over time (in the case of accelerometry). When change over time is analysed, that is called *time domain* analysis. As tremor is periodic by definition, the frequency content of the signal might provide more information than the original waveform (Grimaldi and Manto 2008). Therefore, in the last decades significant effort was put into tremor frequency analysis. The best approach to transform data from the time domain into (sinusoids of different frequencies) the *frequency domain* is fast Fourier transformation, as it is computationally simple and fast (Engin 2007). However, Fourier transformation analysis assumes that the signal is stable over time (Vial et al. 2019). Moreover, it has been shown that tremor frequency is not disease specific (Deuschl et al. 1998). Therefore, frequency domain characteristics are not enough to differentiate among pathological tremor forms (Edwards and Beuter 2000). As a consequence, time domain analysis regained popularity, and the growing number of time domain parameters are used together with frequency domain parameters for tremor analysis nowadays.

Since there is no gold standard or accepted and widely used combination of tremor parameters, research groups choose their own set of tremor characteristics which is appropriate for the aim of their specific study. Here we will present the most common frequency domain and time domain parameters.

Frequency Domain Parameters

Peak frequency – The frequency of the highest peak in the power spectrum of the tremor signal. Synonyms: dominant frequency, peak power frequency.
Median frequency – The frequency below which lies 50% of the power in the spectrum and above which lies the other 50%. Synonym: centre frequency.
Mean frequency – The frequency below which lies 50% of the power calculated by averaging, if frequency distribution follows non-Gaussian distribution. Synonyms: mean power frequency, instantaneous mean frequency.
Frequency dispersion – The width of the frequency range centred at the median frequency that contains 66% of the power in the spectrum. It shows the degree of regularity and, thus, the degree of pathology of tremor. It is high in physiologic tremor and low in pathological tremors. Synonyms: dispersion around the median frequency, variance, power dispersion, second stage tremor frequency range about the median.
Relative power of frequency range – The degree to which a certain frequency range contributes to the total power. Synonyms: proportional power, power percentage.

Harmonic index – The measure of how close the spectrum is to a single narrow peak (as in the case of a simple harmonic oscillator).

Time Domain Parameters

Tremor intensity – The degree of linear or angular displacement of a body part or limb. Synonyms: amplitude, tremor severity, tremor size, tremor energy.
Coherence – Synchrony of two different signals (e.g. EMG and accelerometer).
Entropy – It is a measure of the spread of the data. It gives a single number between 0 and 2, which reflects the predictability of future values in a signal on the basis of previous values. Data with a broad, flat probability distribution will have high entropy (towards 2). Data with a narrow, peaked distribution will have low entropy (towards 0).

11.4.3 Tremor Recording and Analysis in Cerebellar Tremor

As cerebellar tremor has usually low or normal amplitude, 30% of patients with pathological tremor can be missed without neurophysiological tremor assessment (Kovács et al. 2019). Patients with cerebellar lesions in the acute phase of their disease have to be assessed for tremor in hospital settings. Therefore, accelerometry is the best tool, as it is easy to use even in intensive care units. While many research teams use a high-pass filter to eliminate frequency components below 2 Hz, cerebellar tremor should be assessed without filtering out low frequencies, since cerebellar tremor itself is a very low frequency tremor (2.38 ± 0.88 Hz in postural position and 2.91 ± 0.95 Hz in intentional position) (Kovács et al. 2019). Exclusion of frequency components below 2 Hz will make it impossible to detect all characteristic, pathological frequency components of cerebellar tremor. Cerebellar tremor should be looked for in resting, postural and intentional positions as well. Tremor parameters in the low frequency domain are useful to differentiate pathological cerebellar tremor from other pathological tremors and physiologic tremor (Kovács et al. 2019). Centre frequency (CF) or peak frequency, frequency dispersion and relative power of 0.9–3 Hz frequency range are recommended. Most laboratories use peak frequency instead of centre frequency as the centre frequency might be irrelevant in a biological context in cases of bimodal/trimodal spectra that might occur, for instance, in physiologic tremor (Fig. 11.1). In case of low frequency cerebellar tremor, spectra are unimodal, and the power is concentrated into the low frequency range. This way, peak frequency and centre frequency are overlapping (Fig. 11.1) in cerebellar tremor. The overlap of centre and peak frequency is a sign of pathology, too. The relative power of the 0.9–3 Hz frequency range is a very sensitive parameter to quantify the degree of pathological changes. This is higher than 55% in cerebellar tremor, whereas it is lower than 20% in physiologic tremor.

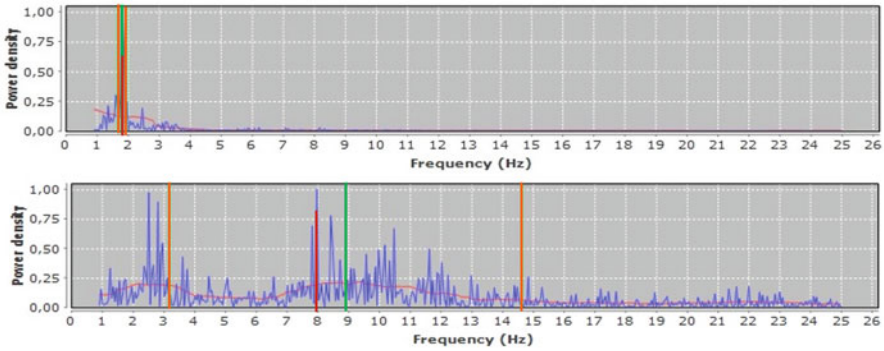

Fig. 11.1 Relation between peak frequency and centre frequency in the bimodal spectrum of physiologic tremor (lower graph) and in the unimodal spectrum of cerebellar tremor (upper graph). Peak frequency is illustrated with the red lines and centre frequency with the green lines. The distance between the yellow lines and the green lines shows frequency dispersion. Note the overlap of centre frequency and peak frequency in pathological, cerebellar tremor

Frequency dispersion is another tool to quantify the degree of pathology. It is lower than 2 Hz in cerebellar tremor and higher than 4 Hz in physiologic tremor. An increase in tremor amplitude might also be a pathological sign but only in case if it is present ipsilaterally to the affected side only (Kovács et al. 2019). Tremor amplitude might be increased in 28% of cases with low frequency cerebellar tremor. Moreover, tremor amplitude might be affected alone, without altered frequency parameters. This tremor form is called high amplitude–normal frequency tremor and it develops in 10% of all patients with cerebellar lesions (Kovács et al. 2019).

11.5 Clinical Characteristics and Neurophysiological Aspects of Cerebellar Tremor

There were only a few systemic studies that focused on the clinical aspects of cerebellar tremor. In 1922, Gordon Holmes provided the first clinical observations on human cerebellar tremor (Holmes 1922), examining gunshot soldiers with cerebellar lesions and patients with cerebellar tumour. He observed three types of tremor with possibly different pathomechanisms: (1) ‘static tremor’, that is, with the present nomenclature, equivalent to postural tremor; (2) tremor ‘when reaching a target’, that is intention tremor; and (3) a third type, involving the head and the trunk. According to his explanation, the main cause of tremor is cerebellar hypotonia and muscular asthenia. He also described as a pathological sign that fine vibration of the upper limb, which might be considered physiologic tremor, disappeared on the affected side.

Data regarding the frequency of cerebellar tremor originating from animal experiments showed different results. The tremor frequency measured on the

forearm of monkeys was 3–5 Hz (Flament and Hore 1988; Brooks et al. 1973), and in other studies it was 5–8 Hz (Atkin and Kozlovskaya 1976). The 3–5 Hz frequency decreased to 1.7–2.5 Hz during isometric contraction of the forearm muscles (Flament and Hore 1988). Holmes estimated the frequency of the third type of tremor (involving the head and the trunk) to be 4 Hz but did not carry out objective measurements. Quantitative tremor registrations in human cerebellar tremor were performed in a few studies only (Lawrenson et al. 2018). Using a goniometer, Cole et al. measured 5–7 Hz upper limb tremor in patients with cerebellar lesions and 8–12 Hz tremor in lower brainstem lesions (Cole et al. 1988). Milanov's EMG studies in patients with cerebellar damage (10 patients with cerebellar degeneration, 4 with multiple sclerosis, 4 with Wilson's disease and 4 with cerebrovascular disease) showed 8–12 Hz frequency that was similar to the frequency range of the physiologic tremor (Milanov 2001). The amplitude of cerebellar tremor is often small (Cole et al. 1988); therefore, it is barely visible on clinical examination (Milanov 2001).

In our recent study on cerebellar tremor, we examined 68 patients with focal cerebellar lesions. Pathological rest tremor was not detected in any patient. We found intention and/or postural tremor in 13 patients (19.11%) based on bedside clinical examination. Tremor severity did not exceed one point on the Fahn-Tolosa-Marin scale. Quantitative tremorometry detected pathological tremor in 47% of all patients. Our measurements proved that as much as two thirds of the patients with pathological cerebellar tremor could be diagnosed only with objective, quantitative tremor assessment. Quantitative parameters of rest tremor did not differ from controls. Pathological alterations were found in postural and intentional positions. Based on quantitative analysis of tremor assessment, the following three different tremor patterns were recognised:

1. Physiologic tremor
2. Low frequency tremor: centre frequency was lower than the lower limit of the normal range in at least two positions (postural, intentional).
3. High amplitude–normal frequency tremor: the tremor amplitude was higher than the higher limit of the normal range in at least two positions (postural, intentional), and it occurred only ipsilaterally to the side of the lesion. Centre frequency was normal in this tremor type.

11.5.1 Physiologic Tremor in Cerebellar Lesion

We registered physiologic tremor in 52.94% of our patients with focal cerebellar lesions. Centre frequency, frequency dispersion, the relative power of tremor in the 0.9–3 Hz frequency range and tremor intensity were normal. The centre frequency was 7–8 Hz. When using weight load, centre frequency significantly decreased (CF: 6.35 ± 1.40, $t = 4.83$, df $= 23$; $p < 0.001$). Frequency dispersion was 4–5 Hz. The relative power of tremor in the 0.9–3 Hz frequency range was $22.83 \pm 7.02\%$ in the

Table 11.2 Mean value and standard deviation of tremor parameters in the three tremor groups

Parameters	**Low frequency tremor** (n=25)		**Physiologic tremor** (n=36)		**Adult controls** (n=30)		**High intensity tremor** (n=4 adults)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Tremor intensity								
RT	0.06	0.02	0.07	0.03	0.06	0.01	0.06	0.02
PT	0.25	0.17	0.19	0.05	0.19	0.04	0.35	0.17
PTwl	0.21	0.11	0.20	0.06	0.18	0.04		
IT	0.34	0.19	0.25	0.07	0.22	0.05	0.51	0.13
Center frequency								
RT	12.82	1.24	13.33	1.55	14.13	1.30	13.26	1.30
PT	2.38	0.88	7.81	1.29	7.87	0.98	8.66	1.67
PTwl	2.50	0.69	6.39	1.40	6.54	1.14		
IT	2.91	0.95	7.12	1.40	8.04	1.06	8.9	1.3
Frequency dispersion								
RT	7.18	0.53	7.15	0.61	6.91	0.86	7.05	0.52
PT	1.50	1.17	4.55	1.07	4.66	0.64	4.33	1.49
PTwl	1.57	1.10	4.02	0.85	4.03	0.93		
IT	1.70	1.47	4.26	1.33	4.75	0.91	2.79	1.14
Relative power of 0.9-3 Hz								
RT	6.69	2.50	6.93	1.85	6.67	1.87	6.67	0.78
PT	56.93	14.08	22.83	7.02	20.68	5.86	18.16	9.68
PTwl	56.88	12.42	29.13	7.59	25.59	7.94		
IT	54.43	15.84	19.86	7.60	17.49	4.83	13.19	10.80

Note: Values marked with red are significantly different from the other groups presented
Abbreviations: *RT* rest tremor, *PT* postural tremor, *PTwl* postural tremor with weight load and *IT* intentional tremor

postural position and 19.86 ± 7.60% in the intentional position. Tremor intensity was on average 0.2–0.25 m/s^2. A typical power spectrum of physiologic tremor is illustrated in Fig. 11.2, upper panel. Mean values for each parameter in each position are presented in Table 11.2.

11.5.2 Low Frequency Tremor in Cerebellar Lesion

Low frequency tremor was found in 36.76% of our patients. Low centre frequency, decreased frequency dispersion and increase of relative power of the 0.9–3 Hz frequency range were characteristic of this tremor. The centre frequency was 2.38 ± 0.88 Hz in the postural position and 2.91 ± 0.95 Hz in the intentional position. Weight load did not decrease the centre frequency. Frequency dispersion was low, around 1.5 Hz. The relative power of the 0.9–3 Hz frequency range was about 50% in each position, which was two times higher than in controls. Tremor intensity, determined by the amplitude of the tremor, was slightly higher than normal in only seven patients (28% of all patients who had low frequency tremor), with mean values between 0.25 and 0.34 m/s^2. In Fig. 11.2, the mid panel illustrates

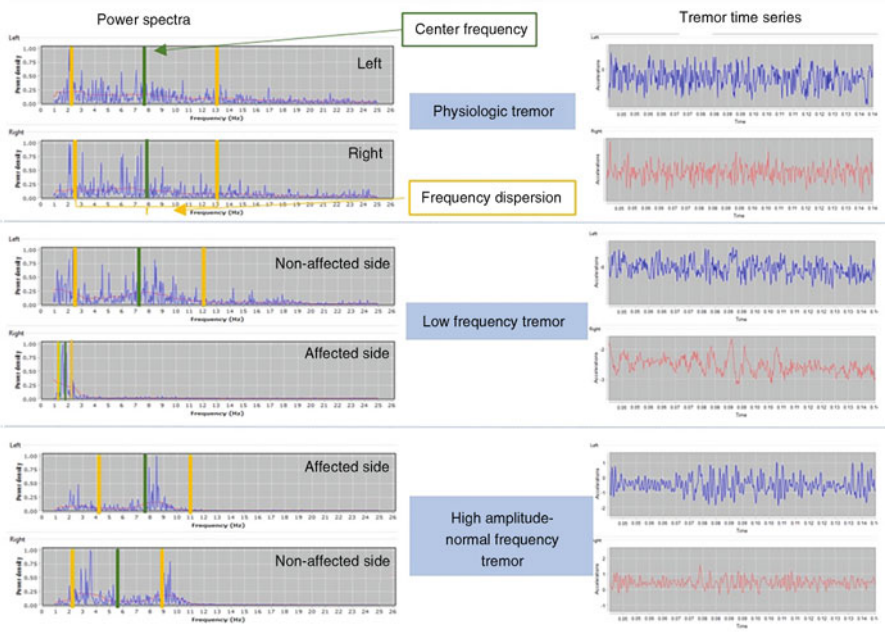

Fig. 11.2 Tremor time series and their power spectra in the three tremor types in patients with focal cerebellar lesion. Figures on the right show tremor time series registered with accelerometer. Figures on the left show power spectra resulted from the fast Fourier transformation of the corresponding time series. Centre frequency (CF) is illustrated with the green line. Frequency dispersion is represented by the distance between the yellow line and the green line. The upper part of the figure shows an example of physiologic tremor, which was collected from a patient suffering from cerebellar metastasis. The lesion involved all cerebellar lobules and deep nuclei on both sides. All tremor parameters were normal: tremor intensity (TI) was 0.14 m/s^2 (left) and 0.2 m/s^2 (right); CF was 7.85 Hz on both sides; frequency dispersion (FD) was 4.8 Hz (left) and 5.8 Hz (right); relative power (RP) of 0.9–3 Hz range was 20.2% (left) and 19.7% (right). The middle plots showing low frequency tremor were recorded from a multiple sclerosis patient with a tumefactive lesion involving lobules I–V, IX– X and the dentate nucleus unilaterally. The tremor on the affected side had normal TI (0.15 m/s^2), decreased CF (1.9 Hz), low FD (0.5 Hz) and increased RP of 0.9–3 Hz range (59.95%). The unaffected side had normal TI (0.16 m/s^2), normal CF (7.1 Hz), normal FD (4.7 Hz) and normal RP of 0.9–3 Hz (20.92%). The lower plots showing high amplitude-normal frequency tremor were recorded from a patient with a tumour (with unidentified histology) involving the upper brainstem and lobules I–V, IX and the dentate and fastigial nucleus unilaterally. The tremor on the affected side had three times higher TI (0.58 m/s^2) compared to the unaffected side (0.25 m/s^2). CF was normal on both sides (7.8 Hz – affected, 5.6 Hz – unaffected), and FD was normal on both sides (3.5 Hz – affected, 3.56 Hz – unaffected). RP of 0.9–3 Hz range was also normal on both sides (25.94% – affected, 24.91 – unaffected)

a typical graph of low frequency tremor, compared to physiologic tremor. Mean values for all parameters and positions are presented in Table 11.2.

11.5.3 High Amplitude–Normal Frequency Tremor in Cerebellar Lesion

High amplitude–normal frequency tremor was found in 7 out of 68 of our patients (10.29%) with focal cerebellar lesions, including four adults and three children. In this tremor type, the centre frequency was normal in both postural and intentional positions (around 8.5–9 Hz). Frequency dispersion was normal in the postural position, but it was decreased in the intentional position (around 2 Hz). Tremor intensity was elevated only ipsilaterally to the side of the lesion. The mean value of tremor intensity was 0.35 ± 0.17 m/s^2 in the postural position and 0.51 ± 0.13 m/s^2 in the intentional position. In children, the normal range was different from those in adults, and normal data were available only for postural position. In children, centre frequency was normal, frequency dispersion was low (around 2 Hz) and tremor intensity was significantly elevated (0.90 ± 0.30 m/s^2). Figure 11.2 lower panel illustrates a typical graph of high amplitude–normal frequency tremor. Mean values for each parameter and position are presented in Table 11.2.

Statistics revealed that patients with physiologic tremor did not differ from controls. In contrast, patients with low frequency tremor had significantly lower frequency dispersion and centre frequency and significantly higher relative power in the 0.9–3 Hz range than patients with physiologic tremor and controls (Kovács et al. 2019).

11.6 Correlation of Imaging Data and Tremor Characteristics in Cerebellar Lesions

Cerebellar functions are topographically arranged, enabling cerebellar modulation of vestibular, sensorimotor and cognitive/limbic domains via cerebrocerebellar circuits (Stoodley and Schmahmann 2018). The primary sensorimotor cerebellum linked with cerebral sensorimotor areas is in the anterior lobe and adjacent parts of lobule VI; the secondary sensorimotor representation is in lobule VIII. Leg and foot are represented in lobules II, III and VIII; the hand is represented in lobules IV, V and VIII. Proximal muscles are represented in the midline, whereas distal muscles are in the lateral parts of the cerebellum. Orofacial movements are represented in the paravermal lobules V and VI. The cognitive cerebellum in the posterior lobe includes lobules VI, VIIA, Crus I and II and lobule VIIB and it is interconnected with the association and paralimbic cerebral cortices. Language skills engage the right, while visual-spatial tasks the left posterolateral cerebellum. Affective/emotional processing and autonomic functions are regulated by the so-called limbic cerebellum in the posterior vermis (Stoodley and Schmahmann 2018). This would account for the following consequences: lesions in the anterior lobe might cause the cerebellar motor syndrome, lesions in the posterior lobe might cause cognitive affective Schmahmann syndrome and lesions in the vermis cause

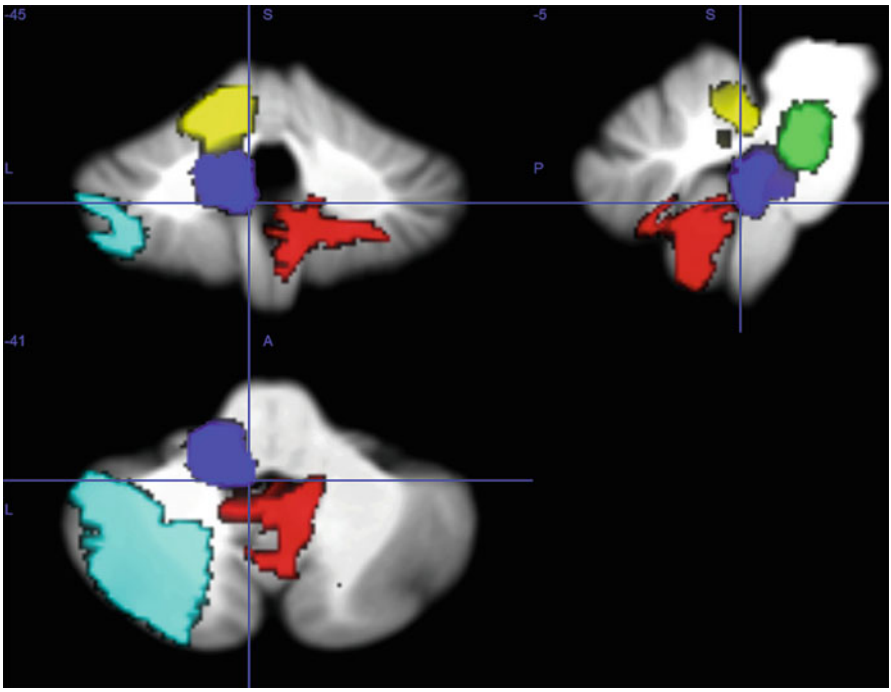

Fig. 11.3 Lesions with characteristic location for various tremor types. Lesions affecting the midline structures are presented in blue. They might be associated with low frequency tremor and normal tremor intensity. Lesions of the anterior lobe (yellow) are associated with low frequency and high intensity tremor. Lesions in the lateral parts of the posterior lobe are shown in pale blue. They usually cause low frequency tremor. Lesions affecting the posterior lobe, together with the brainstem (red), are associated with low frequency tremor (sometimes with high tremor intensity). Upper brainstem lesions (green) cause high intensity-normal frequency tremor. Images were reoriented with the horizontal line defined by the anterior and posterior commissures (ACPC orientation) and the sagittal planes parallel to the midline. Individual lesions were manually defined in MRIcron and saved as region of interest (ROI). Spatially unbiased atlas template of the cerebellum and brainstem (SUIT) was used for normalization, cerebellar lobule segmentation and cerebellar lesion detection. (Figures presenting overlapping lesions were prepared with MRIcron)

vestibular symptoms. Atlases that enable lesion-symptom mapping are available showing the human cerebellum in a proportional stereotactic space (Schmahmann et al. 1999; Diedrichsen et al. 2009, 2011).

In the first systemic study on the relation between cerebellar topography and cerebellar tremor (Kovács et al. 2019), we showed that low frequency tremor might be induced by a variety of lesions involving the midline structures, the anterior lobe and posterior lobe of the cerebellar hemispheres (Fig. 11.3). Our statistical analysis showed that the prevalence of pathological tremor was 45–65% if any cerebellar lobule and deep nucleus were affected (Table 11.3). Even in cases when all cerebellar lobules and the vermis were involved, only 60% of patients developed pathological tremor.

Table 11.3 Percentage of patients with pathological tremor parameters according to the affected cerebellar lobules/deep nuclei and brainstem

Localisation of the lesion	Number of patients with that lobule/nucleus affected	Number of patients with pathologic tremor parameters	Percentage of patients with pathologic tremor parameters
I–IV	11	7	63.63
V	15	8	53.33
Anterior lobe only	5	3	60.00
VI	14	7	50.00
Crus I	15	8	53.33
Crus II–VIIB	17	9	52.94
VIII	19	9	47.36
IX	21	12	57.14
Posterior lobe only	10	6	60.00
X	12	8	66.66
Vermis	13	7	53.84
Whole cerebellum	5	3	60.00
Dentate nucleus	20	11	55.00
Interposed nucleus	13	6	46.15
Fastigial nucleus	8	5	62.50
Brainstem	11	9	81.81

Patients with lesions involving both cerebellar hemispheres do not develop bilateral pathological tremor. Pathological tremor develops ipsilaterally to the more extensively affected cerebellar hemisphere. Lesions affecting the deep cerebellar nuclei do not produce cerebellar tremor more frequently than lesions with intact deep cerebellar nuclei. This finding echoes earlier observations regarding cerebellar ataxia and deep nuclei involvement (Schmahmann et al. 2009). Moreover, neither bilateral involvement nor deep nuclei involvement is associated with statistically lower frequency dispersion, centre frequency or higher tremor intensity. The size of the lesion does not correlate with the severity of the affected tremor parameters (Kovács et al. 2019).

In many examples, we also demonstrated (Kovács et al. 2019) that lesions in the same brain regions of different patients might result in different tremor types (Fig. 11.4). Figure 11.4a shows two different patients with acute ischaemia in the territory of the superior cerebellar artery who had two different tremor types: low frequency tremor in one case and physiologic tremor in the other. Lesions in both patients involved lobules I–VI but that of the tremulous patient affected the vermis, Crus II and lobule VIIB as well. The lesion size of the non-tremulous patient was twice as big as the lesion of the tremulous patient. Figure 11.4b presents two patients with lesions in the territory of the posterior inferior cerebellar artery with various extent. Only one of them developed pathological tremor. The affected cerebellar

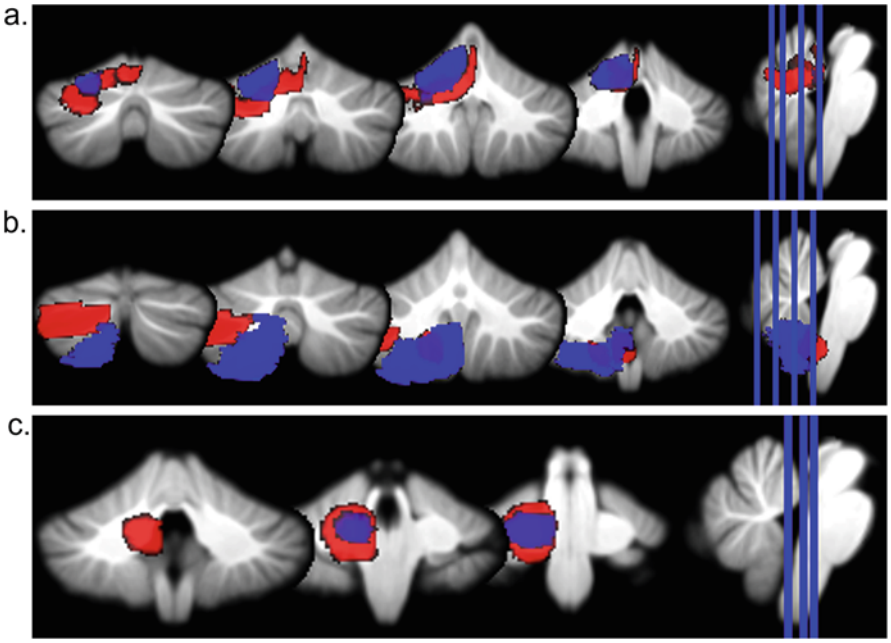

Fig. 11.4 Overlapping lesions associated with various tremor patterns in different patients. Lesions marked with red were associated with low frequency tremor, while lesions in blue with physiologic tremor. (**a**) Overlapping lesions in the territory of the superior cerebellar artery of two different patients. (**b**) Overlapping lesions in the territory of the posterior inferior cerebellar artery of two different patients. (**c**) Overlapping lesions of two different patients with lesions involving the anterior lobe of the cerebellum. Images were reoriented with the horizontal line defined by the anterior and posterior commissures (ACPC orientation) and the sagittal planes parallel to the midline. Individual lesions were manually defined in MRIcron and saved as region of interest (ROI). Spatially unbiased atlas template of the cerebellum and brainstem (SUIT) was used for normalization, cerebellar lobule segmentation and cerebellar lesion detection. (Figures presenting overlapping lesions were prepared with MRIcron)

lobules and nuclei of the tremulous and non-tremulous patient were overlapping, with minor differences. The non-tremulous patient had the most extensive lesion among all patients (Lai 2010) with lesion in the PICA territory. All lesions involving the posterior inferior cerebellar artery territories including the brainstem resulted in pathological tremor. We presented overlapping lesions of two different patients with overlapping lesions in the anterior lobe (Fig. 11.4c), but only one patient developed pathological tremor. The lesion of the tremulous patient affected both lobules IX and X, whereas the lesion of the non-tremulous patient affected only the anterior lobe.

The degree of pathology in tremor parameters does not depend on the lesion location, except on tremor intensity. An increase in tremor intensity is associated with the anterior lobe and midbrain structures (Kovács et al. 2019). A statistical analysis underlines the above observations. Patients with affected lobules I–IV and

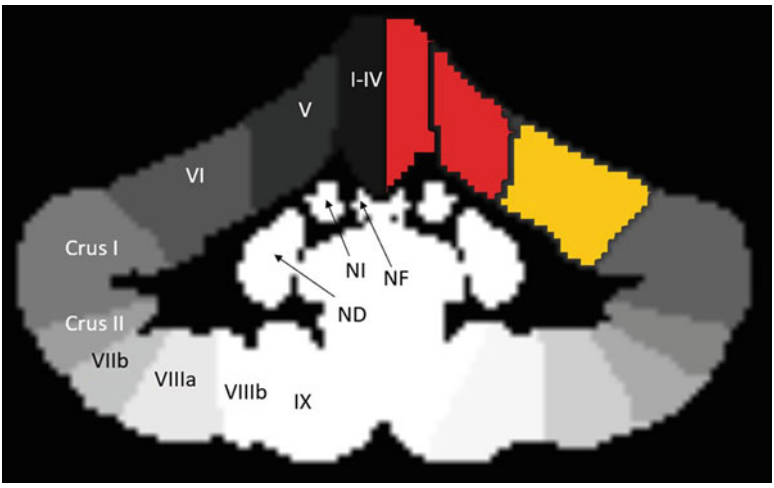

Fig. 11.5 Lesion-tremor map of the cerebellum. The map illustrates all the cerebellar lobules and deep nuclei in different shades of grey. Lobules I–IV and V are illustrated with red. Their involvement is associated with significantly higher tremor intensity in postural and intentional positions. Lobule VI is marked with yellow. Its involvement is associated with elevated tremor intensity in intentional position only

lobule V have significantly higher tremor intensity in both postural and intentional positions than those with intact lobules. Patients with affected lobule VI have significantly higher tremor intensity in intentional position only. Therefore, the anterior lobe and lobule VI are presented on the lesion-tremor map (Fig. 11.5). This map is in accordance with previous somatotopic maps of the cerebellum, which suggested that the main somatotopic representation of the upper limb is in the anterior lobe (Stoodley and Schmahmann 2018). Lobule VI, being part of the posterior lobe, might take part in the cognitive performance required to execute the precision task of maintaining an intentional position via its frontal connections.

The role of the brainstem in tremor genesis was debated (Louis and Lenka 2017). Based on our data, the brainstem seems to play a key role in the pathomechanism of cerebellar tremor. In patients with brainstem involvement (with or without affected cerebellum), the prevalence of pathological tremor tends to be much higher (81.81%) than in those with cerebellar involvement only (Table 11.3) (Kovács et al. 2019). Brainstem lesions are associated with significantly higher postural tremor intensity, significantly lower intentional tremor centre frequency and frequency dispersion and significantly higher relative power of 0.9–3 Hz frequency range than lesions affecting the cerebellum only (Kovács et al. 2019).

The above presented data give a new and interesting insight into lesion-tremor mapping. However, it became evident that they do not fully explain why some patients develop pathological tremor and some others do not, urging the need for new perspectives. Guell et al. offer a different approach by continuous rather than discrete functionally defined brain maps, using functional connectivity patterns

with diffusion map embedding. According to this analysis, the organisation of the cerebellum is sensorimotor-fugal. Regions further from lobules IV, V, VI and VIII are further from motor functions in a gradient from motor to maximally non-motor purposes. Connectivity data confirmed the double motor–triple non-motor organisation in the cerebellum (Guell et al. 2018). This functional approach might provide a useful tool for the examination of tremor generation in the future.

11.7 Differential Diagnosis (Holmes Tremor, Cerebellar Atrophy, Toxin-Induced Cerebellar Disorders)

Tremor might be observed in acute and chronic cerebellar and brainstem lesions, which show different clinical/neurophysiological characteristics from cerebellar tremor.

Cerebellar axial postural tremor (CAPT) is a form of tremor particularly involving the head and the shoulders, present while sitting. It is present when arms are outstretched but diminishes during voluntary action. A similar tremor type was described by Gordon Holmes, who reported a 'third type (tremor), involving the head and the trunk' when examining a patient who had cerebellar lesions (Holmes 1922). In these cases, cerebellar pathology (cerebellar atrophy, haemangioma) is usually evident. The suspected pathophysiology might be the involvement of the cerebello-olivary system and its inhibitory GABAergic function. These lesions are most commonly associated with palatal tremor. A particular feature of this tremor type is the variability of frequency at around 3–10 Hz (between patients, muscles and when measured at different times) (Brown et al. 1997). Topiramate might be effective due to facilitation of GABAergic transmission and antagonism at the AMPA/kainate receptor (Kobylecki et al. 2008).

Holmes tremor (first described by Benedikt in 1889) or midbrain tremor is a low frequency (<5 Hz), irregular, high amplitude tremor. It is present in rest, but its amplitude increases in postural and intentional positions. The pathophysiology of Holmes tremor is not clearly understood. It is associated with contralateral brainstem or thalamic lesions. It develops months or years later after the occurrence of the lesion (Raina et al. 2016), which suggests that it might be due to neuronal reorganisations (Nsengiyumva et al. 2021). According to the site of the lesion, Holmes tremor can be subdivided into two distinct clinical subtypes: Holmes tremor of midbrain origin (no other movement disorders are present, except mild dystonia) and Holmes tremor of thalamic origin (rest tremor is not always present; severe movement disorders might accompany tremor: chorea-like movements, abnormal dystonic posture, pseudoathetosis; joint position sensation loss might also be present). This clinical distinction has implications for clinical management, as pharmacological treatment (levodopa) and deep brain stimulation are unlikely to help in cases of tremor with thalamic origin (Nsengiyumva et al. 2021).

The delayed-onset cerebellar syndrome also develops 3 weeks to 2 years after the lesion. It is characterised by intention tremor and other cerebellar signs (ataxia, dysmetria, dysarthria, dysdiadochokinesia, nystagmus and gait ataxia). It is often progressive and disabling. Underlying lesions are in the thalamus or in the brainstem, with possible disruption of the dentato-rubro-thalamic tract (Louis et al. 1996).

When differentiating cerebellar tremor from the above presented disorders, it is noteworthy that cerebellar tremor has no rest component and its emergence is not delayed. Also, it has a good recovery profile since it usually improves in days to weeks (Kovács et al. 2019).

Chronic cerebellar pathology might also lead to tremor, which is not identical with cerebellar tremor. Fragile X tremor ataxia syndrome (FXTAS) is a neurodegenerative disorder in premutation carriers of FMR1 mutation. Its full mutation form is the leading cause of mental retardation in children. FXTAS – being an X-linked disorder – presents more commonly in males than in females. Clinical signs appear usually after 50 years of age with upper limb tremor and gait ataxia. Other symptoms like peripheral neuropathy, parkinsonism, hypothyroidism, cognitive impairment and psychiatric diseases might also occur. Tremor might resemble essential tremor ('essential tremor-like'), or it might be similar to a parkinsonian tremor (Robertson et al. 2020). MRI features include brain atrophy and white matter lesions in the middle cerebellar peduncle (known as the 'MCP sign') and corpus callosum. Symptoms progressively worsen over time (Cabal-Herrera et al. 2020; Apartis et al. 2012).

Alcoholism and alcohol withdrawal might cause tremor and cerebellar atrophy since the cerebellum is extremely vulnerable to toxic agents. Atrophy mostly involves the anterior part of the vermis. Tremor in alcoholic patients has rarely been investigated by quantitative methods. According to Milanov et al., the frequency of this tremor type is identical with that of enhanced physiologic tremor, 8–12 Hz (Milanov et al. 1996).

11.8 Treatment and Recovery of Cerebellar Tremor

Experimental studies performed in monkeys and rodents showed that cerebellar lesions are followed by a substantial recovery, even when the lesions are extensive (Mitoma et al. 2020). In rats, both hemicerebellectomy and full cerebellectomy are followed by recovery of deficits after a few weeks or months (Federico et al. 2006). When cerebellar nuclei are affected, residual deficits will persist. According to animal experiments, the preservation of the nucleo-fugal pathways is required for compensation (Mitoma et al. 2020). In neonatal rats, the transection of cerebellar peduncles is rapidly followed by reinnervation of the cerebellar cortex (Angaut et al. 1985). The timing of cerebellar lesion is a key factor. Lesions occurring during development show a better recovery course than lesions emerging at adult age (Mitoma et al. 2020). A 13-year-old male recovered spontaneously after enteroviral encephalitis causing bilateral cerebellar atrophy and acute cerebellar signs (Vitaszil

et al. 2005). However, a diffusion tensor imaging MRI study showed complete structural recovery after cerebellar tumour surgery in children (Kim et al. 2014).

Clinical experience suggests that tremor in acute cerebellar lesions ceases or completely recovers in time. However, quantitative follow-up studies are only scarcely available. Recovery of limb ataxia and bradykinesia has been demonstrated, most of it occurred in the first 2 weeks. Improvement during the 3-month follow-up was less obvious (Konczak et al. 2010). On the contrary, in neurodegenerative disorders, tremor and cerebellar ataxia do not improve (Sasaki et al. 2017). Our recent follow-up study in patients with acute cerebellar stroke was the first systemic study to prove that cerebellar tremor recovers in these patients (Kovács et al. 2019). Frequency dispersion and centre frequency were good indicators for tremor recovery (Fig. 11.6). The speed of recovery was different in different patients but pathological

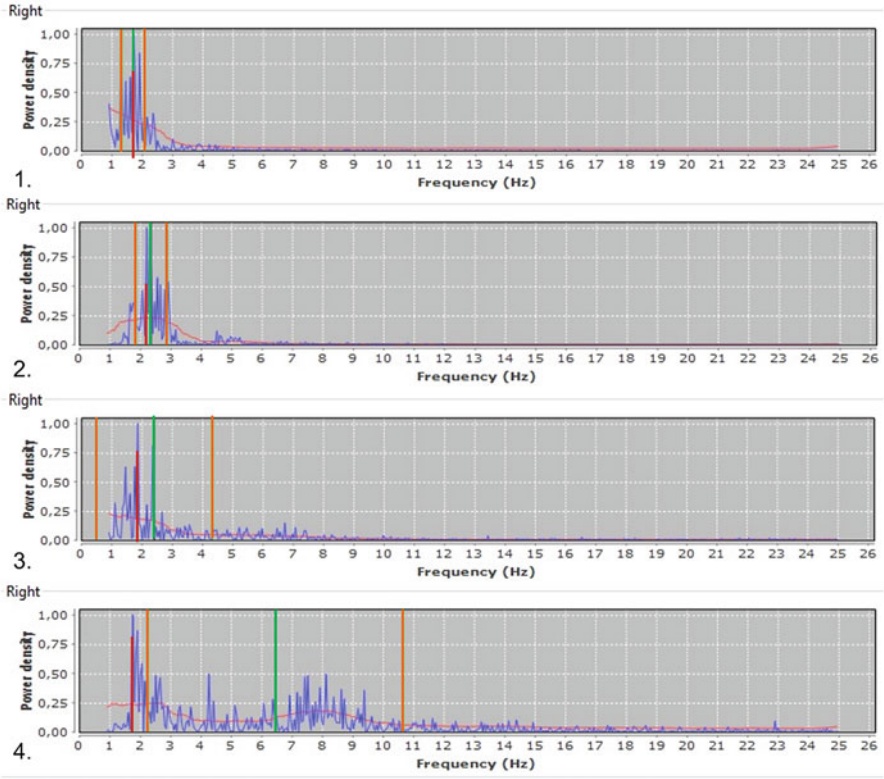

Fig. 11.6 Change of centre frequency and frequency dispersion over time in a patient with acute cerebellar stroke. (1) Five days after symptom/lesion onset. (2) Seven days after symptom/lesion onset. (3) Twelve days after symptom/lesion onset. (4) One month after symptom/lesion onset. Green lines illustrate centre frequency. The distance between the green and the yellow line shows frequency dispersion. Red lines show peak frequency. The figure illustrates that the frequency dispersion progressively grows, and centre frequency becomes higher as tremor components of higher ranges return to the spectrum, and thus the distance between centre and peak frequency grows

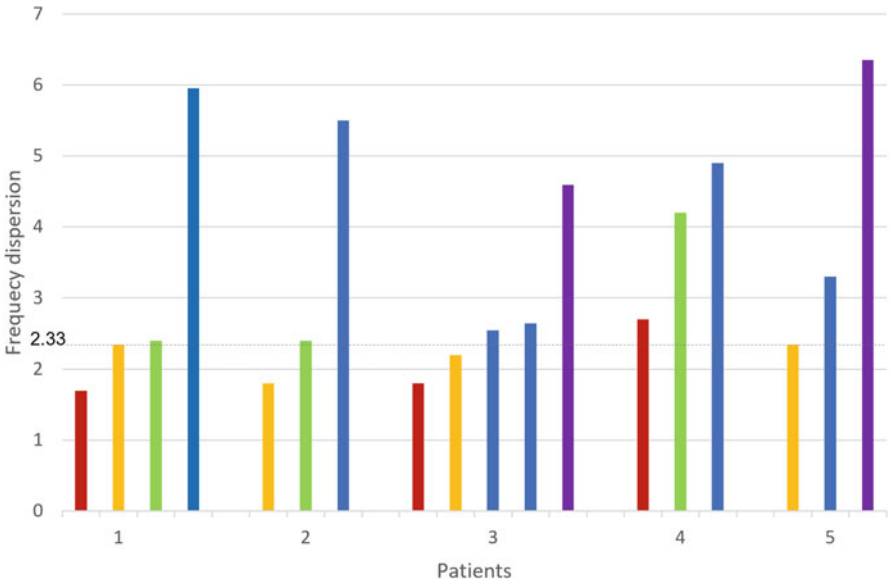

Fig. 11.7 Recovery of intentional tremor in five patients with acute ischemic cerebellar stroke. During follow-up measurements, frequency dispersion gradually increased – as an indicator of recovery. The dashed line shows the lower limit of the normal range of frequency dispersion. Various colours show the different times of measurement. As the figure shows, cerebellar intentional tremor caused by acute cerebellar stroke recovers in 8 weeks

tremor ceased in 3.65 ± 2.66 weeks on average (minimum 1 week, maximum 8 weeks) (Fig. 11.7). There was no correlation between the speed of recovery and quantitative tremor parameters (tremor intensity, frequency dispersion etc.), nor between the speed of recovery and the location and/or size of the lesion (Kovács et al. 2019). In chronic ischaemic lesions (at least 2 months after the acute stroke), no pathological tremor can be found even when using objective tremor analysis methods (Kovács et al. 2019).

The mechanism of spontaneous recovery is not clearly understood. 'Cerebellar reserve is the capacity of the cerebellum to compensate and restore function in response to pathology' (Mitoma et al. 2020) such as stroke, neoplasm and neurodegeneration. Following acute structural damage, e.g. stroke, impaired cerebellar function might be compensated by unaffected cerebellar areas. This is called structural reserve. In contrast, when neuropathology is disseminated through the whole cerebellum, like in neurodegenerative disorders, immune-mediated ataxias, metabolic ataxias etc., the affected area itself might contribute to restoration or preservation of the function. This is called functional reserve (Mitoma et al. 2020).

In patients with acute stroke, structural cerebellar reserve might be responsible for symptom recovery. A plausible technique for the assessment of the preserved

cerebellar motor reserve might be the analysis of the extent of cerebellar atrophy on MRI (Mitoma et al. 2020). The prognosis of cerebellar lesions can be predicted based on the preservation of cerebellar reserve. Early therapeutic intervention is recommended, at the time when cerebellar reserve is preserved. Neuromodulation can potentiate the cerebellar reserve. In progressive disorders, like degenerative ataxias, the treatment might delay progression. In curable cases, a complete recovery is possible. Cury et al. reported a patient with cerebellar stroke and refractory ataxia who had deep brain stimulation of the healthy dentate nucleus (Cury et al. 2019). The procedure resulted in sustained and marked improvement of the patient's symptoms with a slight rebound phenomenon (when the DBS was switched off, the symptoms were worse than at the baseline) (Cury et al. 2019). The exact mechanism of this procedure is not clearly understood. It is suspected that cerebellar modulation might restore the altered cortical excitability asymmetry seen between both motor cortices after a cerebellar hemispheric lesion. Moreover, changes in blood flow and metabolism due to the stimulation might also be involved in pathomechanism.

References

Adanyeguh IM, Perlbarg V, Henry P-G, Rinaldi D, Petit E, Valabregue R, et al. Autosomal dominant cerebellar ataxias: imaging biomarkers with high effect sizes. NeuroImage Clin. 2018;19:858–67.

Agate FJJ, Doshay LJ, Curtis FK. Quantitative measurement of therapy in paralysis agitans. J Am Med Assoc. 1956;160:352–4.

Aly NM, Playfer JR, Smith SL, Halliday DM. A novel computer-based technique for the assessment of tremor in Parkinson's disease. Age Ageing. 2007;36:395–9.

Angaut P, Alvarado-Mallart RM, Sotelo C. Compensatory climbing fiber innervation after unilateral pedunculotomy in the newborn rat: origin and topographic organization. J Comp Neurol. 1985;236:161–78.

Apartis E, Blancher A, Meissner WG, Guyant-Maréchal L, Maltête D, De Broucker T, et al. FXTAS. Neurology [Internet]. 2012;79:1898 LP–1907. Available from: http://n.neurology.org/content/79/18/1898.abstract.

Atkin A, Kozlovskaya IB. Effects of cooling cerebellar nuclei on evoked forearm oscillations. Exp Neurol [Internet]. 1976;50:766–76. Available from: https://www.sciencedirect.com/science/article/pii/001448867690042X.

Barrantes S, Sánchez Egea AJ, González Rojas HA, Martí MJ, Compta Y, Valldeoriola F, et al. Differential diagnosis between Parkinson's disease and essential tremor using the smartphone's accelerometer. PLoS One. 2017;12:e0183843.

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33(1):75–87.

Bostan AC, Strick PL. The basal ganglia and the cerebellum: nodes in an integrated network. Nat Rev Neurosci. 2018;19:338–50.

Breit S, Spieker S, Schulz JB, Gasser T. Long-term EMG recordings differentiate between parkinsonian and essential tremor. J Neurol. 2008;255:103–11.

Brooks VB, Cooke JD, TJS. The continuity of movements. In: Stein RB, Pearson KG, Smith RSRJB, editors. Control of posture and locomotion advances in behavioral biology. Boston: Springer; 1973.

Brown P, Rothwell JC, Stevens JM, Lees AJ, Marsden CD. Cerebellar axial postural tremor. Mov Disord. 1997;12:977–84.

Cabal-Herrera AM, Tassanakijpanich N, Salcedo-Arellano MJ, Hagerman RJ. Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS): pathophysiology and clinical implications. Int J Mol Sci. 2020;21:4391.

Cerminara NL, Aoki H, Loft M, Sugihara I, Apps R. Structural basis of cerebellar microcircuits in the rat. J Neurosci. 2013;33:16427–42.

Ciuti G, Ricotti L, Menciassi A, Dario P. MEMS sensor technologies for human centred applications in healthcare, physical activities, safety and environmental sensing: a review on research activities in Italy. Sensors (Basel) [Internet]. 2015;15:6441–68. Available from: https://pubmed.ncbi.nlm.nih.gov/25808763.

Coenen VA, Allert N, Paus S, Kronenburger M, Urbach HMB. Modulation of the cerebello-thalamo-cortical network in thalamic deep brain stimulation for tremor: a diffusion tensor imaging study. Neurosurgery. 2014;75:657–70.

Cole JD, Philip HI, Sedgwick EM. Stability and tremor in the fingers associated with cerebellar hemisphere and cerebellar tract lesions in man. J Neurol Neurosurg Psychiatry. 1988;51:1558–68.

Colebatch JG, Findley LJ, Frackowiak RS, Marsden CD, Brooks DJ. Preliminary report: activation of the cerebellum in essential tremor. Lancet (London, England). 1990;336:1028–30.

Conway BA, Halliday DM, Farmer SF, Shahani U, Maas P, Weir AI, et al. Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. J Physiol [Internet]. 1995;15(489):917–24. Available from: https://pubmed.ncbi.nlm.nih.gov/8788955.

Cury RG, França C, Barbosa ER, Galhardoni R, Lepski G, Teixeira MJ, et al. Dentate nucleus stimulation in a patient with cerebellar ataxia and tremor after cerebellar stroke: a long-term follow-up. Parkinsonism Relat Disord England. 2019;60:173–5.

D'Angelo E, Casali S. Seeking a unified framework for cerebellar function and dysfunction: from circuit operations to cognition. Front Neural Circuits [Internet]. 2013;6:116. Available from: https://pubmed.ncbi.nlm.nih.gov/23335884.

Dash SK, Stezin A, Takalkar T, George L, Kamble NL, Netravathi M, et al. Abnormalities of white and grey matter in early multiple system atrophy: comparison of parkinsonian and cerebellar variants. Eur Radiol. 2019;29:716–24.

Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13(Suppl 3):2–23.

Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N. A probabilistic MR atlas of the human cerebellum. NeuroImage. 2009;46:39–46.

Diedrichsen J, Maderwald S, Küper M, Thürling M, Rabe K, Gizewski ER, et al. Imaging the deep cerebellar nuclei: a probabilistic atlas and normalization procedure. NeuroImage. 2011;54:1786–94.

Edwards R, Beuter A. Using time domain characteristics to discriminate physiologic and parkinsonian tremors. J Clin Neurophysiol. 2000;17:87–100.

Elble RJ. Origins of tremor. Lancet (London, England). 2000;355:1113–4.

Engin M. A recording and analysis system for human tremor. Measurement. 2007;40:288–93.

Eshner AA. A graphic study of tremor. J Exp Med [Internet]. 1897;2(3):301–12. Available from: https://pubmed.ncbi.nlm.nih.gov/19866834.

Federico F, Leggio MG, Mandolesi L, Petrosini L. The NMDA receptor antagonist CGS 19755 disrupts recovery following cerebellar lesions. Restor Neurol Neurosci. 2006;24:1–7.

Ferrier DTA. Record of experiments illustrative of the symptomatology and degenerations owing lesions of the cerebellum and its peduncles and related structures in monkeys. Philos Trans R Soc London. 1894;185:719–78.

Flament D, Hore J. Comparison of cerebellar intention tremor under isotonic and isometric conditions. Brain Res. 1988;439:179–86.

Gironell A, Ribosa-Nogué R, Gich I, Marin-Lahoz J, Pascual-Sedano B. Severity stages in essential tremor: a long-term retrospective study using the glass scale. Tremor Other Hyperkinet Mov (N Y). 2015;5:299.

Grimaldi G, Manto M-U. Tremor from pathogenesis to treatment. San Rafael: Morgan & Claypool Publishers; 2008.
Grimaldi G, Manto M. Neurological tremor: sensors, signal processing and emerging applications. Sensors (Basel). 2010;10:1399–422. https://doi.org/10.3390/s100201399.
Grimaldi G, Mario M. Mechanisms and emerging therapies in tremor disorders. Springer; 2013.
Grodd W, Hülsmann E, Lotze M, Wildgruber D, Erb M. Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. Hum Brain Mapp. 2001;13:55–73.
Gruol DL, Gruol DL, Noriyuki Koibuchi NK, Mario Manto MM. Essentials of cerebellum and cerebellar disorders: a primer for graduate students. Springer; 2016.
Guell X, Schmahmann JD, Gabrieli JDE, Ghosh SS. Functional gradients of the cerebellum. Elife [Internet]. 2018;7:e36652. Available from: https://pubmed.ncbi.nlm.nih.gov/30106371.
Helmchen C, Hagenow A, Miesner J, Sprenger A, Rambold H, Wenzelburger R, et al. Eye movement abnormalities in essential tremor may indicate cerebellar dysfunction. Brain. 2003;126:1319–32.
Helmich RC, Hallett M, Deuschl G, Toni I, Bloem BR. Cerebral causes and consequences of Parkinsonian resting tremor: a tale of two circuits? Brain. 2012;135:3206–26.
Holmes G. The Croonian Lectures on the clinical symptoms of cerebellar disease and their interpretation. Lancet [Internet]. 1922;200(5158):59–65. Available from: https://www.sciencedirect.com/science/article/pii/S014067360112307X.
Kim M-S, Tak HJ, Son SM. Recovery of cerebellar peduncle injury in a patient with a cerebellar tumor: validation by diffusion tensor tractography. Neural Regen Res [Internet]. 2014;9:1929–32. Available from: https://pubmed.ncbi.nlm.nih.gov/25558245.
Kobylecki C, Marshall AG, Varma A, Kellett MW, Dick JPR, Silverdale MA. Topiramate-responsive cerebellar axial postural tremor. Mov Disord [Internet]. 2008;23:1189–91. Available from: https://doi.org/10.1002/mds.22068.
Konczak J, Pierscianek D, Hirsiger S, Bultmann U, Schoch B, Gizewski ER, et al. Recovery of upper limb function after cerebellar stroke: lesion symptom mapping and arm kinematics. Stroke. 2010;41:2191–200.
Kovács A, Kiss M, Pintér N, Szirmai I, Kamondi A. Characteristics of tremor induced by lesions of the cerebellum. Cerebellum [Internet]. 2019;18(4):705–20. Available from: https://doi.org/10.1007/s12311-019-01027-3.
Kronenbuerger M, Konczak J, Ziegler W, Buderath P, Frank B, Coenen VA, et al. Balance and motor speech impairment in essential tremor. Cerebellum. 2009;8:389–98.
Lai EC. Chapter 10 – Cerebellar disease. In: Rolak LABT-NS, Fifth E, editors. Neurology secrets. 5th Edition [Internet] ed. Philadelphia: Mosby; 2010. p. 157–67. Available from: https://www.sciencedirect.com/science/article/pii/B9780323057127000106.
Larochelle L, Bedard P, Boucher RPL. The rubro-olivo-cerebello-rubral loop and postural tremor in the monkey. J Neurol Sci. 1970;11:53–64.
Lawrenson C, Bares M, Kamondi A, Kovács A, Lumb B, Apps R, et al. The mystery of the cerebellum: clues from experimental and clinical observations. Cerebellum Ataxias [Internet]. 2018;5(1):8. Available from: https://doi.org/10.1186/s40673-018-0087-9.
Lenka A, Louis ED. Revisiting the clinical phenomenology of "Cerebellar Tremor": beyond the intention tremor. The Cerebellum [Internet]. 2019;18(3):565–74. Available from: https://doi.org/10.1007/s12311-018-0994-6.
Lenz FA, Kwan HC, Martin RL, Tasker RR, Dostrovsky JO, Lenz YE. Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. Brain. 1994;117:531–43.
Louis ED. Linking essential tremor to the cerebellum: neuropathological evidence. Cerebellum. 2016;15:235–42.
Louis ED, Lenka A. The Olivary hypothesis of essential tremor: time to lay this model to rest? Tremor Other Hyperkinet Mov (N Y). 2017;7:473.
Louis ED, Lynch T, Ford B, Greene P, Bressman SB, Fahn S. Delayed-onset cerebellar syndrome. Arch Neurol. 1996;53:450–4.

Lukšys D, Jonaitis G, Griškevičius J. Quantitative analysis of Parkinsonian Tremor in a clinical setting using inertial measurement units. Alves da Costa C, editor. Park Dis [Internet]. 2018;2018:1683831. Available from: https://doi.org/10.1155/2018/1683831.

Madelein van der Stouwe AM, Nieuwhof F, Helmich RC. Tremor pathophysiology: lessons from neuroimaging. Curr Opin Neurol. 2020;33:474–81.

Marek M, Paus S, Allert N, Madler B, Klockgether T, Urbach H, et al. Ataxia and tremor due to lesions involving cerebellar projection pathways: a DTI tractographic study in six patients. J Neurol. 2015;262:54–8.

Marr D. A theory of cerebellar cortex. J Physiol. 1969;202:437–70.

McNames J, Shah VV, Mancini M, Curtze C, El-Gohary M, Aboy M, et al. A two-stage tremor detection algorithm for wearable inertial sensors during normal daily activities. In: 2019 41st annual international conference of the IEEE Engineering in Medicine and Biology Society (EMBC); 2019. p. 2535–8.

Milanov I. Electromyographic differentiation of tremors. Clin Neurophysiol. 2001;112:1626–32.

Milanov I, Toteva S, Georgiev D. Alcohol withdrawal tremor. Electromyogr Clin Neurophysiol. 1996;36:15–20.

Mitoma H, Buffo A, Gelfo F, Guell X, Fucà E, Kakei S, et al. Consensus Paper. Cerebellar reserve: from cerebellar physiology to cerebellar disorders. Cerebellum. 2020;19:131–53.

Molinari M, Restuccia D, Leggio MG. State estimation, response prediction, and cerebellar sensory processing for behavioral control. Cerebellum. 2009;8:399–402.

Nicoletti G, Manners D, Novellino F, Condino F, Malucelli E, Barbiroli B, et al. Diffusion tensor MRI changes in cerebellar structures of patients with familial essential tremor. Neurology. 2010;74:988–94.

Nsengiyumva N, Barakat A, Macerollo A, Pullicino R, Bleakley A, Bonello M, et al. Thalamic versus midbrain tremor; two distinct types of Holmes' Tremor: a review of 17 cases. J Neurol. 2021;268:1–11.

Oscarsson O. Functional organization of the spino-and cuneocerebellar tracts. Physiol Rev. 1965;45:495–522.

Park Y-G, Park H-Y, Lee CJ, Choi S, Jo S, Choi H, et al. Ca(V)3.1 is a tremor rhythm pacemaker in the inferior olive. Proc Natl Acad Sci U S A. 2010;107:10731–6.

Popa LS, Hewitt AL, Ebner TJ. Purkinje cell simple spike discharge encodes error signals consistent with a forward internal model. Cerebellum. 2013;12:331–3.

Popa LS, Streng ML, Ebner TJ. Long-term predictive and feedback encoding of motor signals in the simple spike discharge of Purkinje cells. eneuro [Internet]. 2017;4(2):ENEURO.0036–17.2017. Available from: http://www.eneuro.org/content/4/2/ENEURO.0036-17.2017.abstract.

Pullman SL. Spiral analysis: a new technique for measuring tremor with a digitizing tablet. Mov Disord. 1998;13(Suppl 3):85–9.

Raina GB, Cersosimo MG, Folgar SS, Giugni JC, Calandra C, Paviolo JP, et al. Holmes tremor: clinical description, lesion localization, and treatment in a series of 29 cases. Neurology [Internet]. 2016;86:931–8. Available from: https://pubmed.ncbi.nlm.nih.gov/26865524.

Rao AK, Gillman A, Louis ED. Quantitative gait analysis in essential tremor reveals impairments that are maintained into advanced age. Gait Posture. 2011;34:65–70.

Robertson EE, Hall DA, Pal G, Ouyang B, Liu Y, Joyce JM, et al. Tremorography in fragile X-associated tremor/ataxia syndrome, Parkinson's disease and essential tremor. Clin Park Relat Disord [Internet]. 2020;3:100040. Available from: https://www.sciencedirect.com/science/article/pii/S2590112520300086.

Sasaki R, Maki F, Hara D, Tanaka S, Hasegawa Y. Stratification of disease progression in a broad spectrum of degenerative cerebellar ataxias with a clustering method using MRI-based atrophy rates of brain structures. Cerebellum Ataxias [Internet]. 2017;4:9. Available from: https://pubmed.ncbi.nlm.nih.gov/28680650.

Schlerf JE, Verstynen TD, Ivry RB, Spencer RMC. Evidence of a novel somatopic map in the human neocerebellum during complex actions. J Neurophysiol. 2010;103:3330–6.

Schmahmann JD. Cerebellar cognitive affective syndrome and the neuropsychiatry of the cerebellum. In: Handbook of the cerebellum and cerebellar disorders. New York: Springer; 2013. p. 1717–51.

Schmahmann JD, Doyon J, McDonald D, Holmes C, Lavoie K, Hurwitz AS, et al. Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. NeuroImage. 1999;10:233–60.

Schmahmann JD, Macmore J, Vangel M. Cerebellar stroke without motor deficit: clinical evidence for motor and non-motor domains within the human cerebellum. Neuroscience. 2009;162:852–61.

Shawen N, O'Brien MK, Venkatesan S, Lonini L, Simuni T, Hamilton JL, et al. Role of data measurement characteristics in the accurate detection of Parkinson's disease symptoms using wearable sensors. J Neuroeng Rehabil [Internet]. 2020;17:52. Available from: https://doi.org/10.1186/s12984-020-00684-4.

Stoodley CJ, Schmahmann JD. Functional topography of the human cerebellum. Handb Clin Neurol. 2018;154:59–70.

van Brummelen EMJ, Ziagkos D, de Boon WMI, Hart EP, Doll RJ, Huttunen T, et al. Quantification of tremor using consumer product accelerometry is feasible in patients with essential tremor and Parkinson's disease: a comparative study. J Clin Mov Disord [Internet]. 2020;7:4. Available from: https://pubmed.ncbi.nlm.nih.gov/32280482.

Vial F, Kassavetis P, Merchant S, Haubenberger D, Hallett M. How to do an electrophysiological study of tremor. Clin Neurophysiol Pract [Internet]. 2019;4:134–42. Available from: https://www.sciencedirect.com/science/article/pii/S2467981X1930023X.

Vitaszil E, Kamondi A, Csillik A, et al. Asymptomatic cerebellar atrophy after acute enteroviral encephalitis. Dev Med Child Neurol. 2005;47:486–8. https://doi.org/10.1017/s0012162205000939.

Voogd J, Feirabend HKPSJ. Cerebellum and precerebellar nuclei. In: The human nervous system. 3rd ed. Academic Press; 2012. p. 471–545.

Wang JY, Hessl D, Hagerman RJ, Simon TJ, Tassone F, Ferrer E, et al. Abnormal trajectories in cerebellum and brainstem volumes in carriers of the fragile X premutation. Neurobiol Aging. 2017;55:11–9.

Wu T, Hallett M. The cerebellum in Parkinson's disease. Brain. 2013;136:696–709.

Chapter 12
Orthostatic Tremor

Julián Benito-León, Ritwik Ghosh, Souvik Dubey, and Elan D. Louis

Abstract Orthostatic tremor is a rare and enigmatic movement disorder characterized by rapid tremor of both legs and the trunk while standing, which disappears while the patient is either lying down or walking. It may be primary with or without postural arm tremor or associated with other neurological features, mainly parkinsonism ("orthostatic tremor plus"). Other clinical syndromes with tremor during standing have a lower frequency than 13 Hz and are labeled as slow orthostatic tremors or pseudo-orthostatic tremor. There are also some rare examples of secondary (symptomatic) orthostatic tremors associated with non-movement disorders. The pathogenesis of orthostatic tremor remains unclear. However, an accumulating body of evidence suggests a key role of the cerebellum in its pathophysiology; however, other brain regions such as the motor and sensory cortices and the thalamus may also be involved. Although a small number of medications (clonazepam, gabapentin, and dopaminergic drugs) can provide partial relief from tremor in a few patients, the pharmacological treatment is not optimal, and some patients with severe tremor may choose to undergo surgery.

Keywords Electromyogram · Orthostatic tremor · Shaky legs syndrome

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12.1 Introduction

The term "orthostatic tremor," also known as "shaky legs syndrome" (Gates 1993; Benito-León and Porta-Etessam 2000), was first used in 1984 by Heilman (1984), although there may have been earlier descriptions of this entity (Pazzaglia et al. 1970). As there are no published population-based epidemiological data, the prevalence and incidence of orthostatic tremor are unknown; however, it is considered a rare entity. There are several forms of orthostatic tremor, which share the key tremor symptom during standing. Orthostatic tremor may be primary with or without postural arm tremor or associated with other neurological features, mainly parkinsonism ("orthostatic tremor plus") (Gerschlager et al. 2004; Benito-León and Domingo-Santos 2016; Park et al. 2020).

Primary orthostatic tremor is defined as an isolated tremor syndrome, characterized by high-frequency (13–18 Hz) tremor of the legs and an immediate sense of instability when the patient is standing; these are relieved when sitting or walking (Bhatia et al. 2018). There is accumulating evidence that the pathophysiology mainly involves the cerebellum (Thompson et al. 1986; Gerschlager et al. 2004; Benito-León and Domingo-Santos 2016). The diagnosis is clinical, although it can be confirmed by surface electromyographic (EMG) recordings (e.g., from the quadriceps muscle), where there is typically a 13–18 Hz tremor (Fig. 12.1) (Bhatia et al. 2018). Nonetheless, leg, trunk, and even arm muscles may exhibit this tremor, typically absent during tonic activation while the patient is sitting and lying (Bhatia et al. 2018).

A small number of medications may provide partial relief from tremor; however, the pharmacological treatment of orthostatic tremor is not, in general, optimal, and some patients with severe tremor may undergo bilateral deep-brain stimulation, which seems to be effective (Espay et al. 2008; Guridi et al. 2008; Magariños-Ascone et al. 2010; Lyons et al. 2012; Muthuraman et al. 2013; Yaltho and Ondo 2014; Contarino et al. 2015; Coleman et al. 2016; Hassan et al. 2016; Merola et al. 2017; Evidente et al. 2018; Hewitt et al. 2020).

12.2 Epidemiology

Orthostatic tremor is considered to be a rare condition. Although there are no available epidemiological data, in the Neurological Disorders of Central Spain (NEDICES) study (Benito-León et al. 2004), our group detected one patient with orthostatic tremor in a cohort of approximately 4000 elderly subjects (data not published). Orthostatic tremor can begin at any age. However, age at onset may differ depending on whether orthostatic tremor is primary or associated features (Gerschlager et al. 2004). In the study by Gerschlager et al. (2004), which recruited 41 cases of orthostatic tremor, age at onset was significantly earlier in the primary

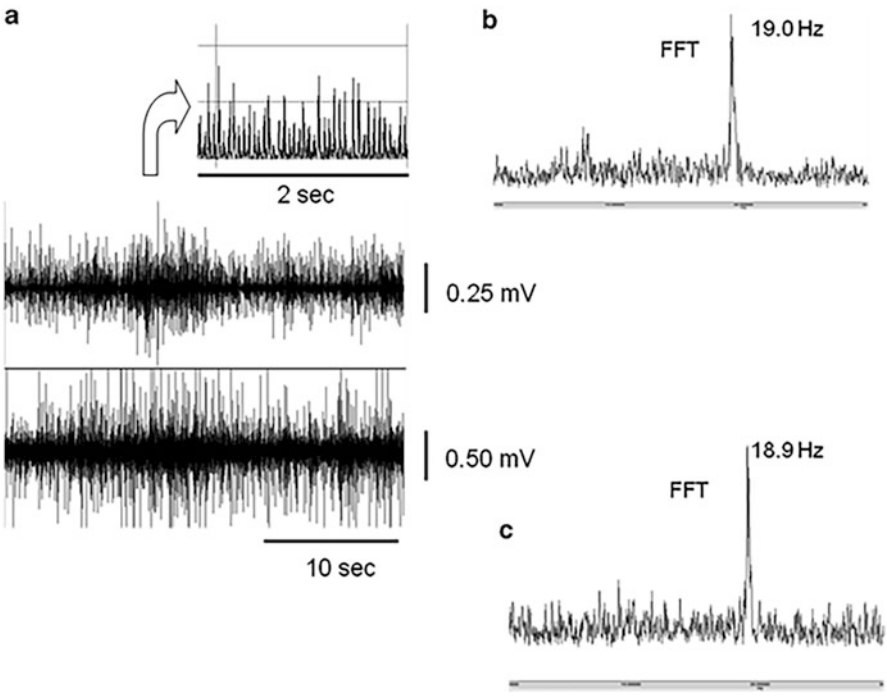

Fig. 12.1 (**a**) Typical surface EMG recording in a patient presenting a primary orthostatic tremor while standing. Recordings in left tibialis anterior (*upper trace*) and left gastrocnemius muscle (*bottom trace*). Gain: ×1000. The *arrow* shows an epoch of 2 s (*rectified trace*). High-frequency bursting is observed. Parts (**b**) and (**c**) correspond to the respective fast Fourier transform (FFT) data. A peak at about 19 Hz is identified in the agonist-antagonist muscle pair

orthostatic tremor (50.4 years ± 15.1) than in the orthostatic tremor with associated features group (61.8 ± 6.4, $p = 0.006$). In the largest series of the literature ($N = 184$), the age at onset was 59.3 years (range 13–85 years) (Hassan et al. 2016). A review of published case series indicates a female predominance (Gerschlager et al. 2004; Piboolnurak et al. 2005; Hassan et al. 2016; Ganos et al. 2016).

Most cases of orthostatic tremor occur sporadically; however, a few examples of familial cases in monozygotic twins (Contarino et al. 2006), siblings (Fischer et al. 2007; Virmani et al. 2012; Bhattacharyya and Das 2013), or in a mother and her son (Piboolnurak et al. 2005) have been reported. In the Yaltho and Ondo (2014) series, a family history of orthostatic tremor was reported in 3/45 (7%) patients. Furthermore, there may be a family history of Parkinson's disease (PD) or other types of tremors (Piboolnurak et al. 2005; Yaltho and Ondo 2014).

Progression of orthostatic tremor has also been noted. While in most of the orthostatic tremor patients, the symptom severity was relatively unchanged over time (Gerschlager et al. 2004), in 6 of their 41 patients, there was a documented

progression of symptom severity (i.e., the amount of time they could stand still) (Gerschlager et al. 2004). A clear spread of tremor was confirmed in four of these, with tremor initially only involving the leg muscles and then spreading proximally to involve the trunk and arm muscles (Gerschlager et al. 2004). In another series, in 11 out of 30 cases, orthostatic tremor was reported to be worse over a 54.4-month follow-up period (Yaltho and Ondo 2014). In the Ganos et al.'s series (2016), which included 68 orthostatic tremor patients with a minimum follow-up of 5 years, 79.4% reported worsening orthostatic tremor symptoms, although there was no change in frequency over time. Patients who reported worsening had significantly longer symptoms than those without reported worsening (Ganos et al. 2016). However, in all the three previous series (Gerschlager et al. 2004; Yaltho and Ondo 2014; Ganos et al. 2016), the progression of symptoms was described by clinical impression and information from the patients. However, Feil et al. (2015) examined 15 patients with primary orthostatic tremor from a clinical cohort over time (5.4 $\pm$ 4.0 years) using objective measurements such as serial posturographic measurements. Posturographic data revealed a significant increase in the total sway path (standing on firm ground with eyes open) from 2.4 $\pm$ 1.3 to 3.4 $\pm$ 1.4 meter/minute ($p = 0.022$) and of the total root mean square values from 9.8 $\pm$ 4.3 to 12.4 $\pm$ 4.8 mm ($p = 0.028$), confirming the progressive nature of the disease (Feil et al. 2015).

Orthostatic tremor may be associated with other movement disorders. Thus, a few orthostatic tremor patients may develop incident PD (Wills et al. 1999; Gerschlager et al. 2004), progressive supranuclear palsy months or years later (de Bie et al. 2007), or dementia with Lewy bodies (Yaltho and Ondo 2014). Similarly, orthostatic tremor may appear in long-standing PD after 10 years (Apartis et al. 2001; Leu-Semenescu et al. 2007) or be associated with essential tremor (Papa and Gershanik 1988; FitzGerald and Jankovic 1991) or dystonia (Kobylecki et al. 2016).

Orthostatic tremor is not widely recognized by physicians who are not movement disorders experts, which often results in misdiagnosis for the unfortunate patients, who may be subjected to inappropriate or unnecessary tests and treatments (Benito-León and Domingo-Santos 2016). It is often misdiagnosed as essential tremor, PD restless legs syndrome, lumbar stenosis, and especially non-organic (psychogenic) balance disorders (Pfeiffer et al. 1999; Gerschlager et al. 2004; Piboolnurak et al. 2005). In this sense, when Pazzaglia et al. (1970) examined the first of their three patients, they were left perplexed and puzzled and doubted its true organic nature. A lack of recognition may lead to misdiagnosis; the fact that the key physical signs are subtle and easily missed can further contribute to misdiagnosis (Gerschlager et al. 2004; Piboolnurak et al. 2005). Indeed, in the study of Gerschlager et al. (2004), 5.7 years elapsed between symptom onset and diagnosis. In line with this, in the study of Hassan et al. (2016), the diagnosis was delayed by a mean of 7.2 years (range 0–44 years).

12.3 Phenomenology and Clinical Features

12.3.1 General Characteristics

Patients with orthostatic tremor primarily report a sense of unsteadiness and a weakness of the legs during stance (Bhatia et al. 2018). These feelings improve on sitting or walking (Bhatia et al. 2018). Patients rarely report tremor or leg pain as a presenting symptom (Gerschlager et al. 2004; Gerschlager and Brown 2011; Piboolnurak et al. 2005; Hassan et al. 2016). To reduce the feeling of unsteadiness, patients compensate by standing with a widened stance and clawing the floor with their toes (Jones and Bain 2011). The onset and cessation of the leg tremor can be quite abrupt with position changes, from sitting to standing and vice versa, and it may depend on the severity of the disease (Piboolnurak et al. 2005). For example, some subjects with mild orthostatic tremor may have to stand still for several minutes for the symptoms to appear (Gerschlager et al. 2004; Gerschlager and Brown 2011; Piboolnurak et al. 2005). The symptoms of orthostatic tremor characteristically decrease markedly on sitting, walking, or leaning against a wall. The need to sit down or to walk can be so disturbing that patients tend to avoid situations in which they have to stand still, such as taking a shower, waiting in line, or standing at a kitchen counter to prepare a meal (Gerschlager et al. 2004; Gerschlager and Brown 2011; Piboolnurak et al. 2005; Hassan et al. 2016). When patients are forced to stand for long periods, they usually try to alternate weight from one leg to the other, walk in the place, or lean on an object such as a chair or a countertop (Gerschlager and Brown 2011). There is also objective evidence of balance instability in patients with orthostatic tremors while standing and during challenging locomotor tasks (Chien et al. 2019). In this sense, orthostatic tremor may be associated with a specific gait disorder with a staggering wide-based walking pattern indicative of a sensory and/or a cerebellar ataxic gait (Gerschlager and Brown 2011; Wuehr et al. 2018; Möhwald et al. 2020; Opri et al. 2020).

Although mild-to-moderate appendicular-truncal ataxia is common in orthostatic tremor (Thompson et al. 2020), falls are not in general an issue. When falling is an issue, it mainly occurs in elderly patients who have additional neurological problems (PD and age-related imbalance, among others) or medication-related unsteadiness (especially benzodiazepines) (Deuschl et al. 1998; Hassan et al. 2016; Bhatia et al. 2018). Frequent falls should alert the clinician to reconsider the diagnosis and pursue other diagnoses such as progressive supranuclear palsy (Gerschlager and Brown 2011).

The tremors affect mostly the legs, but these are often present in other areas such as the hands, cranial muscles, and even the trunk (Köster et al. 1999; Piboolnurak et al. 2005). Indeed, only a small proportion of patients have isolated leg tremors (Piboolnurak et al. 2005). Patients with primary orthostatic tremors may be divided into those without a postural arm tremor. The postural tremor resembles that of patients with essential tremor (Gerschlager et al. 2004). The tremor becomes obvious when the patient maintains their arms outstretched against gravity in front

of their body (e.g., extending the upper limbs horizontally) and typically has a frequency of 5–10 Hz, which may overlap with the frequency seen in patients with essential tremor (Piboolnurak et al. 2005). Most patients with orthostatic tremor have such postural tremor, with the proportion ranging from 77.4% (24 of 31 cases) in Gerschlager et al. (2004) to 92.3% (24 of 26 cases) in Piboolnurak et al. (2005).

Unlike essential tremor (Benito-León and Louis 2006), little information exists about the prevalence of non-motor features in orthostatic tremor. In a series of 29 patients, 58.6% of them had seen a mental health professional during their orthostatic tremor illness (Bhatti et al. 2019). About 24.1% of the subjects had a history of depression, and 10.3% reported a family history of any psychiatric condition (Bhatti et al. 2019). In addition, 37.9% of the subjects screened positive for agoraphobia (Bhatti et al. 2019). In a case-control study involving 16 orthostatic tremor patients and 32 healthy matched controls, diagnosis (orthostatic tremor vs. healthy control) was associated with poor performance on tests of executive function, visuospatial ability, verbal memory, visual memory, and language tests and on a number of the Personality Assessment Inventory subscales (somatic concerns, anxiety-related disorders, depression, and antisocial features) (Benito-León et al. 2016a). Of note was that older-onset orthostatic tremor (>60 years) patients had poorer scores on cognitive and personality testing compared with their younger-onset orthostatic tremor counterparts (Benito-León et al. 2016b). Orthostatic tremor patients might have deficits in specific aspects of neuropsychological functioning, particularly those thought to rely on the integrity of the prefrontal cortex, which suggests the involvement of frontocerebellar circuits (Benito-León et al. 2016a, b, c). Psychiatric comorbidities, personality disturbances, and cognitive dysfunction could be disease-associated non-motor manifestations of orthostatic tremor. In this sense, these non-motor features correlate with magnetic resonance imaging. In a resting-state functional magnetic resonance imaging study, orthostatic tremor patients ($N = 13$) showed increased connectivity in resting-state networks involved in cognitive processes (default mode network and frontoparietal networks) and decreased connectivity in the cerebellum and sensorimotor networks (Benito-León et al. 2016b). Notably, changes in network integrity were associated not only with duration but also with cognitive function (Benito-León et al. 2016b). Finally, in the default mode network and medial visual network, increased connectivity was associated with worse performance on different cognitive domains (Benito-León et al. 2016b).

12.3.2 Clinical Examination

The leg tremor is characteristical of high frequency (13–18 Hz), which means it may not be visible on routine examination (Gerschlager et al. 2004; Gerschlager and Brown 2011; Piboolnurak et al. 2005), and this may make the diagnosis challenging. When patients complain that they feel unsteady on their feet, clinicians may overlook the possibility of orthostatic tremor and focus on other unsteady

causes. The examination reveals a rapid tremor of the legs on standing, which may sometimes be palpable, but not visible, as a fine-amplitude rippling of leg muscles (e.g., the gastrocnemius or quadriceps muscles) with an associated knee tremor; the tremor may be more easily felt than seen because of its high frequency (Ramtahal and Larner 2009). It may also be useful to place the diaphragm of a stethoscope over the gastrocnemius muscle while the patient is standing. In some instances, the tremor may be heard, sounding rather like the distant rotor blades of a helicopter (Brown 1995).

12.3.3 Diagnosis

The diagnosis of primary orthostatic tremor is based on history and physical examination and confirmed by electrophysiological testing (Bhatia et al. 2018). The EMG is performed in the lower limbs while the patient is standing so that any rhythmic activity in the 13–18 Hz range that is uniquely highly coherent among affected body parts may be detected and recorded (Bhatia et al. 2018; Jones and Bain 2011). This rhythmic activity disappears when the patient is seated or lifted off the ground.

Arriving at the correct diagnosis is dependent on the medical history and detailed clinical and electrophysiological (EMG) investigations. Although the definition of orthostatic tremor states that the tremor frequency should be confirmed by EMG, in practice, accelerometry is an acceptable alternative in cases with typical symptoms (Jones and Bain 2011). Electrocardiogram recorded in the standing position could also be a simple, non-invasive tool to screen for or support the clinical diagnosis of orthostatic tremor. Littmann (2010) reported a patient with an orthostatic tremor in whom telemetry strips revealed continuous gross 13–18 Hz of oscillatory artifact, present while standing and identical to the frequency of EMG oscillations recorded from the thigh muscles of patients with orthostatic tremor. Preliminary data suggest that smartphone accelerometry may be an alternative to surface EMG in diagnosing OT with a sensitivity of 83% and specificity of 100% (Calvo and Ferrara 2021).

In 2018, the Consensus Statement on the Classification of Tremors from the Task Force of Tremor of the International Parkinson and Movement Disorder Society proposed the term “pseudo-orthostatic tremor” (also known as slow orthostatic tremor) to describe all orthostatic tremors <13 Hz (Bhatia et al. 2018). In pseudo-orthostatic tremor, EMG coherence analysis reveals significant bilateral coupling at tremor frequency between EMG recorded from the lower limb, upper limb, and axial muscles (coherence 0.2–0.8), which is absent in controls under normal conditions, and patients with orthostatic myoclonus, and is not as strong as that seen in orthostatic tremor in the 13–18 Hz range (coherence 0.8–1) (Williams et al. 2010). While multiple lines of evidence separate this slow type of orthostatic tremor from classical (fast) orthostatic tremor, clinical and electrophysiological overlap may occur (Hassan and Caviness 2019). Primary cases and secondary causes are identified, similar to classical (fast) orthostatic tremor (Hassan and Caviness

2019). Notwithstanding, pseudo-orthostatic tremor would be a hodgepodge of many conditions and presentations resembling classical (fast) orthostatic tremor, many of which present with subharmonic peaks of an actual classical orthostatic tremor (Wee et al. 1986), or nonrhythmical presentations, which are unlikely "tremor" and would therefore speak against inclusion into an expanded spectrum of orthostatic tremor (Benito-León and Domingo-Santos 2016).

12.3.4 Laboratory Workup

Currently, there are no laboratory findings that are typical of orthostatic tremor. Hence, the purpose of laboratory investigations is to help exclude other disorders or possible symptomatic cases. Among certain patients, screening investigations should include thyroid function tests, serum protein electrophoresis to rule out gammopathies, vitamin B12 levels, diagnostic studies to exclude Wilson's disease (e.g., serum ceruloplasmin), and dopamine transporter imaging to rule out PD. Brain magnetic resonance imaging is recommended to rule out structural causes of orthostatic tremor such as pontine and midbrain lesions or cerebellar atrophy. In some patients with bilateral pyramidal tract signs or a sensory level, spinal MRI is mandatory to detect spinal cord lesions (Lee et al. 2012). However, these investigations are usually normal in orthostatic tremor cases.

12.3.5 Differential Diagnosis

Overall, the differential diagnosis includes several conditions characterized by imbalance, unsteadiness, or tremor while standing.

Tremor of the legs may occur in essential tremor, but always with upper limb tremor, and at frequencies lesser than 12 Hz, unlike orthostatic tremor (Benito-León and Louis 2006). There is currently a debate about whether orthostatic tremor is a particular condition or a variant of essential tremor. The main reason to consider the link between orthostatic tremor and essential tremor is that a considerable number of orthostatic tremor patients have a 5–10 Hz postural or kinetic arm tremor, although few of them have a family history of essential tremor (Piboolnurak et al. 2005). However, those lower frequency arm oscillations in orthostatic tremor may represent a subharmonic of the higher frequency tremors typical of orthostatic tremor, spreading throughout the body (McAuley et al. 2000). The tremor of orthostatic tremor has two unique features: first, its high frequency (13–18 Hz) and, second, high coherence values between homologous muscles of the two legs (e.g., the left and right quadriceps) (Jones and Bain 2011; Muthuraman et al. 2013). These findings are quite different from those of essential tremor, in which tremor typically has a lower frequency (4–12 Hz) and in which there are low coherence values between homologous muscles of the right and the left side (Benito-León

and Louis 2006; Jones and Bain 2011). Also, the tremor temporarily abates after ethanol intake in a few orthostatic tremor patients (Britton et al. 1992; Gerschlager et al. 2004; Piboolnurak et al. 2005), in contrast with essential tremor, in which the tremor abates in a larger proportion of patients (Benito-León and Louis 2006). In contrast to the tremor of essential tremor, orthostatic tremor shows little response to propranolol (Gerschlager et al. 2004; Piboolnurak et al. 2005). Finally, a data mining approach to magnetic resonance imaging-derived brain volume and cortical thickness data permitted the investigators to differentiate between these two types of tremor with an accuracy of 100%, suggesting that orthostatic tremor and essential tremor are distinct conditions (Benito-León et al. 2019a).

Orthostatic myoclonus is a disorder that was first reported in 15 elderly subjects by authors at the Mayo Clinic (Glass et al. 2007). Similar to orthostatic tremor, this condition is characterized by muscle contractions associated with an upright stance and is diagnosed using surface EMG recordings (van Gerpen 2014). As in orthostatic tremor, there are bursts of muscle contraction; however, in orthostatic myoclonus, the bursts are shorter in duration, nonrhythmic, and irregular than those of orthostatic tremor. Seven of the patients described by Glass et al. (2007) had a neurodegenerative disorder, and two had a systemic illness known to be associated with myoclonus (Glass et al. 2007). Leu-Semenescu et al. (2007) also described this syndrome in three PD patients complaining of unsteadiness on standing.

In PD, low (4–6 Hz)-frequency leg tremor is rarely seen while patients are standing. In general, this type of tremor response to dopaminergic drugs is good (Kim and Lee 1993; Leu-Semenescu et al. 2007). Thomas et al. (2007) reported four patients with a disabling tremor during standing that appeared years before parkinsonian symptoms were evident. The tremor, whose main frequency was 6.2–6.9 Hz, with sporadic subharmonics at 8–18 Hz, was refractory to gabapentin and dramatically responded to levodopa administration (Thomas et al. 2007).

12.3.6 Severity Assessment and Health-Related Quality of Life in Orthostatic Tremor

Limited tools are available for the severity and disability assessment of orthostatic tremor. Recently, the self-administered 10-item Orthostatic Tremor Severity and Disability Scale has been validated for capturing orthostatic tremor-related severity and disability (Merola et al. 2020).

There is increasing recognition that the global well-being of patients with chronic neurological diseases is an important outcome in research and clinical practice alike (Benito-León et al. 2003, 2012). Subjective (i.e., self-reported) measures of health-related quality of life may serve to alert clinicians to areas that would otherwise be overlooked (Benito-León et al. 2003, 2012). Orthostatic tremor is not always a benign condition, and it may negatively impact patients' health-related quality of life, including occupational and daily living activities, as the patients

tend to avoid situations where they have to stand still (Jones and Bain 2011). Only three studies have examined the health-related quality of life in orthostatic tremor (Gerschlager et al. 2003; Rodrigues et al. 2005; Maugest et al. 2018). Gerschlager et al. (2003) applied the SF-36 and the Beck Depression Inventory to measure health-related quality of life and depression, respectively, in 20 orthostatic tremor patients (Gerschlager et al. 2003). All dimensions of the SF-36 were markedly reduced in orthostatic tremor patients, and depression was found in 11 out of 20 patients (Gerschlager et al. 2003). Rodrigues et al. (2005), using a modified PD questionnaire (PDQ-39), analyzed the health-related quality of life of six orthostatic tremor patients included in an open-label add-on study gabapentin. They observed that mobility, activities of daily living, bodily discomfort, emotional well-being, and cognition were affected in patients with orthostatic tremor, and these problems improved slightly with treatment (Rodrigues et al. 2005). Maugest et al. (2018) analyzed the health-related quality of life of 40 primary orthostatic patients from a multicenter study, using eight quantitative scales and a qualitative study that employed semi-structured interviews. Health-related quality of life in primary orthostatic patients was severely affected, fearing falling as the main predictor of its worsening (Maugest et al. 2018).

12.4 Secondary (Symptomatic) Orthostatic Tremor

The vast majority of cases of orthostatic tremor are primary (idiopathic), with normal brain magnetic resonance imaging, normal laboratory workup, and no evidence of other associated conditions. However, there have been a few reports of patients whose orthostatic tremor was associated with other features, mainly parkinsonism and specifically PD ("orthostatic tremor plus") (Gerschlager et al. 2004). Of the 41 patients in the study by Gerschlager et al. (2004), other additional neurological features were evident in 10 (Gerschlager et al. 2004). Specifically, six had parkinsonism (four had typical PD, one had vascular parkinsonism and restless legs syndrome, and one had drug-induced parkinsonism). Of the remaining four patients, two also had restless legs syndrome, one had tardive dyskinesia of uncertain etiology, and one had orofacial dyskinesias of uncertain etiology (Gerschlager et al. 2004). In the Mestre et al. (2012) series, one of their 26 patients also had PD, one parkinsonism, one progressive supranuclear palsy, one restless leg syndrome, two multifocal action tremor, one hand dystonia, and one proven pathological dementia with Lewy bodies. Concerning this latter, of the 45 patients included in the series of Yaltho and Ondo (2014), one was diagnosed with dementia with Lewy bodies preceded by orthostatic tremor for 20 years.

Some rare examples of orthostatic tremor cases are associated with other non-movement disorder conditions. Thus, secondary (symptomatic) cases have been described in patients with nontumoral aqueduct stenosis (Gabellini et al. 1990), relapsing polyradiculoneuropathy (Gabellini et al. 1990), head trauma (Sanitate and Meerschaert 1993), pontine and midbrain lesions (Fig. 12.2) (Benito-León et al.

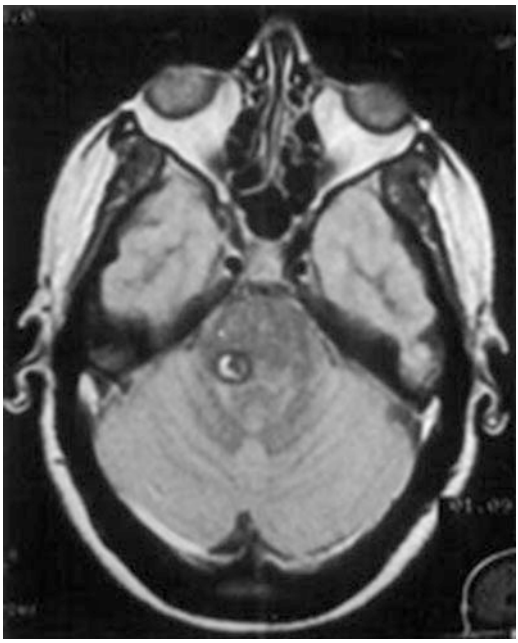

Fig. 12.2 Symptomatic orthostatic tremor caused by a lesion in the posterior fossa. Axial T1-weighted image shows a right pontine lesion, compatible with a cavernoma. Case 1 from Benito-León et al. (1997). Reprinted with permission from Wolters Kluwer Health

1997; Setta and Manto 1998; Vetrugno et al. 2010), cerebellar degeneration (Manto et al. 1999; Sarva et al. 2016), paraneoplastic syndrome associated with small-lung cancer (Gilhuis et al. 2005), recreational use of solvents (Cruz Tabuenca et al. 2017), Graves' disease (Tan et al. 2008; Lin et al. 2013; Mazzucchi et al. 2014), biclonal IgG and IgA lambda gammopathy of undetermined significance (Stich et al. 2009), stiff-person syndrome (Vetrugno et al. 2013), thiamine deficiency (Nasrallah and Mitsias 2007), vitamin B12 deficiency (Benito-León and Porta-Etessam 2000), spinal cord lesion (Lee et al. 2012), multiple sclerosis (Baker et al. 2009), adult-onset Alexander disease (Stitt et al. 2018), REEP1 mutation (formerly *SPG31*), which is almost exclusively associated with a pure hereditary spastic paraparesis phenotype (Erro et al. 2014), C10orf2 TWINKLE mutation, which raises the possibility of mitochondrial dysfunction and loss of mitochondrial DNA integrity in the pathogenesis of orthostatic tremor (Milone et al. 2013), and hip replacement surgery (Adebayo et al. 2014).

It seems that pseudo-orthostatic tremor is more frequently associated with other conditions. In the Bicart-Sée et al. (2021) series that included 10 patients with primary orthostatic tremor and 17 with pseudo-orthostatic tremor, a movement disorder was associated with 30% of primary orthostatic tremor, among them one CADASIL patient. In contrast, extrapyramidal or cerebellar disorders were reported in 100% of pseudo-OT, including three Wilson's disease patients (Bicart-Sée et al. 2021).

12.5 Pathophysiology

Although the central network contributors of orthostatic tremor are not clear, there is evidence suggesting that this condition originates due to the impairment of a network that involves the primary leg sensory-motor cortex, the supplementary motor area, the thalamus, and the cerebellum (Muthuraman et al. 2013; Lenka et al. 2017; Gallea et al. 2016; Antelmi et al. 2018). Several clinical, electrophysiological, and functional or structural neuroimaging studies have suggested the key role of the cerebellum in its pathophysiology (Benito-León and Domingo-Santos 2016).

In a cohort of 18 orthostatic tremor patients, most had signs of cerebellar dysfunction, and a substantial portion also showed proprioceptive deficits in the long-term course (Feil et al. 2015). A few symptomatic orthostatic tremor cases have cerebellar atrophy or have lesions in the pons or midbrain (Benito-León et al. 1997; Setta and Manto 1998; Manto et al. 1999; Vetrugno et al. 2010; Sarva et al. 2016). In addition, one positron emission tomography study of four patients with orthostatic tremor revealed bilateral activation of the cerebellar hemispheres and activation of the cerebellar vermis, thalamus, and lentiform nucleus (Wills et al. 1996). A more recent positron emission tomography study of ten patients with orthostatic tremor confirmed ponto-cerebello-thalamo-primary motor cortical activations underlying primary orthostatic tremor (Schöberl et al. 2017). While lying, patients had significantly increased regional cerebral glucose metabolism in the pontine tegmentum, posterior cerebellum (including the dentate nuclei), and ventral posterolateral nucleus of the ventral intermediate and ventral posterolateral nucleus thalamus, and the primary motor cortex bilaterally compared to controls (Schöberl et al. 2017). In line with this study (Schöberl et al. 2017), a diffusion tensor imaging study demonstrated white matter changes preferentially located in the cerebellum, its efferent pathways, and the pontine tegmentum and key components of the frontal-thalamic-cerebellar circuit (Benito-León et al. 2019b). Of special interest in that study (Benito-León et al. 2019b) was the increased mean diffusivity values of the posterior lobe of the cerebellum (left cerebellar lobule VI), which belongs to the sensorimotor cerebello-cerebral network. The involvement of this structure has also been observed in a multimodal approach addressing the morphological and functional alterations of 17 patients with orthostatic tremor (Gallea et al. 2016). In this landmark study, the researchers found a bilateral decrease in gray matter volume in cerebellar lobule VI, positively correlated with longer disease duration and worse scores of postural instability (Gallea et al. 2016).

Further, cerebellar lobule VI showed increased functional connectivity both with the bilateral supplementary motor area, which could play an important role in postural balance control, and with lower limb representation of the primary motor cortices (Gallea et al. 2016). Of note was that this higher level of functional connectivity was associated with higher tremor severity (Gallea et al. 2016). After 5 days of repeated cerebellar stimulation, cerebellar lobule VI showed a bilaterally decreased functional connectivity with the supplementary motor area and the primary motor cortex leg and trunk area compared to baseline (Gallea et

al. 2016). The researchers also found a bilateral increase of gray matter volume in supplementary motor areas that correlated positively with disease duration and electrophysiological tremor characteristics (Gallea et al. 2016). Gray matter volume in the cerebellar vermis was increased bilaterally and correlated positively with longer disease duration and better ability to maintain a standing position, suggestive of compensatory mechanisms that might develop in the vermis over the disease evolution (Gallea et al. 2016). In short, lobule VI impairment could be crucial in the core pathological process of orthostatic tremor and the contribution of its output pathways to the premotor and motor cortices in the postural imbalance (Gallea et al. 2016; Benito-León et al. 2019b).

The tremors recorded in each leg have high coherence. In other words, they have an almost constant phase relationship, which is not typical for most other pathological tremors (Jones and Bain 2011; Muthuraman et al. 2013). These findings suggest that the orthostatic tremors detected in each leg originate from the same central tremor generator (Jones and Bain 2011; Muthuraman et al. 2013). In addition, 16 Hz EMG bursts are time-locked in the arm, leg, truncal, and even facial muscles and are bilateral (McAuley et al. 2000). Finally, the fact that orthostatic tremor can be reset by electrical stimulation, placed over the posterior fossa, but not by peripheral nerve stimuli, supports this hypothesis (Wu et al. 2001).

Concerning unsteadiness, Yarrow et al. (2001), using force platform recordings, showed that the unsteadiness reported by orthostatic tremor patients is at least partly due to increased postural sway. However, in another study that assessed body sway under several conditions, the researchers demonstrated that subjective unsteadiness does not arise simply from an awareness of increased body sway (Fung et al. 2001). The authors postulated that the sensation of unsteadiness arises from a tremulous disruption of proprioceptive afferent activity from the legs. This disturbance gives rise to increased co-contracting drive to the leg muscles to stiffen the joints and increase stability. Since muscle activity remains tremor-locked, the tremulous proprioceptive feedback is increased, which then further increases the sensation of unsteadiness and so on, setting up and perpetuating a vicious cycle (Fung et al. 2001). By contrast, Sharott et al. (2003) showed that a 16 Hz tremor could be provoked in healthy individuals who were made unsteady through vestibular galvanic stimulation or leaning backward (Sharott et al. 2003). Schöberl et al. (2017), in their positron emission tomography study, also detected that the glucose metabolism was relatively decreased in mesiofrontal cortical areas (i.e., the medial prefrontal cortex, supplementary motor area, and anterior cingulate cortex) and the bilateral anterior insula in orthostatic tremor patients while lying and standing. Because the mesiofrontal hypometabolism correlated with increased body sway in posturography, they hypothesized that a mesiofrontal deactivation could play a pivotal role in the development of postural unsteadiness during prolonged standing (Schöberl et al. 2017).

On the other hand, Gallea et al. (2016) hypothesized that the bilateral supplementary motor area could receive constant erroneous messages from impaired processing of the lower limb proprioceptive afferents in cerebellar lobules IV, VI, and IX leading to the unsteadiness sensation in the patients with orthostatic tremor

while standing. In line with this latter, in an electroencephalogram-EMG coherence study in patients with orthostatic tremor, cerebellar and supplementary motor area sources were among the areas of the network oscillating at orthostatic tremor frequency, which led their authors to hypothesize that changes of cortico-muscular coherence were associated with desynchronization of lower limb proprioceptive feedback causing unsteadiness. (Muthuraman et al. 2013).

Orthostatic tremor is not, however, always associated with orthostasis. It can be classified as an orthostasis-independent action tremor in at least some patients. The tremors may occur during isometric contraction of the arm or leg muscles independent of stance and are absent in the upright position without weight-bearing (Boroojerdi et al. 1999).

There is some evidence of a potential role of the nigrostriatal dopaminergic system in the generation of orthostatic tremor. An association of orthostatic tremor with parkinsonism and treatment effects of L-dopa and dopamine agonists have been reported (Wills et al. 1999; Finkel 2000; Katzenschlager et al. 2003; Gerschlager et al. 2004). Using 123I-FP-CIT single-photon emission computed tomography, the dopaminergic system was affected in a group of 11 orthostatic tremor patients, although to a lesser extent than in PD (Katzenschlager et al. 2003). Compared to a group of 12 PD patients, tracer uptake in orthostatic tremor patients was significantly higher and more symmetrical, and the caudate and putamen were equally affected. A study using transcranial sonography to examine the morphology of the substantia nigra in four orthostatic tremor patients (Spiegel et al. 2005) showed echogenicity in all of them (unilateral in three and bilateral in one patient), suggesting the presence of nigrostriatal dopaminergic deficits. However, these findings are not universal, and other functional imaging studies have shown intact serotonergic and dopaminergic systems (Vaamonde et al. 2006; Trocello et al. 2008; Wegner et al. 2008; Ganos et al. 2016).

Orthostatic tremor shares some important features with neurodegenerative diseases. First, OT is a progressive disorder (Gerschlager et al. 2004; Yaltho and Ondo 2014; Feil et al. 2015; Ganos et al. 2016), suggesting the underlying pathological process may not be static. Second, patients who initially present with isolated orthostatic tremor often later develop neurodegenerative diseases, including Parkinson's disease (Wills et al. 1999; Gerschlager et al. 2004), progressive supranuclear palsy (de Bie et al. 2007), or dementia with Lewy bodies (Yaltho and Ondo 2014). Third, a single voxel proton magnetic resonance spectroscopy of 14 patients with orthostatic tremor showed a significant decrease in N-acetyl-aspartyl-glutamate and N-acetyl-aspartate (NAA) in patients versus healthy controls (Benito-León et al. 2016c). A similar decrease in NAA was seen in the cerebellar vermis and cerebellar white matter. Reductions in cerebral cortical and cerebellar NAA suggest neuronal damage or loss in orthostatic tremor, making it a neurodegenerative disease (Benito-León et al. 2016c). In this sense, longitudinal studies are required to confirm this possibility (Benito-León et al. 2016c).

The conceptualization of orthostatic tremor as a neurodegenerative disease has some clinical implications as it indicates that there is cellular and molecular pathophysiology of OT and the disease is not merely the result of an electrical

disarrangement (Benito-León and Domingo-Santos 2016). In addition, this makes identifying modifiable risk factors more important, along with strategies aimed at disease prevention (Benito-León and Domingo-Santos 2016).

12.6 Treatment

12.6.1 General Considerations

Patients with orthostatic tremor may be unable to continue full-time work, and financial problems may arise. As with other chronic diseases, it is important to consider the illness's psychological and social impact on patients. Physicians should coordinate care with other healthcare professionals to address these social and psychological issues. The impact of the disease on the patient's family should also be taken into account. It may be beneficial for orthostatic tremor patients to bring their spouse or partner to a consultation to help them better understand the disease and discuss their difficulties and concerns.

Patient-centered associations (http://www.orthostatictremor.org/) may help offer individual and group support, education, and advice. Through such interactions, patients may benefit by learning to cope with the many practical day-to-day difficulties of those living with this disease.

There are physical aids and certain lifestyle changes that may be helpful in patients with mild orthostatic tremor. Physical aids may offer some symptomatic relief. For example, portable stools may permit patients to sit rather than stand when they are waiting in line or are at social events. A tripod walking stick could also be helpful for this purpose. Furthermore, weight reduction may be helpful in overweight patients (Jones and Bain 2011).

12.6.2 Pharmacological Agents

Overall, medical therapy often yields insufficient benefits. As a result of the rarity of this condition, there are no well-designed randomized controlled trials. Several drugs have been empirically used to treat orthostatic tremor, including clonazepam, gabapentin, propranolol, levetiracetam, valproic acid, primidone, phenobarbital, topiramate, zonisamide, carbidopa/levodopa, perampanel, and pramipexole (Gerschlager et al. 2004; Piboolnurak et al. 2005; Gironell and Marín-Lahoz 2019). Such treatments have side effects, and it is important to carefully consider whether the benefits outweigh any side effects in each patient. Treatment should be initiated when the tremor interferes with the patient's ability to perform daily activities. Surgery may be the final option for a select group of patients who have not responded adequately to medications.

Of all the medications, clonazepam is considered the first-line medication in treating primary and secondary orthostatic tremor (Benito-León et al. 1997; Pradalier et al. 2002). This drug reduces tremors in about one-third of people who have the disorder. However, in some patients, it eliminates orthostatic tremor almost entirely (Pradalier et al. 2002). However, it is unclear whether this benefit is sustained over time (Papa and Gershanik 1988; Uncini et al. 1989; FitzGerald and Jankovic 1991; Britton et al. 1992; McManis and Sharbrough 1993; Benito-León et al. 1997; Gerschlager et al. 2004; Piboolnurak et al. 2005). Clonazepam is typically started at 0.5 mg daily, preferably at night, and, if tolerated, gradually titrated upward to 2 mg three times a day (Jones and Bain 2011). Second-line therapies, either as monotherapy or in combination, include gabapentin in doses ranging from 300 to 2400 mg per day (Evidente et al. 1998; Onofrj et al. 1998; Rodrigues et al. 2005, 2006), and others with variable benefit, such as primidone (van der Zwan et al. 1988; FitzGerald and Jankovic 1991; McManis and Sharbrough 1993), sodium valproate (Piboolnurak et al. 2005), carbamazepine (Gerschlager et al. 2004), phenobarbital (Cabrera-Valdivia et al. 1991), and intravenous immunoglobulin (Hegde et al. 2011). Dopaminergic drugs may be helpful in some patients over a short period, especially those who subsequently develop PD (Gerschlager and Brown 2011). Pramipexole, a dopaminergic agonist, was effective in a single patient with orthostatic tremor (Finkel 2000). Wills et al. (1999) described a series of eight orthostatic tremor patients treated with levodopa. Five of them experienced benefits and elected to remain on long-term treatment (Wills et al. 1999). By contrast, a 2-month open-label trial of levodopa treatment (600 mg per day) led to a small improvement in two of five patients but no significant overall change and no sustained benefit (Katzenschlager et al. 2003). Perampanel, an antiepileptic drug that blocks glutamate-mediated postsynaptic excitation, was tested in 20 patients with primary orthostatic tremor (Gironell and Marín-Lahoz 2019). Eight patients withdrew due to adverse effects. Of the 12 patients who completed the study, 92% indicated that their primary orthostatic tremor symptoms had improved after 1 month (Gironell and Marín-Lahoz 2019). However, this improvement was not sustained by follow-up at 3 months (Gironell and Marín-Lahoz 2019). AbobotulinumtoxinA was ineffective in eight primary orthostatic tremor patients enrolled in a randomized, double-blind, placebo-controlled cross-over design study (Bertram et al. 2013).

12.6.3 Non-pharmacological Treatments

Advances in surgical interventions may offer patients an alternative treatment modality when pharmacotherapy is inadequate. The sustained benefit of bilateral deep-brain stimulation of the ventral intermediate thalamic nucleus has been reported in a few orthostatic tremor patients (Espay et al. 2008; Guridi et al. 2008; Magariños-Ascone et al. 2010; Lyons et al. 2012; Muthuraman et al. 2013; Yaltho and Ondo 2014; Contarino et al. 2015; Coleman et al. 2016; Hassan et al. 2016;

Merola et al. 2017; Evidente et al. 2018; Hewitt et al. 2020). Clinical benefits were sustained for 6 months in the report by Yaltho and Ondo (2014), for six and 10 months in the report by Evidente et al. (2018), for at least 1 year in the report by Magariños-Ascone et al. (2010), for 7 and 16 months in the report by Coleman et al. (2016), for 18 months in the report by Espay et al. (2008), for 30 months in the report by Lyons et al. (2012), for 3 years in the report by Hassan et al. (2016), for 4 years in the report by Guridi et al. (2008), and up to 6 years in the report by Hewitt et al. (2020). In Contarino et al.'s (2015) report, the efficacy of stimulation on tremor decreased 1 year after surgery and did not improve with parameter adjustments (Contarino et al. 2015). Over time, tremor slowly worsened, and at the last follow-up (5 years after surgery), stimulation, although still effective, could not produce optimal clinical improvement (Contarino et al. 2015). In a retrospective multicenter international registry that included 17 patients with deep-brain stimulation of the ventral intermediate thalamic nucleus, of which 12 had previously been published partially in case reports (Espay et al. 2008; Guridi et al. 2008; Magariños-Ascone et al. 2010; Lyons et al. 2012; Muthuraman et al. 2013; Yaltho and Ondo, 2014; Contarino et al. 2015; Coleman et al. 2016; Hassan et al. 2016), there was a 21.6% improvement in the composite activities of daily living/instrumental activities of the daily living score, which gradually attenuated (12.5%) in the subgroup of patients with an additional long-term follow-up (8 of 17) (Merola et al. 2017). The latency of symptoms on standing significantly improved, both in the short term and in the long term (Merola et al. 2017). However, three patients obtained no/minimal benefit from the procedure (Merola et al. 2017). Some patients have not improved with deep-brain stimulation of the ventral intermediate thalamic nucleus. Lehn et al. (2017) reported a 68-year-old male with orthostatic tremor who did not improve significantly after bilateral thalamic stimulation. Clinical benefits receded after 3 months in another patient treated with unilateral deep-brain stimulation of the ventral intermediate thalamic nucleus (Espay et al. 2008).

Zona incerta is another target for tremor control. Bilateral caudal zona incerta deep-brain stimulation was effective in four orthostatic tremor patients (Gilmore et al. 2019). Chronic spinal cord stimulation at the level of the lower thoracic spine demonstrated beneficial effects with long-term follow-up in four patients with medically intractable primary orthostatic tremor (Krauss et al. 2006; Blahak et al. 2016). A single session of trans-spinal direct current stimulation, a non-invasive method to modulate spinal cord circuits, may be useful to improve instability in primary orthostatic tremor (Lamy et al. 2021).

12.7 Summary

Orthostatic tremor is a rare and enigmatic movement disorder characterized by tremor of the legs and trunk, present on standing and improving on walking or sitting. The origin and mechanism of this condition are not well understood; notwithstanding, neurophysiological and functional imaging studies suggest a key

role of the cerebellum in its pathophysiology, although other brain regions such as the motor and sensory cortices, and the thalamus, may also be involved. Orthostatic tremor is generally considered to be a distinct and primarily "idiopathic" disorder, with normal brain magnetic resonance imaging and laboratory workup; however, symptomatic orthostatic tremor cases have been described as well. Although a small number of medications (clonazepam, gabapentin, and dopaminergic drugs) can provide partial relief from tremor in a few patients, the pharmacological treatment of orthostatic tremor is not optimal, and some patients with severe tremor may choose to undergo surgery that may be effective, but sometimes with a reduction in the effect over time. We are now seeing the clinical expansion of the concept of orthostatic tremor to include other neurological features (cerebellar dysfunction signs) and non-motor features (cognitive problems, psychiatric problems), the heterogeneity of pharmacological response profiles and clinical progression, and the association of orthostatic tremor with other neurodegenerative diseases such as Parkinson's disease and other types of parkinsonism. We propose that orthostatic tremor might be a family of diseases, unified by the presence of lower limbs tremor, but further characterized by etiological and clinical heterogeneity.

References

Adebayo PB, Gunduz A, Kiziltan ME, Kiziltan G. Upper limbs spread of orthostatic tremor following hip replacement surgery. Neurol India. 2014;62:462–3.

Antelmi E, Rocchi L, Cocco A, Erro R, Latorre A, Liguori R, Plazzi G, Berardelli A, Rothwell J, Bhatia KP. Cerebellar and brainstem functional abnormalities in patients with primary orthostatic tremor. Mov Disord. 2018;33:1024–5.

Apartis E, Tison F, Arné P, Jedynak CP, Vidailhet M. Fast orthostatic tremor in Parkinson's disease mimicking primary orthostatic tremor. Mov Disord. 2001;16:1133–6.

Baker M, Fisher K, Lai M, Duddy M, Baker S. Slow orthostatic tremor in multiple sclerosis. Mov Disord. 2009;24:1550–3.

Benito-León J, Domingo-Santos Á. Orthostatic tremor: an update on a rare entity. Tremor Other Hyperkinet Mov (N Y). 2016;6:411.

Benito-León J, Louis ED. Essential tremor: emerging views of a common disorder. Nat Clin Pract Neurol. 2006;2:666–78.

Benito-León J, Porta-Etessam J. Shaky-leg syndrome and vitamin B12 deficiency. N Engl J Med. 2000;342:981.

Benito-León J, Rodríguez J, Ortí-Pareja M, Ayuso-Peralta L, Jiménez-Jiménez FJ, Molina JA. Symptomatic orthostatic tremor in pontine lesions. Neurology. 1997;49:1439–41.

Benito-León J, Morales JM, Rivera-Navarro J, Mitchell A. A review about the impact of multiple sclerosis on health-related quality of life. Disabil Rehabil. 2003;25:1291–303.

Benito-León J, Bermejo-Pareja F, Morales-González JM, Porta-Etessam J, Trincado R, Vega S, Louis ED. Neurological Disorders in Central Spain (NEDICES) Study Group. Incidence of Parkinson disease and parkinsonism in three elderly populations of central Spain. Neurology. 2004;62:734–41.

Benito-León J, Cubo E, Coronell C, on behalf of the ANIMO Study Group. Impact of apathy on health-related quality of life in recently diagnosed Parkinson's disease: The ANIMO study. Mov Disord. 2012;27:211–8.

Benito-León J, Louis ED, Puertas-Martín V, Romero JP, Matarazzo M, Molina-Arjona JA, Domínguez-González C, Sánchez-Ferro Á. Cognitive and neuropsychiatric features of orthostatic tremor: a case-control comparison. J Neurol Sci. 2016a;361:137–43.

Benito-León J, Louis ED, Manzanedo E, Hernández-Tamames JA, Álvarez-Linera J, Molina-Arjona JA, Matarazzo M, Romero JP, Domínguez-González C, Domingo-Santos Á, Sánchez-Ferro Á. Resting state functional MRI reveals abnormal network connectivity in orthostatic tremor. Medicine (Baltimore). 2016b;95:e4310.

Benito-León J, Louis ED, Mato-Abad V, Dydak U, Álvarez-Linera J, Hernández-Tamames JA, Molina-Arjona JA, Malpica N, Matarazzo M, Romero JP, Sánchez-Ferro Á. In vivo neurometabolic profiling in orthostatic tremor. Medicine (Baltimore). 2016c;95(37):e4848.

Benito-León J, Louis ED, Mato-Abad V, Sánchez-Ferro A, Romero JP, Matarazzo M, Serrano JI. A data mining approach for classification of orthostatic and essential tremor based on MRI-derived brain volume and cortical thickness. Ann Clin Transl Neurol. 2019a;6:2531–43.

Benito-León J, Romero JP, Louis ED, Sánchez-Ferro A, Matarazzo M, Molina-Arjona JA, Mato-Abad V. Diffusion tensor imaging in orthostatic tremor: a tract-based spatial statistics study. Ann Clin Transl Neurol. 2019b;6:2212–22.

Bertram K, Sirisena D, Cowey M, Hill A, Williams DR. Safety and efficacy of botulinum toxin in primary orthostatic tremor. J Clin Neurosci. 2013;20:1503–5.

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM, Deuschl G; Tremor Task Force of the International Parkinson and Movement Disorder Society Consensus. Statement on the classification of tremors from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33:75–87.

Bhattacharyya KB, Das D. Familial orthostatic tremor and essential tremor in two young brothers: a rare entity. Ann Indian Acad Neurol. 2013;16:276–8.

Bhatti DE, Thompson RJ, Malgireddy K, Syed NM, Bayer B, Bessette D, Fleisher MH, Murman DL, Torres-Russotto D. Anxiety spectrum disorders are common in patients with orthostatic tremor. Clin Park Relat Disord. 2019;1:10–2.

Bicart-Sée L, Thibault JL, Poujois A, Woimant F, Bouquet-Castiglione F, Lozeron P, Kubis N. Associated co-morbidities in a retrospective cohort of orthostatic tremor. J Neurol. 2021;268:467–73.

Blahak C, Sauer T, Baezner H, Wolf ME, Saryyeva A, Schrader C, Capelle HH, Hennerici MG, Krauss JK. Long-term follow-up of chronic spinal cord stimulation for medically intractable orthostatic tremor. J Neurol. 2016;263:2224–8.

Boroojerdi B, Ferbert A, Foltys H, Kosinski CM, Noth J, Schwarz M. Evidence for a non-orthostatic origin of orthostatic tremor. J Neurol Neurosurg Psychiatry. 1999;66:284–8.

Britton TC, Thompson PD, van der Kamp W, Rothwell JC, Day BL, Findley LJ, Marsden CD. Primary orthostatic tremor: further observations in six cases. J Neurol. 1992;239:209–17.

Brown P. New clinical sign for orthostatic tremor. Lancet. 1995;346:306–7.

Cabrera-Valdivia F, Jiménez-Jiménez FJ, García Albea E, Tejeiro-Martínez J, Vaquero Ruipérez JA, Ayuso-Peralta L. Orthostatic tremor: successful treatment with phenobarbital. Clin Neuropharmacol. 1991;14:438–41.

Calvo NE, Ferrara JM. Diagnosis of orthostatic tremor using smartphone accelerometry. BMC Neurol. 2021;21:457.

Chien JH, Torres-Russotto D, Wang Z, Gui C, Whitney D, Siu KC. The use of smartphone in measuring stance and gait patterns in patients with orthostatic tremor. PLoS One. 2019;14(7):e0220012.

Coleman RR, Starr PA, Katz M, Glass GA, Volz M, Khandhar SM, Ostrem JL. Bilateral Ventral Intermediate Nucleus Thalamic Deep Brain Stimulation in Orthostatic Tremor. Stereotact Funct Neurosurg. 2016;94:69–74.

Contarino MF, Welter ML, Agid Y, Hartmann A. Orthostatic tremor in monozygotic twins. Neurology. 2006;66:1600–1.

Contarino MF, Bour LJ, Schuurman PR, Blok ER, Odekerken VJ, van den Munckhof P, de Bie RM, van Rootselaar AF. Thalamic deep brain stimulation for orthostatic tremor: Clinical and neurophysiological correlates. Parkinsonism Relat Disord. 2015;21:1005–7.

Cruz Tabuenca H, Camacho Velásquez JL, Rivero Sanz E, Sánchez Valiente S, López Del Val J. Orthostatic tremor secondary to recreational use of solvents. Neurologia. 2017;32:401–3.

de Bie RM, Chen R, Lang AE. Orthostatic tremor in progressive supranuclear palsy. Mov Disord. 2007;22:1192–4.

Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13 Suppl 3:2–23.
Erro R, Cordivari C, Bhatia KP. SPG31 presenting with orthostatic tremor. Eur J Neurol. 2014;21:e34–5.
Espay AJ, Duker AP, Chen R, Okun MS, Barrett ET, Devoto J, Zeilman P, Gartner M, Burton N, Miranda HA, Mandybur GT, Zesiewicz TA, Foote KD, Revilla FJ. Deep brain stimulation of the ventral intermediate nucleus of the thalamus in medically refractory orthostatic tremor: preliminary observations. Mov Disord. 2008;23:2357–62.
Evidente VG, Adler CH, Caviness JN, Gwinn KA. Effective treatment of orthostatic tremor with gabapentin. Mov Disord. 1998;13:829–31.
Evidente VGH, Baker ZJ, Evidente MH, Garrett R, Lambert M, Ponce FA. Orthostatic tremor is responsive to bilateral thalamic deep brain stimulation: report of two cases performed asleep. Tremor Other Hyperkinet Mov (N Y). 2018;8:566.
Feil K, Böttcher N, Guri F, Krafczyk S, Schöberl F, Zwergal A, Strupp M. Long-term course of orthostatic tremor in serial posturographic measurement. Parkinsonism Relat Disord. 2015;21:905–10.
Finkel MF. Pramipexole is a possible effective treatment for primary orthostatic tremor (shaky leg syndrome). Arch Neurol. 2000;57:1519–20.
Fischer M, Kress W, Reiners K, Rieckmann P. Orthostatic tremor in three brothers. J Neurol. 2007;254:1759–60.
FitzGerald PM, Jankovic J. Orthostatic tremor: an association with essential tremor. Mov Disord. 1991;6:60–4.
Fung VS, Sauner D, Day BL. A dissociation between subjective and objective unsteadiness in primary orthostatic tremor. Brain. 2001;124:322–30.
Gabellini AS, Martinelli P, Gullì MR, Ambrosetto G, Ciucci G, Lugaresi E. Orthostatic tremor: essential and symptomatic cases. Acta Neurol Scand. 1990;81:113–7.
Gallea C, Popa T, García-Lorenzo D, Valabregue R, Legrand AP, Apartis E, Marais L, Degos B, Hubsch C, Fernández-Vidal S, Bardinet E, Roze E, Lehéricy S, Meunier S, Vidailhet M. Orthostatic tremor: a cerebellar pathology? Brain. 2016;139:2182–97.
Ganos C, Maugest L, Apartis E, Gasca-Salas C, Cáceres-Redondo MT, Erro R, Navalpotro-Gómez I, Batla A, Antelmi E, Degos B, Roze E, Welter ML, Mestre T, Palomar FJ, Isayama R, Chen R, Cordivari C, Mir P, Lang AE, Fox SH, Bhatia KP, Vidailhet M. The long-term outcome of orthostatic tremor. J Neurol Neurosurg Psychiatry. 2016;87:167–72.
Gates PC. Orthostatic tremor (shaky legs syndrome). Clin Exp Neurol. 1993;30:66–71.
Gerschlager W, Brown P. Orthostatic tremor – a review. Handb Clin Neurol. 2011;100:457–62.
Gerschlager W, Katzenschlager R, Schrag A, Lees AJ, Brown P, Quinn N, Bhatia KP. Quality of life in patients with orthostatic tremor. J Neurol. 2003;250:212–5.
Gerschlager W, Münchau A, Katzenschlager R, Brown P, Rothwell JC, Quinn N, Lees AJ, Bhatia KP. Natural history and syndromic associations of orthostatic tremor: a review of 41 patients. Mov Disord. 2004;19:788–95.
Gilhuis HJ, van Ommen HJ, Pannekoek BJ, Sillevis Smitt PA. Paraneoplastic orthostatic tremor associated with small cell lung cancer. Eur Neurol. 2005;54:225–6.
Gilmore G, Murgai A, Nazer A, Parrent A, Jog M. Zona incerta deep-brain stimulation in orthostatic tremor: efficacy and mechanism of improvement. J Neurol. 2019;266:2829–37.
Gironell A, Marín-Lahoz J. Primary orthostatic tremor: experience of Perampanel use in 20 patients. Tremor Other Hyperkinet Mov (N Y). 2019;9.
Glass GA, Ahlskog JE, Matsumoto JY. Orthostatic myoclonus: a contributor to gait decline in selected elderly. Neurology. 2007;68:1826–30.
Guridi J, Rodríguez-Oroz MC, Arbizu J, Alegre M, Prieto E, Landecho I, Manrique M, Artieda J, Obeso JA. Successful thalamic deep brain stimulation for orthostatic tremor. Mov Disord. 2008;23:1808–11.
Hassan A, Ahlskog JE, Matsumoto JY, Milber JM, Bower JH, Wilkinson JR. Orthostatic tremor: Clinical, electrophysiologic, and treatment findings in 184 patients. Neurology. 2016;86:458–64.

Hassan A, Caviness J. Slow orthostatic tremor: Review of the current evidence. Tremor Other Hyperkinet Mov (N Y). 2019;9.
Hegde M, Glass GA, Dalmau J, Christine CW. A case of slow orthostatic tremor, responsive to intravenous immunoglobulin. Mov Disord. 2011;26:1563–5.
Heilman KM. Orthostatic tremor. Arch Neurol. 1984;41:880–1.
Hewitt AL, Klassen BT, Lee KH, Van Gompel JJ, Hassan A. Deep brain stimulation for orthostatic tremor: A single-center case series. Neurol Clin Pract. 2020;10:324–32.
Jones L, Bain PG. Orthostatic tremor. Pract Neurol. 2011;11:240–3.
Katzenschlager R, Costa D, Gerschlager W, O'Sullivan J, Zijlmans J, Gacinovic S, Pirker W, Wills A, Bhatia K, Lees AJ, Brown P. [123I]-FP-CIT-SPECT demonstrates dopaminergic deficit in orthostatic tremor. Ann Neurol. 2003;53:489–96.
Kim JS, Lee MC. Leg tremor mimicking orthostatic tremor as an initial manifestation of Parkinson's disease. Mov Disord. 1993;8:397–8.
Kobylecki C, Silverdale MA, Dick JP, Kellett MW, Marshall AG. Dystonia associated with idiopathic slow orthostatic tremor. Tremor Other Hyperkinet Mov (N Y). 2016;5:351.
Köster B, Lauk M, Timmer J, Poersch M, Guschlbauer B, Deuschl G, Lücking CH. Involvement of cranial muscles and high intermuscular coherence in orthostatic tremor. Ann Neurol. 1999;45:384–8.
Krauss JK, Weigel R, Blahak C, Bäzner H, Capelle HH, Grips E, Rittmann M, Wöhrle JC. Chronic spinal cord stimulation in medically intractable orthostatic tremor. J Neurol Neurosurg Psychiatry. 2006;77:1013–6.
Lamy JC, Varriale P, Apartis E, Mehdi S, Blancher-Meinadier A, Kosutzka Z, Degos B, Frismand S, Simonetta-Moreau M, Meunier S, Roze E, Vidailhet M. Trans-spinal direct current stimulation for managing primary orthostatic tremor. Mov Disord. 2021;36:1835–42.
Lee HM, Kwon DY, Park MH, Koh SB, Kim SH. Symptomatic orthostatic tremor with progressive cognitive impairment in spinal cord lesions. Clin Neurol Neurosurg. 2012;114:1329–31.
Lehn AC, O'Gorman C, Olson S, Salari M. Thalamic ventral intermediate nucleus deep brain stimulation for orthostatic tremor. Tremor Other Hyperkinet Mov (N Y). 2017;7:479.
Lenka A, Pal PK, Bhatti DE, Louis ED. Pathogenesis of primary orthostatic tremor: current concepts and controversies. Tremor Other Hyperkinet Mov (N Y). 2017;7:513.
Leu-Semenescu S, Roze E, Vidailhet M, Legrand AP, Trocello JM, Cochen V, Sangla S, Apartis E. Myoclonus or tremor in orthostatism: an under-recognized cause of unsteadiness in Parkinson's disease. Mov Disord. 2007;22:2063–9.
Lin FC, Wu MN, Chen CH, Huang P. Slow orthostatic tremor as the first manifestation of Grave's disease. Mov Disord. 2013;28:1158–9.
Littmann L. Fact or artifact? The electrocardiographic diagnosis of orthostatic tremor. J Electrocardiol. 2010;43:270–3.
Lyons MK, Behbahani M, Boucher OK, Caviness JN, Evidente VG. Orthostatic tremor responds to bilateral thalamic deep brain stimulation. Tremor Other Hyperkinet Mov (N Y). 2012;2:tre-02-30-85-9.
Magariños-Ascone C, Ruiz FM, Millán AS, Montes E, Regidor I, Del Alamo de Pedro M, Figueiras-Méndez R. Electrophysiological evaluation of thalamic DBS for orthostatic tremor. Mov Disord. 2010;25:2476–7.
Manto MU, Setta F, Legros B, Jacquy J, Godaux E. Resetting of orthostatic tremor associated with cerebellar cortical atrophy by transcranial magnetic stimulation. Arch Neurol. 1999;56:1497–500.
Maugest L, McGovern EM, Mazalovic K, Doulazmi M, Apartis E, Anheim M, Bourdain F, Benchetrit E, Czernecki V, Broussolle E, Bonnet C, Falissard B, Jahanshahi M, Vidailhet M, Roze E. Health-related quality of life is severely affected in primary orthostatic tremor. Front Neurol. 2018;8:747.
Mazzucchi S, Frosini D, Calabrese R, Bonuccelli U, Ceravolo R. Symptomatic orthostatic tremor associated with Graves' disease. Neurol Sci. 2014;35:929–31.
McAuley JH, Britton TC, Rothwell JC, Findley LJ, Marsden CD. The timing of primary orthostatic tremor bursts has a task specific plasticity. Brain. 2000;123:254–66.

McManis PG, Sharbrough FW. Orthostatic tremor: clinical and electrophysiologic characteristics. Muscle Nerve. 1993;16:1254–60.

Merola A, Fasano A, Hassan A, Ostrem JL, Contarino MF, Lyons M, Krauss JK, Wolf ME, Klassen BT, van Rootselaar AF, Regidor I, Duker AP, Ondo W, Guridi J, Volkmann J, Wagle Shukla A, Mandybur GT, Okun MS, Witt K, Starr PA, Deuschl G, Espay AJ. Thalamic deep brain stimulation for orthostatic tremor: a multicenter international registry. Mov Disord. 2017;32:1240–4.

Merola A, Torres-Russotto DR, Stebbins GT, Vizcarra JA, Shukla AW, Hassan A, Marsili L, Krauss JK, Elble RJ, Deuschl G, Espay AJ. Development and validation of the orthostatic tremor severity and disability scale (OT-10). Mov Disord. 2020;35:1796–801.

Mestre TA, Lang AE, Ferreira JJ, Almeida V, de Carvalho M, Miyasaki J, Chen R, Fox S. Associated movement disorders in orthostatic tremor. J Neurol Neurosurg Psychiatry. 2012;83(7):725–9.

Milone M, Klassen BT, Landsverk ML, Haas RH, Wong LJ. Orthostatic tremor, progressive external ophthalmoplegia, and Twinkle. JAMA Neurol. 2013;70:1429–31.

Möhwald K, Wuehr M, Schenkel F, Feil K, Strupp M, Schniepp R. The gait disorder in primary orthostatic tremor. J Neurol. 2020;267(Suppl 1):285–91.

Muthuraman M, Hellriegel H, Paschen S, Hofschulte F, Reese R, Volkmann J, Witt K, Deuschl G, Raethjen J. The central oscillatory network of orthostatic tremor. Mov Disord. 2013;28:1424–30.

Nasrallah KM, Mitsias PD. Orthostatic tremor due to thiamine deficiency. Mov Disord. 2007;22:440–1.

Onofrj M, Thomas A, Paci C, D'Andreamatteo G. Gabapentin in orthostatic tremor: results of a double-blind cross-over with placebo in four patients. Neurology. 1998;51:880–2.

Opri E, Hu W, Jabarkheel Z, Hess CW, Schmitt AC, Gunduz A, Hass CJ, Okun MS, Wagle SA. Gait characterization for patients with orthostatic tremor. Parkinsonism Relat Disord. 2020;71:23–7.

Papa SM, Gershanik OS. Orthostatic tremor: an essential tremor variant? Mov Disord. 1988;3:97–108.

Park S, Lim JG, Chang HJ, Oh E. What shall we do for the patients with shaky leg syndrome? A review of 23 patients. Neurodegener Dis. 2020;20:46–54.

Pazzaglia P, Sabattini L, Lugaresi E. On an unusual disorder of erect standing position (observation of 3 cases). Riv Sper Freniatr Med Leg Alien Ment. 1970;94:450–7.

Piboolnurak P, Yu QP, Pullman SL. Clinical and neurophysiologic spectrum of orthostatic tremor: case series of 26 subjects. Mov Disord. 2005;20:1455–61.

Pfeiffer G, Hinse P, Humbert T, Riemer G. Neurophysiology of orthostatic tremor. Influence of transcranial magnetic stimulation. Electromyogr Clin Neurophysiol. 1999;39:49–53.

Pradalier A, Apartis E, Vincent D, Campinos C. Primary orthostatic tremor. Rev Med Interne. 2002;23:193–7.

Ramtahal J, Larner AJ. Shaky legs? Think porthostatic tremor! Age Ageing. 2009;38:352–3.

Rodrigues JP, Edwards DJ, Walters SE, Byrnes ML, Thickbroom G, Stell R, Mastaglia FL. Gabapentin can improve postural stability and quality of life in primary orthostatic tremor. Mov Disord. 2005;20:865–70.

Rodrigues JP, Edwards DJ, Walters SE, Byrnes ML, Thickbroom GW, Stell R, Mastaglia FL. Blinded placebo cross-over study of gabapentin in primary orthostatic tremor. Mov Disord. 2006;21:900–5.

Sanitate SS, Meerschaert JR. Orthostatic tremor: delayed onset following head trauma. Arch Phys Med Rehabil. 1993;74:886–9.

Sarva H, Severt WL, Jacoby N, Pullman SL, Saunders-Pullman R. Secondary orthostatic tremor in the setting of cerebellar degeneration. J Clin Neurosci. 2016;27:173–5.

Schöberl F, Feil K, Xiong G, Bartenstein P, la Fougére C, Jahn K, Brandt T, Strupp M, Dieterich M, Zwergal A. Pathological ponto-cerebello-thalamo-cortical activations in primary orthostatic tremor during lying and stance. Brain. 2017;140:83–97.

Setta F, Manto MU. Orthostatic tremor associated with a pontine lesion or cerebellar disease. Neurology. 1998;51:923.

Sharott A, Marsden J, Brown P. Primary orthostatic tremor is an exaggeration of a physiological response to instability. Mov Disord. 2003;18:195–9.
Spiegel J, Behnke S, Fuss G, Becker G, Dillmann U. Echogenic substantia nigra in patients with orthostatic tremor. J Neural Transm. 2005;112:915–20.
Stich O, Fritzsch C, Heimbach B, Rijntjes M. Orthostatic tremor associated with biclonal IgG and IgA lambda gammopathy of undetermined significance. Mov Disord. 2009;24:154–5.
Stitt DW, Gavrilova R, Watson R, Hassan A. An unusual presentation of late-onset Alexander's disease with slow orthostatic tremor and a novel GFAP variant. Neurocase. 2018;24:266–8.
Tan EK, Lo YL, Chan LL. Graves disease and isolated orthostatic tremor. Neurology. 2008;70:1497–8.
Thompson PD, Rothwell JC, Day BL, Berardelli A, Dick JP, Kachi T, Marsden CD. The physiology of orthostatic tremor. Arch Neurol. 1986;43:584–7.
Thomas A, Bonanni L, Antonini A, Barone P, Onofrj M. Dopa-responsive pseudo-orthostatic tremor in parkinsonism. Mov Disord. 2007;22:1652–6.
Thompson R, Bhatti DE, Hellman A, Doss SJ, Malgireddy K, Shou J, Srikanth-Mysore C, Bendi S, Bertoni JM, Torres-Russotto D. Ataxia prevalence in primary orthostatic tremor. Tremor Other Hyperkinet Mov (N Y). 2020;10:54.
Trocello JM, Zanotti-Fregonara P, Roze E, Apartis E, Legrand AP, Habert MO, Devaux JY, Vidailhet M. Dopaminergic deficit is not the rule in orthostatic tremor. Mov Disord. 2008;15:1733–8.
Uncini A, Onofrj M, Basciani M, Cutarella R, Gambi D. Orthostatic tremor: report of two cases and an electrophysiological study. Acta Neurol Scand. 1989;79:119–22.
Vaamonde J, García A, Flores JM, Ibáñez R, Gargallo L. Study of presynaptic nigrostriatal pathway by 123-I-FD-CIT-SPECT (datscan SPECT) in primary orthostatic tremor. Neurologia. 2006;21:37–9.
van der Zwan A, Verwey JC, van Gijn J. Relief of orthostatic tremor by primidone. Neurology. 1988;38:1332.
van Gerpen JA. A retrospective study of the clinical and electrophysiological characteristics of 32 patients with orthostatic myoclonus. Parkinsonism Relat Disord. 2014;20:889–93.
Vetrugno R, D'Angelo R, Alessandria M, Mascalchi M, Montagna P. Orthostatic tremor in a left midbrain lesion. Mov Disord. 2010;25:793–5.
Vetrugno R, Fabbri M, Antelmi E, D'Angelo R, Rinaldi R. Orthostatic tremor heralding the onset of stiff-person syndrome. Neurology. 2013;81:1361–2.
Virmani T, Louis ED, Waters C, Pullman SL. Familial orthostatic tremor: an additional report in siblings. Neurology. 2012;7:288–9.
Wee AS, Subramony SH, Currier RD. Orthostatic tremor' in familial-essential tremor. Neurology. 1986;36:1241–5.
Wegner F, Strecker K, Boeckler D, Wagner A, Preul C, Lobsien D, Sabri O, Hesse S. Intact serotonergic and dopaminergic systems in two cases of orthostatic tremor. J Neurol. 2008;255:1840–2.
Williams ER, Jones RE, Baker SN, Baker MR. Slow orthostatic tremor can persist when walking backward. Mov Disord. 2010;25:795–7.
Wills AJ, Thompson PD, Findley LJ, Brooks DJ. A positron emission tomography study of primary orthostatic tremor. Neurology. 1996;46:747–52.
Wills AJ, Brusa L, Wang HC, Brown P, Marsden CD. Levodopa may improve orthostatic tremor: case report and trial of treatment. J Neurol Neurosurg Psychiatry. 1999;66:681–4.
Wu YR, Ashby P, Lang AE. Orthostatic tremor arises from an oscillator in the posterior fossa. Mov Disord. 2001;16:272–9.
Wuehr M, Schlick C, Möhwald K, Schniepp R. Walking in orthostatic tremor modulates tremor features and is characterized by impaired gait stability. Sci Rep. 2018;8:14152.
Yaltho TC, Ondo WG. Orthostatic tremor: a review of 45 cases. Parkinsonism Relat Disord. 2014;20:723–5.
Yarrow K, Brown P, Gresty MA, Bronstein AM. Force platform recordings in the diagnosis of primary orthostatic tremor. Gait Posture. 2001;13:27–34.

Chapter 13
Posttraumatic Tremor and Other Posttraumatic Movement Disorders

Jose Fidel Baizabal-Carvallo and Joseph Jankovic

Abstract Trauma, defined as a form of mechanical stress, is followed by a series of reactions aimed to repair the damage, promote healing, and recruit host defense mechanisms. It is believed that the motor system may be involved in some of these mechanisms giving rise to loss of motor control and a variety of abnormal movements. Movement disorders (MDs) following trauma have been recognized in the medical literature since 1888 when Gowers described two patients with involuntary movements after neck and thumb trauma. Many types of MDs have been described following trauma, including dystonia, tremor, parkinsonism, chorea, tics, myoclonus, hemifacial spasm, hemimasticatory spasm, "jumping post-amputation stump," painful legs (arms) and moving toes (fingers), and synkinesias secondary to aberrant nerve regeneration.

Keywords Posttraumatic · Movement disorders · Tremor · Dystonia · Parkinsonism · Functional · Injury

13.1 Introduction

Stress is defined as a state of threatened or disturbed homeostasis provoked by an internal or external stimulus (Black 2002). Trauma can be considered a cause of mechanical stress. After trauma, the organism responds with a series of reactions aimed to repair the damage, promote healing, and recruit host defense mechanisms.

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It is believed that the motor system may be involved in some of these mechanisms giving rise to loss of motor control and a variety of abnormal movements. Movement disorders (MDs) following trauma have been recognized in the medical literature since 1888 when Gowers described two patients with involuntary movements after neck and thumb trauma (Gowers 1888). Many types of MDs have been described following trauma, including dystonia, tremor, chorea, tics, myoclonus, hemifacial spasm, hemimasticatory spasm, "jumping post-amputation stump," painful legs (arms) and moving toes (fingers), synkinesias secondary to aberrant regeneration, and parkinsonism (Cardoso and Jankovic 1995; Jankovic 2009a).

13.2 Classification of Posttraumatic Movement Disorders

Posttraumatic MDs are classified according to their primary phenomenology and the site of the initial trauma. Direct trauma to the central nervous system (CNS), also known as traumatic brain injury (TBI) (Krauss and Jankovic 2002) or spinal cord injury, and peripheral trauma (soft tissues, peripheral nerves, and cranial nerves) have been documented to cause various involuntary movements and other MDs (Jankovic 2009a, b). Despite the obvious temporary relationship between the trauma and subsequent MDs, the cause-and-effect relationship and the mechanisms of the disturbances in such disorders are not always well understood.

Along with local evidence of injury, the time between the trauma and the onset of the movement disorder is a key feature in establishing a cause-and-effect relationship (Table 13.1). In some instances, however, a definite cause-and-effect relationship cannot be established, partially due to various circumstances, including recall bias, delayed effects, and even medico-legal issues (Scarano and Jankovic 1998). This is particularly true in patients with peripherally induced MDs, as trauma in these instances may be relatively minor and seemingly inconsequential (Nobrega et al. 2002). In 1988, we proposed a set of operational criteria, such as regional evidence of injury and a maximum latency of 1 year after the trauma, in order to classify the motor disturbance as posttraumatic, peripherally induced movement disorder (Jankovic and Van der Linden 1988) (Table 13.1). Although these diagnostic criteria have been relatively well accepted, some authors have allowed latencies of 2 (Marsden et al. 1984) and up to 8 years (Weiner 2001; Schott 1985). In a review of cases with peripherally induced MDs, 95% of reported cases had a latency shorter than 1 year after trauma, with a median of 21 days, but the clinical characteristics did not differ between patients with latencies less and more than a year (van Rooijen et al. 2011). Despite controversies about the existence of peripherally induced tremor, dystonia, and parkinsonism, other MDs have a more generalized acceptance of a peripheral origin, including hemifacial spasm (Wang and Jankovic 1998), segmental myoclonus (Jankovic and Pardo 1986), edentulous orodyskinesias (Koller 1983; Blanchet et al. 2008), and amputation stump dyskinesias (Jankovic and Glass 1985; Kulisevsky et al. 1992).

Table 13.1 Proposed criteria for movement disorders induced by peripheral trauma

1. The injury should be severe enough to cause local symptoms, persisting or requiring medical attention, for at least 2 weeks after trauma
2. The onset of involuntary movements must have occurred within 1 year after the trauma
3. The abnormal movements should be anatomically related to the site of trauma
(a) Absence of other etiologies explaining the origin of the involuntary movement (b) Presence of reflex sympathetic dystrophy (c) Poor response to conventional treatment

13.3 Trauma to the Central Nervous System

In this part of the chapter, we will discuss the effects of head trauma in the pathogenesis of different MDs as well as diagnostic procedures and treatment options.

13.3.1 Movement Disorders Following Traumatic Brain Injury

MDs are well-recognized complications of head trauma. They have been reported following different types of head trauma, and the prevalence seems to be related to the severity of the TBI. A study aimed to address the frequency and characteristics of MDs after severe head trauma, defined as a Glasgow coma score (GCS) equal to or less than 8. The authors studied 221 patients, of whom 26.6% developed a MD, described as transient in 23 patients (10.4%) and persistent in 27 (12.2%). Kinetic cerebellar outflow tremor was the most common movement disorder (9%), followed by dystonia (4%) in individuals with persistent MDs (Krauss 2015). Generalized brain edema was significantly associated with the appearance of MDs, including kinetic tremor and dystonia (Krauss et al. 1996). In this study, subdural and epidural hematomas were not associated with MDs. Only 5.4% of patients suffered disabling low-frequency kinetic tremor (2.5–4 Hz), dystonia, or both. These MDs were associated with significantly lower GCS on admission. Dystonia had a longer latency (up to 2 years) compared with kinetic tremor (6 months), but significant overlap was observed between both MDs. Although the pathogenesis of these posttraumatic MDs is not known, a variety of pathological changes have been documented following TBI. For example, diffuse axonal injury (DAI) and small deposits of hemosiderin in the dentatothalamic pathway have been demonstrated on MRI in patients with TBI, affecting the ipsilateral pre-decussational dentatothalamic pathway in 56% and the contralateral post-decussational pathway in 28% of all cases (Krauss et al. 1995).

MDs have been reported in 10.6% of patients with mild-to-moderate craniocerebral trauma (GCS $\geq$9), the most common being low amplitude postural, kinetic tremor resembling enhanced physiological or kinetic tremor. The MDs were more frequently observed in patients with GCS between 9 and 14 than those with a score

of 15 (Krauss et al. 1997a). Most patients have a transient tremor and do not require pharmacological treatment. A 5–6 Hz tremor has been reported in patients with moderate head trauma, without a clear relationship with cerebellar damage (Biary et al. 1989). The frequency of MDs following head trauma has also been studied in children. In a survey of 289 children with severe traumatic head injury, tremor was reported in 45% of cases; it usually appears within the first 18 months after head injury and resolves spontaneously in most cases (Johnson and Hall 1992). Other authors have reported a "basal ganglia syndrome" in 4 of 31 (13%) children with a severe closed head injury, with hemiballism in half of those patients (Costeff et al. 1990).

13.3.2 Holmes and Other Tremors Following Traumatic Brain Injury

Tremor is considered the most common MD following TBI. In a study of 30 patients followed prospectively after head trauma, tremor occurred alone or in combination with dystonia in 44.7% of patients, followed by parkinsonism (17.2%) and dystonia (13.8%) (Manjunath et al. 2019).

Cerebellar outflow tremor following midbrain trauma is one of the most common forms of posttraumatic tremor (Krauss 2015). This tremor, characterizes by prominent postural and intention tremor, often occurs in patients suffering severe head trauma (GCS <8 points) (Iwadate et al. 1989). Besides tremor, patients usually show other neurological deficits related to midbrain damage such as oculomotor nerve palsy or hemiparesis. Disruption of the dentate-rubro-thalamic tract has been considered the pathophysiological basis of this type of tremor; however, diffuse white matter lesions are frequently the most common MRI finding in patients with posttraumatic MDs followed by thalamic (16.7%) and brainstem (16.7%) damage (Manjunath et al. 2019). Interestingly, the onset of tremor and dystonia after brain injury may be delayed by several weeks or months (up to 18.5 months) but the mechanism of this delayed-onset movement disorder is not well understood (Scott and Jankovic 1996; Netravathi et al. 2012). Tremor in patients with TBI has shown a broad range of frequencies, between 2 and 7.5 Hz, but when thalamic and striatal lesions coexist with white matter lesions, tremor frequency tends to be lower (around 3.7 Hz). TBI-related tremors tend to be associated with irregular EMG bursts, contrasting with the more regular bursts of essential and other forms of tremor (Netravathi et al. 2010).

Holmes tremor (HT), also known as "midbrain" or "rubral" tremor, is considered one of the most common posttraumatic tremor types. Typically caused by lesions affecting the midbrain, it has a relatively low frequency (<4.5 Hz) with an irregular resting, postural, and action component (Holmes 1904; Deuschl et al. 1998; Lenka and Jankovic 2021a). It has been proposed that the occurrence of cerebellar (action tremor) and parkinsonian (rest tremor) features in HT reflects a combined lesion in

the cerebellothalamic (i.e., dentatothalamic and dentatorubral tracts) rubro-olivary and nigrostriatal pathways. The phenomenology of HT overlaps with another low-frequency rhythmic movement called myorhythmia (Baizabal-Carvallo et al. 2015). Patients with HT may or not have contralateral parkinsonian symptoms. However, contralateral striatal dopaminergic denervation has been demonstrated with functional imaging using [^{123}I]FP-CIT SPECT in some cases of HT (Remy et al. 1995; Reese et al. 2011; Zijlmans et al. 2002). The onset of HT varies from weeks to several months after the insult; however, a delayed onset of 23 years after TBI has been reported (Krack et al. 1994).

Pharmacological treatment of tremor secondary to TBI with propranolol, primidone, benzodiazepines, carbamazepine, levodopa, and anticholinergics provides variable, but mostly disappointing, results (Ellison 1978; Harmon et al. 1991; Jacob and Chand 1998). Botulinum toxin injections can be used to relieve the tremor temporarily (Jankovic and Brin 1991; Anandan and Jankovic 2021). Marked improvement in contralateral HT and pain has been observed with thalamotomy and stimulation of the ventral intermedius nucleus (Vim) (Broggi et al. 1993). Deep brain stimulation (DBS) of the Vim, however, may not be enough to suppress contralateral posttraumatic tremor. Therefore, high-frequency stimulation of the contralateral ventralis oralis anterior (Voa) and posterior (Vop) along with the Vim DBS has been reported to successfully suppress the tremor and even abolish contralateral hemiballism (Foote and Okun 2005; Foote et al. 2006; Martínez-Mañas et al. 2002; Krauss et al. 1994). Stimulation of the contralateral Vim/Vop/zona incerta (Zi) complex has provided sustained moderate to marked benefits in tremor leading to improved quality of life in selected patients with posttraumatic tremor (Rojas-Medina et al. 2016). Additionally, a combination of globus pallidus internus (GPi) and Vim has been used following a tratographic-guided approach, providing a 67% benefit in tremor and dystonia (Gadot et al. 2021).

13.3.3 Dystonia Following Traumatic Brain Injury

Dystonia is a movement disorder characterized by involuntary, sustained or spasmodic, repetitive, and patterned contractions of muscles, leading to twisting and other abnormal postures. There are many causes of dystonia, including head trauma. Hemidystonia represents the most frequent type of dystonia following head trauma (Krauss et al. 1992; Svetel et al. 2004; Wijemanne and Jankovic 2009). Since the first report by Austregesilio in 1928 (Austregesilo and Marques 1928), several series have correlated hemidystonia with structural lesions of the contralateral caudate, putamen, and thalamus (Pettigrew and Jankovic 1985; Wijemanne and Jankovic 2009); pallidal lesions resulting in dystonia are relatively rare (Münchau et al. 2000). In patient series of symptomatic hemidystonia from different etiologies, head injury accounted for 7–9% of all cases (Marsden et al. 1985). There is a predominance in men, which probably reflects the male preponderance of craniocerebral trauma. Most patients suffer from the syndrome in their infancy and adolescence. The

delay between the head trauma and the onset of dystonia is variable. In a series of 18 cases with severe head trauma, the onset varied from 1 month to 9 years (median 18 months). This interval was longer than in patients with mild head trauma (median: 14 days, range: 3 days to 5 years) (Lee et al. 1994). In that series, up to 90% of patients presented with a focal form of dystonia, but spreading to other limbs or body parts is common in the following months or years, leading to segmental, hemi-, multifocal, or generalized dystonia (Lee et al. 1994). Latency to the onset of dystonia may be related to the age at the time of the injury. In one study, a mean latency between the injury and dystonia of 25.5 years was observed in infants (2 years or younger), whereas a delay of 4.9 years was observed in children between 6 and 17 years, and much shorter latency was observed in adults (Scott and Jankovic 1996). Hemidystonia has also been attributed to traumatic vascular damage affecting the lateral lenticulostriate branches of the middle cerebral artery (Maki et al. 1980). Dystonia has also been reported following ischemic damage produced by blunt or penetrating carotid artery injuries (Krauss and Jankovic 1997a). Preliminary evidence suggests that traumatic brain damage may be associated with tau pathology in the putamen and globus pallidus (Iacono et al. 2018). Whether such pathological changes explain the pathogenesis of posttraumatic dystonia should be further clarified.

Dystonia has been reported after traumatic pontomesencephalic lesions associated with brainstem hemorrhage and DAI (Loher and Krauss 2009). Patients have a mean onset of dystonia 6 months after the initial brainstem insult and usually present with a combination of hemidystonia, cervical dystonia, and cerebellar outflow tremor. Anatomical structures typically involved include the pontomesencephalic tegmentum and the post-decussational superior cerebellar peduncles, and the accompanying tremor suggests the involvement of the dentatothalamic pathways (Deuschl et al. 1998; Loher and Krauss 2009). It has been observed that mesencephalic lesions extending to the thalamus are associated with unilateral appendicular or hand dystonia, while pontomesencephalic lesions are related to more severe hemidystonia or cervical dystonia (Loher and Krauss 2009; Tränkle and Krauss 1997). A 4–5 Hz postural and rest tremor with action-induced dystonia has been described 2 years after penetrating trauma affecting the contralateral diencephalic–mesencephalic regions involving the substantia nigra and subthalamic region (Krauss et al. 1997b). Symptomatic cervical dystonia has been described with lesions in the posterior fossa, particularly affecting the cerebellopontine angle (Krauss et al. 1997c). The origin of acquired hemidystonia secondary to basal ganglia or thalamic lesions has been assessed by regional cerebral blood flow studies and attributed to frontal overactivity secondary to disruption of inhibitory control by the basal ganglia (Ceballos-Baumann et al. 1995).

A syndrome characterized by paroxysmal autonomic instability with focal dystonia (PAID) has been characterized in patients with severe brain lesions following trauma, ischemia, or hypoxia, usually observed in the intensive care unit (Blackman et al. 2004). Central nervous system infections, intracranial hemorrhage, and limbic encephalitis may also present with PAID (Cardoso-Vale et al. 2020). Patients present with marked agitation, diaphoresis, hyperthermia, hypertension,

tachycardia, tachypnea, and muscular hypertonia with intermittent dystonic posturing (Srinivasan et al. 2007). EEG is usually normal. Differential diagnoses include neuroleptic malignant syndrome, malignant hyperthermia, autonomic epileptic seizures, pheochromocytoma, autonomic dysreflexia, and central fever. Treatment can be attempted with opioid medications such as IV hydromorphine, morphine, or fentanyl patches; nonselective beta-blockers, or the dopamine receptor agonist, bromocriptine. Central acting alpha-2 agonists such as clonidine or dexmedetomidine may also be employed. The latter has been proposed as a rescue therapy for unresponsive PAID patients to other pharmacological options (Goddeau et al. 2007) Worsening has been observed with dopamine receptor antagonists such as haloperidol (Rabinsten 2004).

There are controversies about the role of head trauma in the development of organic dystonia. In a study of 202 patients with dystonia, and 202 age and age-matched controls, head or facial trauma with loss of consciousness increased the risk of developing dystonia (Defazio et al. 1998). A higher frequency of previous cranial and facial trauma was found in a group of 159 patients with blepharospasm (Defazio et al. 1999). However, in an Italian multicenter study conducted by the same group of authors in 177 patients with primary adult-onset cranial dystonia and 217 controls with primary hemifacial spasm, no association between trauma and dystonia was found, and a previous history of trauma did not modify the age at onset of cranial dystonia (Martino et al. 2007). The presence of the DYT1 mutation does not seem to increase the risk of secondary dystonia (Bressman et al. 1997). However, it has been recognized that trauma is a trigger factor in patients carrying DYT1 mutations (Edwards et al. 2003).

Dystonia secondary to head trauma can be treated similarly to primary dystonia with a trial of anticholinergics, levodopa, or botulinum toxin injections (Jankovic 2009a, b). However, DBS of the GPi, subthalamic nucleus, or thalamus has provided significant and sustained benefit in cases of posttraumatic hemi- and cervical dystonia with a reduction in the Burke-Fahn-Marsden dystonia rating scale from 52.4% to 78.6% (Li et al. 2019). The Voa and Vop nuclei have been useful to treat posttraumatic dystonia in individuals with severe basal ganglia damage resulting from TBI (Owen et al. 2022). DBS should be considered in cases with a lack of response to pharmacological treatment (Loher et al. 2000; Chang et al. 2002). Sequential thalamotomy of the Vop and Vim has provided long-term benefits in a patient with focal hand dystonia resulting from cervical whiplash injury (Miura et al. 2022).

13.3.4 Single Head Trauma, Parkinson's Disease, and Parkinsonism

The relationship between trauma and Parkinson's disease (PD) was first proposed by James Parkinson in 1817 in his "*Essay on the Shaking Palsy*" when he theorized that

the location of the injury was in the superior cervical spine (Parkinson 1817). The concept of head trauma and PD was revitalized during World War I, when cases of concussion associated with mesencephalic injuries were reported. In the following decades, cases with posttraumatic hemorrhagic lesions in the basal ganglia and mesencephalus developing parkinsonism were recognized. Direct lesions to the substantia nigra have been reported secondary to injuries by knives, screwdrivers, shell splinters, or gunshots, presenting with hemiparkinsonism (Rondot et al. 1994; Krauss et al. 1997b). Parkinsonism has been reported 4 weeks following severe head trauma (Abu Talh et al. 2017).

Despite its rarity, parkinsonism following severe head trauma is well documented (Goetz and Stebbins 1991), although the pathogenesis is not always well understood. Mechanical lesions to the mesencephalon can produce transient dysfunction of the nigrostriatal system in humans (Slevin et al. 1987). MRI studies have shown hematomas in the putamen and substantia nigra in the acute stage and hemosiderin deposits in the midbrain 3 months after the injury (Bhatt et al. 2000). Transcranial ultrasound examinations have shown decreased echogenicity of the substantia nigra in posttraumatic parkinsonism, in marked contrast with hyper-echogenicity observed in patients with idiopathic PD (Kivi et al. 2005). Functional imaging with [^{18}F]-fluorodopa PET in six patients with contralateral parkinsonian tremor following a traumatic peduncular lesion showed severe dopaminergic denervation of the basal ganglia, more marked than in patients with idiopathic PD (Turjanski et al. 1997; Remy et al. 1995). Proton magnetic resonance spectroscopy studies have shown a marked reduction in the concentration of *N*-acetylaspartate in the lenticular nuclei of patients with posttraumatic parkinsonism, compared to patients with PD and controls (Davie et al. 1995). Patients with parkinsonism secondary to head trauma usually show a good response to levodopa (Bhatt et al. 2000). However, in cases with refractory tremor, combined DBS of the Vim and dorsolateral STN resulted in a marked reduction of contralateral rest tremor, rigidity, and bradykinesia in a patient with posttraumatic hemiparkinsonism (Romanelli et al. 2003; Reese et al. 2011).

The prognosis of parkinsonism following head trauma is variable. Reversible parkinsonism has been reported in the context of chronic subdural hematoma (Krul and Wokke 1987; Bostantjopoulou et al. 2009) with compression of the midbrain from central herniation (Trosch and Ransom 1990).

Despite clear pathological evidence that severe TBI with selective damage to the nigrostriatal structures causes parkinsonism, the question if mild-to-moderate head trauma can cause PD has also been addressed in several experimental animal and human cohort or case-control studies. Brain tissues of rats, investigated 60 days following TBI, showed a marked reduction of tyrosine hydroxylase enzyme expression in the substantia nigra pars compacta indicating loss of dopaminergic neurons, combined with an increase in resident inflammatory cells such as microglia and accumulation of alpha-synuclein (Acosta et al. 2015). The latter finding occurs as early as 1 week following experimental TBI in rats and comprises alpha-, beta- and gamma-synucleins (Uryu et al. 2003). Increased expression of inflammatory markers including cyclooxygenase-2, inducible nitric oxide synthase, enhanced

transcriptional activity, and a decrease in brain derived neurotrophic factors was detected 30 days following controlled cortical impact in mice (Impellizzeri et al. 2016). Another series of experiments showed a loss of 15% of dopaminergic neurons ipsilateral to TBI in rats (Hutson et al. 2011). This effect was amplified by exposure to paraquat, a widely distributed herbicide (Hutson et al. 2011). Besides alpha-synuclein, upregulation of proteins implicated in the pathogenesis of PD such as leucine-rich repeat kinase 2 (LRRK2) has been documented to occur in experimental rat models of TBI (Delic et al. 2020).

In the last four decades, a number of retrospective or case-control studies have established a potential causal relationship between TBI and the risk of PD (Factor and Weiner 1991; Tanner et al. 1987; Taylor et al. 1999; Bower et al. 2003; Rugbjerg et al. 2008). A large prospective cohort study did not confirm the association between PD and head trauma (Williams et al. 1991). However, a meta-analysis performed in 2013, which included 22 studies (19 case-control, 2 nested case-control studies, and 1 cohort study), concluded that TBI is related to an increased risk of PD, OR: 1.57, 95% CI: 1.35–1.83 (Jafari et al. 2013). However, it has been argued that reverse causation can explain the increased risk of PD in patients with TBI, as such patients have an increased risk to fall, may be involved in motor vehicle accidents, and have other risks for TBI. A large and nationwide population-based study from Denmark showed that a history of severe head injury did not appear to increase the risk for PD more than a decade after trauma (Spangenberg et al. 2009). However, in a study including 379 neurologist-confirmed PD cases and 230 controls, an increased risk for PD was found among patients with TBI and loss of consciousness (OR: 1.57) with a significant effect of age at first injury ($P = 0.004$) (Taylor et al. 2016). This is similar to the finding from a case-controlled study involving 93 twin pairs discordant for PD, which showed that prior head injury with amnesia or loss of consciousness resulted in a significantly increased risk of PD (Goldman et al. 2006). Another study, however, did not find an association between the length of loss of consciousness and the risk for PD (Kenborg et al. 2015). These studies may have recall bias, as there is often a considerable time lag between the injury and the onset of symptoms (Bhatt et al. 2000). In a study involving 325,870 military veterans identified in the Veteran Health Administration database, those with previous TBI had a 56% increased incidence of PD (Gardner et al. 2018). The risk increased with the severity of prior trauma and was still significant after adjusting for demographic, medical, and psychiatric comorbidities (Gardner et al. 2018). Other studies have confirmed an increased risk of PD even after controlling for smoking, coffee, and alcohol consumption (Nicoletti et al. 2017).

13.3.5 Pugilistic Parkinsonism, Dementia, and Chronic Traumatic Encephalopathy

Pugilistic parkinsonism is a form of posttraumatic parkinsonism. It is secondary to the cumulative effect of multiple subconcussive blows over many years and bouts.

A correlation between the severity of the neurological manifestations and the length of career and number of bouts has been reported (Casson et al. 1984). The cognitive decline and behavioral changes associated with boxing are frequently seen along with pugilistic parkinsonism, and the syndrome has also been referred to as "punch drunk," "goofy," "slug-nutty," and more formally as "dementia pugilistica." Brain damage using a multimodal approach, including clinical, neuroimaging, and EEG, has been documented in up to 87% of former and active boxers (Casson et al. 1984). The syndrome usually presents with behavioral (e.g., apathy, depression, irritability, impulsiveness, suicidality) or cognitive changes; later in the course of the disease parkinsonism may occur, along with speech and oculomotor abnormalities in the context of declining cognition (Gavett et al. 2011). Other manifestations including cerebellar dysfunction have been identified as part of the syndrome (Factor et al. 1988). Postmortem examinations in these patients have revealed petechial hemorrhages and degeneration of the substantia nigra, with a notable lack of Lewy bodies (Koller et al. 1989). More recently, pathological studies have demonstrated accumulation of tau protein (tauopathy), similar to the findings in "chronic traumatic encephalopathy" (CTE), but whether each bout of TBI leads to stepwise accumulation of tau protein or a degenerative phase is reached at a certain point of the disease is still debatable (Castellani and Perry 2017). It has been shown that high-exposure professional boxers with an apolipoprotein epsilon4 allele have significantly greater scores on a scale measuring chronic encephalopathy than those without the allele (Jordan et al. 1997). The clinical and pathological effects of repetitive trauma have been recognized to occur in other sports besides boxing, including American football, professional wrestling, hockey, and soccer, as well as other activities related to repetitive head trauma, such as epileptic seizures, head banging, and physical abuse (Gavett et al. 2011).

In the last five decades, evidence of a neurodegenerative disorder secondary to repetitive trauma has led to the recognition of CTE, characterized by the presence of hyperphosphorylated tau in neurofibrillary tangles, also affecting astrocytes, with a more patchy distribution than Alzheimer's disease and predominantly at the sulcal depths of the cerebral cortex (McKee et al. 2009; McKee 2020). Such distribution of tau protein has been assessed in vivo in retired NFL players with cognitive and neuropsychiatric symptoms by means of flortaucipir in positron emission tomography (PET) (Stern et al. 2019). These studies have shown a pattern of tau protein deposits according to pathological findings in CTE (Stern et al. 2019). Beta-amyloid deposits have been reported in up to 45% of individuals with CTE; however, such deposits are considered a function of age and ApoEe4 allele inheritance and not a primary neuropathological finding of CTE (McKee et al. 2010). CTE seems to correlate with the burden of repetitive head trauma. In a study of 202 deceased American football players, with a mean of 15 years in football participation, 87% had CTE pathology (Mez et al. 2017). The severity of neuropathology increased in professional players. Among patients with severe CTE pathology, 85% had dementia (Mez et al. 2017). In addition to American football players, professional soccer players also have been found to have an increased risk for CTE-like neurodegeneration (Mackay et al. 2019).

Lewy body disease (LBD) pathology in cortical and subcortical structures has also been identified in patients with CTE (Adams et al. 2018). Neocortical LBD is mostly associated with a threshold of over 8 years of play in contact sports athletes; the latter is related to dementia (Adams et al. 2018). Moreover, TBI has been independently associated with probable REM-sleep behavior disorder (RBD). The frequency of RBD is related to the number of years of contact sports participation (Adams et al. 2020). Posttraumatic RBD was associated with Lewy body pathology, but more commonly with neurofibrillary tangles and pretangles deposition mostly in the dorsal and median raphe nuclei (Adams et al. 2020). Further prospective studies should clarify the rate of conversion to PD in posttraumatic RBD. However, a case-control study showed that in patients with PD, the number of previous head trauma directly correlated with total tau levels in the CSF, whereas sport-related head trauma was related to young onset PD (Schirinzi et al. 2021).

13.3.6 Hemiballismus, Tics, and Other Hyperkinetic Movement Disorders Following Traumatic Brain Injury

Hemiballismus and hemichorea are known to occur following TBI (Dewey and Jankovic 1989; Richardson et al. 1987). Posttraumatic hemiballism is associated with a severe closed head injury. Hemorrhagic lesions of the STN may result in hemiballismus as early as 1 day after brain injury (Kim et al. 2008). Hemiballimus has been deemed to occur about 3 weeks following trauma (Netravathi et al. 2012). However, a delay of 6 months has been reported in a patient who recovered from coma (King et al. 2001). Paroxysmal dyskinesias have also been reported after brain injury (Blakeley and Jankovic 2002; Drake et al. 1986). Putaminal lesions have been observed in single cases of paroxysmal MDs (Biary et al. 1994). Positron emission tomographic scans showed abnormal metabolism in the contralateral basal ganglia during an attack of paroxysmal posttraumatic dystonia (Perlmutter and Raichle 1984). Posttraumatic tic and tourettism have been identified in some patients following head trauma (Singer et al. 1989; Siemers and Pascuzzi 1990; Majumdar and Appleton 2002; Ranjan et al. 2011). In a series of six patients with tics after craniocerebral trauma, all patients were male, and the mean age at the time of trauma was 28 years. The injury was moderate or mild in five cases, and neuroimaging studies did not reveal lesions in the basal ganglia (Krauss and Jankovic 1997b). However, extensive periventricular and subcortical leukoencephalopathy was observed in one case with tics and marked obsessive–compulsive behavior secondary to brain injury (Krauss and Jankovic 1997b). Myoclonus, opsoclonus, stereotypies, akathisia, and galloping tongue have also been described in patients with TBI (Keane 1984; Stewart 1989; Desai et al. 2010).

13.4 Trauma to Peripheral Nervous System and Soft Tissues

Several different movement disorders have been described following peripheral trauma. In this second part of this chapter, we will discuss these MDs individually, although overlap among them may exist. Table 13.2 summarizes the characteristics of these MDs from a meta-analysis of 713 patients.

13.4.1 Peripherally Induced Tremor and Parkinsonism

Tremor following peripheral trauma is a well-recognized movement disorder. In a recent systematic review and meta-analysis, tremor was the second most common peripherally induced MD after dystonia and represented 25% of all cases (van

Table 13.2 Clinical characteristics of peripherally induced movement disorders in 713 patients

Demographics
Female: 64%
Age of onset (median): 38 years
Type of movement disorder
Dystonia 72%
Tremor 25%
Myoclonus 13%
Spasm 11%
Painful limbs and moving toes or fingers 6%
Parkinsonism, chorea, tics: 4%
Type of trauma
Soft tissue injury 43%
Fracture 10%
Surgery 10%
Other 12%
Nerve entrapment 18%
Amputation 2%
Location of trauma
Limb: 66%
Neck and/or shoulder 25%
Oromandibular/vocal cords 6%
Truncal region 25%
Spread to other body regions: 19%
Multifocal: 37%
Generalized: 25%
Contralateral: 12%
Ipsilateral: 11%
Segmental: 10%

Modified from van Rooijen et al. (2011)

Rooijen et al. 2011). In a study of 28 cases with peripherally induced tremor and parkinsonism, trauma preceded the neurological manifestations by a mean of 47 days (Cardoso and Jankovic 1995). In 20 of these patients, the movement disorder spread beyond the site of initial trauma. Several potential predisposing factors have been identified in patients with peripherally induced tremor. In a study of 23 patients with tremor and dystonia induced by peripheral trauma, 15 patients (65%) had conditions that may increase the risk of peripherally induced MDs, including use of neuroleptics or stimulants, AIDS-related complex, family history of essential tremor or dystonia, premature birth, and developmental delay; in this study, the authors carefully excluded patients with possible functional (psychogenic) FMDs (Jankovic and Van der Linden 1988). Immobilization has also been reported as a cause of tremor induction or exacerbation (Cole et al. 1989; Herbaut and Soeur 1989).

Neck whiplash injuries have been reported preceding limb tremor (Ellis 1997). Some of these cases show root and/or spinal cord damage. Some studies have demonstrated electromyography evidence of traumatic nerve injury preceding the tremor (Costa et al. 2006; Jankovic and Van der Linden 1988). Tremor and other movement disorders have been described in six patients following intervertebral cervical and lumbar disc surgery, with a latency of 1 day to 12 months after the surgical procedure. In these cases, the MD is usually accompanied by persistent dermatomal pain, with an anatomical distribution closely related to the root or spinal segment involved in the surgery (Capelle et al. 2004).

Peripheral trauma as a cause of parkinsonism has been suggested since the late nineteenth century (Factor et al. 1988). However, the concept was barely studied until the end of the last century, when well-documented cases of peripheral trauma preceding parkinsonism were reported in the literature. In those cases, the anatomical onset of parkinsonism is related to the site of trauma. In a series of 11 patients reported by Cardoso and Jankovic, seven of them showed clinical improvement with levodopa. Three patients were investigated with (^{18}F) fluorodopa uptake and raclopride binding. The authors reported findings similar to those encountered in patients with idiopathic PD, excluding a functional (i.e., psychogenic) origin of the disorder. The lack of response to levodopa in some cases suggests the possibility of postsynaptic changes possibly induced by the trauma itself (Cardoso and Jankovic 1995). A case of peripherally induced symmetric parkinsonisms failed to improve after subthalamic deep brain stimulation (Baizabal-Carvallo and Jankovic 2014). CNS reorganization has been proposed as one of the underlying mechanisms of peripherally induced tremor and parkinsonism. In an animal model with adult rats exposed to 6-hydroxydopamine to produce dopamine depletion in their brain, the rats behave normally in their cage; however, they became akinetic after exposure to severe cold, tail shock, and glucose deprivation (Snyder et al. 1985). The neurological impairment was related to the intensity of stress and was reversible with dopaminergic agents (Snyder et al. 1985). These findings suggest the possibility of a subclinical dopaminergic loss may express when the organism is exposed to a severe enough peripheral stimulus; however, more clinical and

Table 13.3 Characteristics of primary and fixed dystonia

	Primary or idiopathic dystonia	Fixed dystonia
Gender predominance	Variable, depends on the type of dystonia	Female
Induced by action	Typical, it may be task specific	No
Improvement by sensory tricks	Usually	No
Association with complex regional pain syndrome	Rare	Yes, frequently
Overflow phenomenon	Common	No
Association with trauma	Yes, but less than 5% of cases	Yes, typically preceded by minor trauma
Response to pharmacological treatment	Moderate to good	Usually poor

experimental evidence (i.e., animal models) is needed to clarify how this actually occurs.

13.4.2 Peripherally Induced Limb Dystonia

Dystonia is defined as abnormal muscle contractions frequently holding a body part in an abnormal posture, often associated with tremor (Fahn et al. 1998). Peripherally induced dystonia may present with a pattern similar to other organic dystonias, with sensory tricks, action-induced and even task-specific dystonic postures or task-specific dystonic tremor indistinguishable from primary dystonia (Fletcher et al. 1991; Frucht et al. 2000; Jankovic and Van der Linden 1988; Cavallieri et al. 2019). Another manifestation of peripherally induced dystonia is fixed dystonia (Table 13.3) (Schrag et al. 2004). Trauma in peripherally induced dystonia is usually to soft tissues, but fractures, operations, limb overuse, and immobilization by casting may also precede or aggravate dystonia (Okun et al. 2002; Singer and Papapetropoulos 2005; Schott 1985; Elbert and Rockstroh 2004). This form of dystonia is often encountered in individuals who require repetitive performance of a particular task, such as musicians (Jankovic and Ashoori 2008) and athletes, including long-distance runners (Wu and Jankovic 2006; Lenka and Jankovic 2021b). Monkeys trained to perform repetitive hand grip opening and closing were found to have a reorganization and enlargement of the contralateral primary somatosensory cortical area 3b, which has connections with putamen (Topp and Byl 1999; Meunier et al. 2001). This observation may have implications for the mechanism of dystonia associated with repetitive strain injuries ("the overuse syndromes") (Jankovic 2009a, b).

Fixed dystonia is considered the most frequent form of peripherally induced, posttraumatic dystonia and is characterized by the limitation of passive range of motion, contractures, and absence of sensory tricks (Thenganatt and Jankovic 2019). The association of fixed dystonia with trauma is strong as up to 68% of patients who present with this syndrome have a preceding traumatic event, which differs from the 5% in patients with classical dystonia (Schrag et al. 2004). Fixed dystonia is not exclusively related to trauma and may occur after acquired neurodegenerative disorders like corticobasal degeneration (Vanek and Jankovic 2001). Other neurological or mechanical disorders may resemble fixed dystonia, including stiff-limb syndrome and atlantoaxial dislocations (Suchowersky and Calne 1988). It can also be observed without previous history of trauma; in those cases, an underlying functional etiology is frequently suspected. Other MDs frequently coexist with posttraumatic fixed dystonia in the same or different limb, including painful spasms, tremor, and involuntary jerks (Schrag et al. 2004). Fixed dystonia shares features with functional dystonia including the frequent coexistence of somatoform disorders, active resistance against passive movement, pain, and lack of response to sensory tricks (Schrag et al. 2004; Hawley and Weiner 2011).

The prognosis of fixed dystonia is generally considered poor. In a study that aimed to assess the clinical and neuropsychiatric evolution in 41 patients with fixed dystonia, 83% were women and had a mean duration of illness of 11.8 years (Ibrahim et al. 2009). After a mean follow-up of 7.6 years, 31% of patients worsened, 46% were the same, 23% improved, and only 6% had a major remission. The presence of CRPS at baseline predicted a worse outcome. A substantial proportion of these patients suffered anxiety and depression or meet the diagnostic criteria for somatoform disorders. Pharmacological therapy is usually unsuccessful in patients with fixed posttraumatic dystonia. Contralateral pallidal and thalamic DBS did not improve dystonia in a single report of a woman with posttraumatic painful leg dystonia (Capelle et al. 2006). Treatment with occupational, physical therapy, and psychotherapy has resulted in at least modest benefit in some patients (Schrag et al. 2004).

13.4.3 Complex Regional Pain Syndrome and Dystonia

Peripherally induced, posttraumatic dystonia may coexist with pain or complex regional pain syndrome (CRPS), characterized by the combination of pain, sensory, autonomic, trophic, and motor manifestations usually preceded by trauma (Schwartzman 1993). The condition is classified as type I when no evidence of peripheral nerve lesion can be identified and type II when peripheral nerve damage is documented (Marinus et al. 2011). Patients usually present after minor or moderate tissue injury. Fractures are the most frequent type of associated trauma (45%), followed by sprain (18%) and elective surgery (12%) (de Mos et al. 2007). The severity of trauma is not necessarily linked to the development of CRPS, and sporadic onset has been reported in up to 10% of patients (Marinus et al. 2011).

Table 13.4 Budapest diagnostic criteria for complex regional pain syndrome (CRPS)

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three (clinical diagnostic criteria) or four *Sensory*: hyperesthesia or allodynia *Vasomotor*: temperature asymmetry, skin color changes, or skin color asymmetry *Sudomotor or edema*: local edema, sweating changes, or asymmetry *Motor or trophic*: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
3. Must display at least one sign at the time of diagnosis in two or more of the following categories: *Sensory:* hyperalgesia (to pinprick) or allodynia (to light touch, deep somatic pressure, or joint movement) *Vasomotor:* temperature asymmetry, skin color changes, or asymmetry *Sudomotor or edema:* edema, sweating changes, or sweating asymmetry *Motor or trophic*: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
4. No other diagnosis better explains the signs and symptoms

CRPS is at least three times more common in females than males, and the incidence of CRPS increases with age (de Mos et al. 2007). Diagnosis of CRPS is based on the Orlando criteria, released by the International Association for the Study of Pain, or the modified version called Budapest criteria, which has a higher specificity and considers motor symptoms, including MDs (Table 13.4). Risk factors for the development of CRPS include female sex, fibromyalgia, rheumatoid arthritis, dysautonomia, neuropathic inflammation, and psychodynamic factors such as post-traumatic stress disorder (Taylor et al. 2021). Several motor symptoms and MDs have been described along with CRPS, including focal dystonia, tremor, weakness, difficulty initiating movement, increased muscle tone, and brisk osteotendinous reflexes (Birklein et al. 2000; Schwartzman and Kerrigan 1990). Dystonia is the most frequent MD observed in patients with CRPS, and the term "causalgia–dystonia" has been used to refer to the coexistence of both conditions (Bhatia et al. 1993; Van Rijn et al. 2007). In a study that included 185 patients with CRPS, MDs were identified in 121 patients, with dystonia being the most prevalent (91%) (Van Rijn et al. 2007). Patients with dystonia were 11 years younger and more often had CRPS in multiple limbs. The interval between the onset of CRPS and dystonia varied from 1 week in 26% of patients to more than 1 year in 27% of cases.

The nature of dystonia in patients with CRPS has been a source of numerous debates and some authors argue that the features are most likely "pseudoneurologic" or "psychogenic" in origin, currently known as "functional dystonia" (Verdugo and Ochoa 2000; Hawley and Weiner 2011). The term "posttraumatic syndrome" instead of posttraumatic dystonia has been proposed by some authors (Kumar and Jog 2011; Thenganatt and Jankovic 2019). When dystonia is present in patients with CRPS, more than 90% is of fixed type; however, a combination of fixed and mobile-type dystonia can be found in some patients with CRPS (van Rooijen et al. 2011). CRPS has been proposed to be mediated via central sensitization involving upregulation of glutamate receptors (Kuner 2010).

Since CRPS-related dystonia does not respond to intravenous ketamine (a glutamatergic antagonist), additional CNS neuroplastic changes have been suggested to play a role in this syndrome (Marinus et al. 2011). Furthermore, spinal GABAergic mechanism may also play a role in dystonia associated with CRPS as intrathecal baclofen (a GABA type B receptor agonist), but not glycine (the main inhibitory neurotransmitter in the spinal cord), improved dystonia in a dose–response manner (van Rijn et al. 2009; Munts et al. 2009). The observation that motor signs associated with CRPS improve after sympathectomy or sympathetic blockade suggests a contribution of the autonomic sympathetic system to the pathogenesis of CRPS-related dystonia (Marsden et al. 1984; Schwartzman and Kerrigan 1990). However, improvement of dystonia after anesthetic blockade of sympathetic ganglia is not strongly supported by published studies (Hord and Oaklander 2003). Other treatments include a short course of oral corticosteroids, intranasal or intramuscular calcitonin, botulinum toxin type A, intravenous biphosphonates, gabapentin, and spinal cord stimulation (Kemler et al. 2004; Eisenberg et al. 2007). A short course of steroids may provide a meaningful improvement in some patients. Intravenous bisphosphonates have shown benefit in small trials, owing to their modulating inflammatory effects (Taylor et al. 2021). Graded motor imagery and mirror therapy are the physical therapy approaches that have provided the greatest benefit with significant improvement in pain and quality of life, according to a review assessing 171 patients with CRPS type 1 enrolled in randomized clinical trials (Méndez-Rebolledo et al. 2017). As a large proportion of patients fail to perceive a satisfactory improvement with physiotherapy or pharmacological approaches, spinal cord stimulation (SCS) has been increasingly used to treat CRPS. Evidence shows that SCS can provide benefits in perceived pain relief, pain intensity, and quality of life; however, limited benefit has been observed for improvement in function, resolution of symptoms, and psychological and sleep impact (Visnjevac et al. 2017). In those instances, high-frequency SCS at 10 kHz (HF10-SCS) has been used successfully as rescue therapy for short periods (1 week) with improvement in two-thirds of cases (Gill et al. 2019).

13.4.4 Posttraumatic Cervical and Shoulder Dystonia

Cervical dystonia has also been described following neck trauma (Ellis 1997; Troung et al. 1991; Goldman and Ahlskog 1993). “Acute-onset” cervical dystonia appears within 3 months following trauma, usually in the first 4 weeks after the injury. These patients usually exhibit marked limitation of the range of motion of the neck, abnormal postures without much phasic movements, sustained laterocollis, shoulder elevation, and trapezius hypertrophy, typically without sensory tricks and with poor response to pharmacological therapy (O’Riordan and Hutchinson 2004). Pain is a common complaint, often accompanied by nondermatomal sensory loss (Sa et al. 2003; Frei et al. 2004). Intravenous sodium amytal often improves the abnormal postures and pain in these patients (Sa et al. 2003). In these cases,

clinicians should rule out neck muscle contractures leading to abnormal head postures, that is, "pseudodystonia"; posttraumatic lesion of the eleventh cranial nerve may also lead to shoulder elevation and head turning mimicking neck dystonia (Suchowersky and Calne 1988; Cossu et al. 2004).

Another type of posttraumatic cervical dystonia occurs between 3 and 12 months after the injury with clinical manifestations resembling nontraumatic idiopathic cervical dystonia, with gradual progression of motor symptoms, frequent sensory tricks, and better neck mobility (Tarsy 1998). In these cases, the cause-and-effect relationship between the trauma and the cervical dystonia may be difficult to establish, especially since 10–20% of patients with cervical dystonia report a preceding trauma. Congenital muscular torticollis can be considered another type of posttraumatic cervical dystonia; patients may present with contractures due to fibrosis of the sternocleidomastoid and other neck muscles. Patients usually complain of neck pain and decreased range of motion of the neck. While most cases start during infancy or early childhood, some cases are not diagnosed until adulthood (Collins and Jankovic 2006). Cervical dystonia has been reported following cervical and lumbar disc surgery, usually associated with dermatomal or segmental pain (Capelle et al. 2004). Oral anticholinergics, baclofen, botulinum toxin injections, or pallidal or STN DBS are treatment options in patients with cervical dystonia (Jankovic 2009b; Ostrem et al. 2007, 2011).

Traumatic shoulder injuries have also been reported as a cause of dystonia or dystonic tremor (Atadzhanov and Mwaba 2007; Höllinger and Burgunder 2000). Fixed shoulder postures can also develop after shoulder trauma (Thyagarajan et al. 1998). In a series of 13 patients with isolated focal dystonic shoulder elevation, nine patients developed the syndrome after shoulder trauma, two developed the symptoms after chronic heavy labor, and one had cervical radiculopathy. Most patients had trapezius muscle hypertrophy, but a good response to botulinum toxin injections is the rule in these cases (Wright and Ahlskog 2000).

13.4.5 Other Forms of Peripherally Induced Dystonia

Other potential causes of posttraumatic dystonia include blepharospasm. Up to 12.1% of patients reported a history of ocular lesions preceding the onset, in large series of 264 patients (Grandas et al. 1988). Oromandibular dystonia (OMD) may follow face, mouth, or jaw trauma. In a large study, 27 patients with peripherally induced OMD had a mean age at the onset of 50 years, and there was a 2:1 female preponderance (Sankhla et al. 1998). Age at onset, gender predominance, and clinical phenomenology in patients with posttraumatic, peripherally induced OMD were similar to those features in patients with idiopathic OMD. Both groups responded well to botulinum toxin therapy. Edentulous patients may develop dyskinesias that can be considered a form of peripherally induced dystonia; these patients usually display inadequate dental occlusal relationships and unretentive dentures (Blanchet et al. 2008). Dental procedures have been reported to trigger

OMD and cranial dystonia, in some cases accompanied by painful paraesthesias spreading to the tongue, lips, and neck (Schrag et al. 1999).

In an animal model of peripherally induced dystonia, dystonia-like movements were noted after a peripheral nerve lesion in wild-type (wt) and Tor1a+/− mice that express 50% torsin A (Ip et al. 2016). After the nerve crush injury, abnormal posturing was noted in the lesioned hind limb of both mutant and wt mice, but the phenomenon was more severe in the mutant mice (Rauschenberger et al. 2021).

13.4.6 Functional Movement Disorders Following Peripheral Trauma

Functional (previously known as psychogenic) movement disorders (FMD) following trauma are well recognized. In particular, the syndrome of fixed dystonia following trauma has been mainly attributed to functional/psychogenic mechanisms as discussed above (Schrag et al. 2004; Thenganatt and Jankovic 2019). In a review of 713 patients with peripherally induced MDs reported in the literature by van Rooijen and colleagues, a diagnosis of "psychogenicity" or functional cause was noted in 14% (van Rooijen et al. 2011). Patients with FMDs induced by peripheral trauma had more frequently fixed dystonia (90% vs. 58%) and tremor (38% vs. 22%) compared to patients with non-FMDs induced by peripheral trauma, and less often mobile dystonia (6% vs. 22%) and myoclonus (6% vs. 15%) (van Rooijen et al. 2011). FMDs usually have an abrupt onset, inconsistency over time, multiple somatization, false neurological signs, and distractibility.

13.4.7 Pathophysiology of Peripherally Induced Tremor and Other Movement Disorders

The cause-and-effect relationship between peripheral trauma and movement disorders is still a controversial topic, as no biomarker has been recognized in these patients. Furthermore, the pre-traumatic state of patients is largely unknown making it difficult to establish a temporal relationship between MDs and trauma. Pathological changes such as aberrant reinnervation, remyelination or late inflammatory changes, sensitization of peripheral nociceptors, and ectopic or ephaptic transmission of nerve impulses have been proposed as mechanisms for peripherally induced MDs (Goetz and Pappert 1992; Jankovic 1994). The association of MDs and pain suggests that peripherally induced MDs may originate in a manner that is analogous to phantom limb pain and CRPS (Jankovic and Glass 1985; van Hilten et al. 2007). Experimental studies have shown that sectioning the peripheral roots or nerves in animals can change synaptic processing at spinal segmental and suprasegmental levels (Kaas et al. 1983). Following peripheral nerve sectioning, reorganizational

neuroplasticity occurs in two phases: one immediate and the other more delayed leading to increased excitatory or decreased inhibitory mechanism in the CNS. For example, reduction in the GABA-A receptor binding in layer IV of primate somatosensory cortex has been reported to occur 2–5 h after peripheral nerve transection (Wellman et al. 2002), whereas GABA-B receptor binding is decreased in layer IV 1 month after nerve injury, with an increased binding expression of glutamatergic AMPA receptors in layer IV of the somatosensory cortex (Garraghty et al. 2006). These findings suggest that the late cortical changes identified in primates after injuries of the peripheral nervous system resemble the *N*-methyl-D-aspartate (NMDA)-dependent long-term potentiation observed in the hippocampus (Garraghty et al. 2006). In humans, for example, it is well known that after limb amputation, there is a marked reorganization of the somatosensory cortex (Karl et al. 2001) with possible preservation of the movement representation (Mercier et al. 2006). Recently, it has been suggested that amputation or deafferentation results in plasticity of connections between the brain and the body with disappearance of the cortical motor representation but preservation of the sensory representation of the limb, which may explain the phantom pain phenomenon (Sumitani et al. 2010). This may explain why intensive motor training with a reduction in cortical reorganization correlates with a reduction of phantom limb pain (Maclver et al. 2008). Reorganization of the cerebral cortex has also been demonstrated with extensive limb use (Elbert and Rockstroh 2004). Peripheral nerve injury is not only associated with physiological cortical changes, as plastic changes in the spinal cord, brainstem nuclei, and thalamus have been demonstrated, leading to atrophy and degeneration of some substrates as well as reorganization and sprouting of other structures (Navarro et al. 2007). We postulate that some of these changes may occur in response to abnormal peripheral perturbation and may also be the origin of involuntary movements in susceptible individuals. Changes in the cortical representation of affected limbs have been consistently demonstrated in patients with nontraumatic organic dystonia (Hallet 2006). Interestingly, patients with functional dystonia show similar cortical and spinal abnormalities to organic dystonia, with short and long cortical inhibition, cortical silent period, and reciprocal inhibition of the forearm (Espay et al. 2006; Baizabal-Carvallo et al. 2019). Although some have suggested that these changes could be the consequence rather than the cause of the dystonia, many of these abnormalities are found in asymptomatic body parts, suggesting that the abnormalities are the ones that predispose to dystonia, and predisposed individuals can develop organic or functional dystonia depending on the contributing factors (Hallet 2010; Baizabal-Carvallo et al. 2019).

13.4.8 Other Peripherally Induced Movement Disorders

Hemifacial spasm is perhaps the best example of peripherally induced movement disorder (Jankovic 2009a, b). Vascular compression of the VII cranial nerve is the suspected etiology in up to 80% of patients. The age of onset is 48.5 years, and

symptoms include involuntary, unilateral, intermittent, irregular, tonic, or clonic contractions of muscles innervated by the ipsilateral facial nerve (Wang and Jankovic 1998). Other causes are found in 19% of patients and include Bell's palsy (11%), facial nerve injury (6%), demyelination, and brain vascular insults (Yaltho and Jankovic 2011). Imitators of hemifacial spasm include tics, myoclonus, hemimasticatory spasm, dystonia, and functional cases.

Segmental myoclonus has been reported in a series of 37 patients with a mean age of onset of 48.5 years. Traumatic etiologies were identified for brachial (acute cervicomedullary trauma) and spinal myoclonus (laminectomy, spinal cord injury, postoperative pseudomeningocele, laparotomy, thoracic sympathectomy, lumbosacral radiculopathy, spinal extradural block, and electrical injury), and cervical spondylosis (Jankovic and Pardo 1986). Treatment with clonazepam and tetrabenazine has proved effective in most patients (Jankovic and Pardo 1986).

Spasms in amputation stumps are another, well-recognized form of peripherally induced MDs or segmental myoclonus, often associated with phantom sensory phenomena, severe pain, and lack of response to pharmacological therapy (Tyvaert et al. 2009; Jankovic and Glass 1985). Pain, however, is not a universal feature of amputation stumps (Kulisevsky et al. 1992). Treatment with botulinum toxin and local xylocaine has been reported useful in these patients (Tyvaert et al. 2009) and in one case responded to oral pramipexole (Seidel et al. 2011).

"Painful legs and moving toes" syndrome is considered another form of peripherally induced movement disorder. It is characterized by involuntary continuous or intermittent writhing movements of one or more toes associated with pain, usually of neuropathic quality (Reich 2011). Similar movements can be observed without pain "painless legs-moving toes" (Walters et al. 1993) and in the upper extremities "painful arms-moving fingers" (Supiot et al. 2002). The mean age at onset is in the seventh decade, and most patients present with bilateral involuntary movements (Alvarez et al. 2008). A lesion of the peripheral nerve and root is suspected as the primary cause (Alvarez et al. 2008) although in most cases the specific cause cannot be found (Reich 2011). Treatment includes oral agents for neuropathic pain like gabapentin, botulinum toxin injections, spinal blocks, and spinal cord stimulation (Reich 2011). Other peripherally induced movement disorders include hemimasticatory spasms (Cruccu et al. 1994) and tics (Erer and Jankovic 2008; Factor and Molho 1997).

13.5 Conclusions

In conclusion, posttraumatic movement disorders can originate from direct TBI or peripheral trauma. Kinetic, cerebellar outflow tremor is the most common MD following TBI. There is emerging evidence supporting the role of isolated head trauma as a risk factor for the development of PD, organic dystonia, and other MDs, although repeated head trauma may lead to CTE, "dementia pugilistica," or pugilistic parkinsonism. Peripherally induced MDs are still a controversial area as some

cases have been documented to have a functional etiology. Nevertheless, we believe that there is an important subset of patients in whom the MD after a peripheral injury has an organic basis. Evidence from animal models supports the existence of reorganizational changes in the CNS following peripheral tissue trauma that led to increased excitability or decreased inhibition, which has been documented in other, organic, MDs. Treatment of posttraumatic movement disorders may be challenging, but botulinum toxin injection and stereotactic functional neurosurgery, including DBS, coupled with physical and occupational therapy have shown promising results in patients with disabling posttraumatic MDs.

References

Abu Talh K, Sulaiman M, Joshi D, Hamed S. Development of Parkinsonism symptoms immediately after severe head injury. Neurosciences (Riyadh). 2017;22(4):308–10.

Acosta SA, Tajiri N, de la Pena I, Bastawrous M, Sanberg PR, Kaneko Y, Borlongan CV. Alpha-synuclein as a pathological link between chronic traumatic brain injury and Parkinson's disease. J Cell Physiol. 2015;230(5):1024–32.

Adams JW, Alosco ML, Mez J, et al. Association of probable REM sleep behavior disorder with pathology and years of contact sports play in chronic traumatic encephalopathy. Acta Neuropathol. 2020;140(6):851–62.

Adams JW, Alvarez VE, Mez J, et al. Lewy body pathology and chronic traumatic encephalopathy associated with contact sports. J Neuropathol Exp Neurol. 2018;77(9):757–68.

Alvarez MV, Driver-Dunckley EE, Caviness JN, Adler CH, Evidente VG. Case series of painful legs and moving toes: clinical and electrophysiologic observations. Mov Disord. 2008;23:2062–6.

Anandan C, Jankovic J. Botulinum toxin in movement disorders: an update. Toxins (Basel). 2021;13(1):42.

Atadzhanov M, Mwaba P. Upper limb tremor induced by peripheral nerve injury. Neurology. 2007;69:1381.

Austregesilo A, Marques A. Dystonies. Rev Neurol. 1928;2:562–75.

Baizabal-Carvallo JF, Cardoso F, Jankovic J. Myorhythmia: phenomenology, etiology, and treatment. Mov Disord. 2015;30(2):171–9.

Baizabal-Carvallo JF, Hallett M, Jankovic J. Pathogenesis and pathophysiology of functional (psychogenic) movement disorders. Neurobiol Dis. 2019;127:32–44.

Baizabal-Carvallo JF, Jankovic J. Deep brain stimulation of the subthalamic nucleus for peripherally induced parkinsonism. Neuromodulation. 2014;17(1):104–6.

Bhatia KP, Bhatt MH, Marsden CD. The causalgia-dystonia syndrome. Brain. 1993;116:843–51.

Bhatt M, Desai J, Mankodi A, Elias M, Wadia N. Posttraumatic akinetic-rigid syndrome resembling Parkinson's disease: a report on three patients. Mov Disord. 2000;15:313–7.

Biary N, Cleeves L, Findley L, Koller WC. Post-traumatic tremor. Neurology. 1989;39:103–6.

Biary N, Singh B, Bahou Y, Al Deeb M, Sharif H. Posttraumatic paroxysmal nocturnal hemidystonia. Mov Disord. 1994;9:98–9.

Birklein F, Riedl B, Sieweke N, Weber M, Neundorfer B. Neurological findings in complex regional pain syndromes – analysis of 145 cases. Acta Neurol Scand. 2000;101:262–9.

Black PH. Stress and the inflammatory response: a review of neurogenic inflammation. Brain Behav Immun. 2002;16:622–53.

Blackman JA, Patrick PD, Buck ML, Rust RS Jr. Paroxysmal autonomic instability with dystonia after brain injury. Arch Neurol. 2004;61:321–8.

Blakeley J, Jankovic J. Secondary paroxysmal dyskinesias. Mov Disord. 2002;17:726–34.

Blanchet PJ, Popovici R, Guitard F, Rompre PH, Lamarche C, Lavigne GJ. Pain and denture condition in edentulous orodyskinesia: comparision with tardive dyskinesia and control subjects. Mov Disord. 2008;23:1837–42.

Bostantjopoulou S, Katsarou Z, Michael M, Petridis A. Reversible parkinsonism due to chronic bilateral subdural hemathomas. J Clin Neurosci. 2009;16(3):458–60.

Bower JH, Maraganore DM, Peterson BJ, McDonnell SK, Ahlskog JE, Rocca WA. Head trauma preceding PD: a case-control study. Neurology. 2003;60:1610–5.

Bressman SB, de Leon D, Raymond D, Greene PE, Brin MF, Fahn S, Ozelius LJ, Breakefield XO, Kramer PL, Risch NJ. Secondary dystonia and the DYT1 gene. Neurology. 1997;48:1571–7.

Broggi G, Brock S, Franzini A, Geminiani G. A case of posttraumatic tremor treated by chronic stimulation of the thalamus. Mov Disord. 1993;8:206–8.

Capelle HH, Wöhrle JC, Weigel R, Bazner H, Grips E, Krauss JK. Movement disorders after intervertebral disc surgery: coincidence or causal relationship? Mov Disord. 2004;19:1202–8.

Capelle HH, Grips E, Weigel R, Blahak C, Hansjörg B, Wohrle JC, Krauss JK. Posttraumatic peripherally-induced dystonia and multifocal deep brain stimulation: case report. Neurosurgery. 2006;59:E702.

Cardoso F, Jankovic J. Peripherally induced tremor and parkinsonism. Arch Neurol. 1995;52(3):263–70.

Cardoso Vale T, Echenique L, Barsottini OGP, Pedroso JL. Paroxysmal autonomic instability with dystonia after severe traumatic brain injury. Tremor Other Hyperkinet Mov (N Y). 2020;10:12.

Casson IR, Siegel O, Sham R, Campbell EA, Tarlau M, DiDomenico A. Brain damage in modern boxers. JAMA. 1984;251:2663–7.

Castellani RJ, Perry G. Dementia Pugilistica Revisited. J Alzheimers Dis. 2017;60(4):1209–21.

Cavallieri F, Valzania F, Vercueil L, Moro E, Fraix V. A case of peripherally induced task-specific "Lipstick Dystonic Tremor". Tremor Other Hyperkinet Mov (N Y). 2019;9

Ceballos-Baumann AO, Passingham RE, Marsden CD, Brooks DJ. Motor reorganization in acquired hemidystonia. Ann Neurol. 1995;37:746–57.

Chang JW, Choi JY, Lee BW, Kang UJ, Chung SS. Unilateral globus pallidus internus stimulation improves delayed onset post-traumatic cervical dystonia with an ipsilateral focal basal ganglia lesion. J Neurol Neurosurg Psychiatry. 2002;73:588–90.

Cole JD, Illis LS, Sedgewick EM. Unilateral essential tremor after wrist immobilization: a case report. J Neurol Neurosurg Psychiatry. 1989;52:286–7.

Collins A, Jankovic J. Botulinum toxin injection for congenital muscular torticollis presenting in children and adults. Neurology. 2006;67:1083–5.

Cossu G, Melis M, Melis G, et al. Persistent abnormal shoulder elevation after accessory nerve injury and differential diagnosis with post-traumatic focal shoulder-elevation dystonia: report of a case and literature review. Mov Disord. 2004;19:1109–11.

Costa J, Henriques R, Barroso C, Ferreira J, Atalaia A, de Carvalho M. Upper limb tremor induced by peripheral nerve injury. Neurology. 2006;67:1884–6.

Costeff H, Groswasser Z, Goldstein R. Long-term follow-up review of 31 children with severe closed head trauma. J Neurosurg. 1990;73:684–7.

Cruccu G, Inghilleri M, Berardelli A, Pauletti G, Casali C, Coratti P, Frisardi G, Thompson PD, Manfredi M. Pathology of hemimasticaotry spasm. J Neurol Neurosurg Psychiatry. 1994;57:43–50.

Davie CA, Pirtosek Z, Barker GJ, Kingsley DPE, Miller DH, Lees AJ. Magnetic resonance spectroscopic study of parkinsonism related to boxing. J Neurol Neurosurg Psychiatry. 1995;58:688–91.

de Mos M, de Bruijn AGJ, Huygen FJPM, et al. The incidence of complex regional pain syndrome: a population-based study. Pain. 2007;129:12–20.

Defazio G, Berardelli A, Abbruzzese G, et al. Possible risk factors for primary adult onset dystonia: a case-control investigation by the Italian Movement Disorders Study group. J Neurol Neurosurg Psychiatry. 1998;64:25–32.

Defazio G, Berardelli A, Abbruzzese G, et al. Risk factors for spread of primary adult onset blepharospasm: a multicentre investigation of the Italian movement disorders study group. J Neurol Neurosurg Psychiatry. 1999;67:613–9.
Delic V, Beck KD, Pang KCH, Citron BA. Biological links between traumatic brain injury and Parkinson's disease. Acta Neuropathol Commun. 2020;8(1):45.
Desai A, Nierenberg DW, Duhaime AC. Akathisia after mild traumatic head injury. J Neurosurg Pediatr. 2010;5:460–4.
Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorders Society on tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13(Suppl 3):2–23.
Dewey RB Jr, Jankovic J. Hemiballism-hemichorea: clinical and pharmacologic findings in 21 patients. Arch Neurol. 1989;46:862–7.
Drake ME, Jackson RD, Miller CA. Paroxysmal choreoathetosis after head injury. J Neurol Neurosurg Psychiatry. 1986;49:837–8.
Edwards M, Wood N, Bhatia K. Unusual phenotypes in DYT1 dystonia: a report of five cases and a review of the literature. Mov Disord. 2003;18:706–11.
Eisenberg E, Geller R, Brill S. Pharmacotherapy options for complex regional pain syndrome. Expert Rev Neurother. 2007;7:521–31.
Elbert T, Rockstroh B. Reorganization of human cerebral cortex: the range of changes following use and injury. Neuroscientist. 2004;10:129–41.
Ellis RJ. Tremor and other movement disorders after whiplash type injuries. J Neurol Neurosurg Psychiatry. 1997;63:110–2.
Ellison PH. Propranolol for severe post-head injury action tremor. Neurology. 1978;28:197–9.
Erer S, Jankovic J. Adult onset tics after peripheral injury. Parkinsonism Relat Disord. 2008;14:75–6.
Espay AJ, Morgante F, Purzner J, Gunraj CA, Lang AE, Chen R. Cortical and spinal abnormalities in psychogenic dystonia. Ann Neurol. 2006;59:825–34.
Factor SA, Molho ES. Adult-onset tics associated with peripheral injury. Mov Disord. 1997;12:1052–5.
Factor SA, Weiner WJ. Prior history of head trauma in Parkinson's disease. Mov Disord. 1991;6:225–9.
Factor SA, Sanchez-Ramos J, Weiner WJ. Trauma as an etiology of parkinsonism: a historical review of the concept. Mov Disord. 1988;3:30–6.
Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Adv Neurol. 1998;78:1–10.
Fletcher NA, Harding AE, Marsden CD. The relationship between trauma and idiopathic torsion dystonia. J Neurol Neurosurg Psychiatry. 1991;54:713–7.
Foote KD, Okun MS. Ventralis intermedius plus ventralis oralis anterior and posterior deep brain stimulation for posttraumatic Holmes tremor: two leads may be better than one: technical note. Neurosurgery. 2005;56:E445.
Foote KD, Seignourel P, Fernandez HH, Romrell J, Whidden E, Jacobson C, Rodriguez RL, Okun MS. Dual electrode thalamic deep brain stimulation for the treatment of posttraumatic and multiple sclerosis tremor. Neurosurgery. 2006;58:280–5.
Frei KP, Pathak M, Jenkins S, Truong DD. Natural history of posttraumatic cervical dystonia. Mov Disord. 2004;19:1492–8.
Frucht S, Fahn S, Ford B. Focal task-specific dystonia induced by peripheral trauma. Mov Disord. 2000;15:348–50.
Gadot R, Shofty B, Najera RA, Anand A, Banks G, Khan AB, LoPresti MA, Vanegas Arroyave N, Sheth SA. Case report: dual target deep brain stimulation with externalized programming for post-traumatic complex movement disorder. Front Neurosci. 2021;15:774073.
Gardner RC, Byers AL, Barnes DE, Li Y, Boscardin J, Yaffe K. Mild TBI and risk of Parkinson disease: a chronic effects of Neurotrauma Consortium Study. Neurology. 2018;90(20):e1771–9.
Garraghty PE, Arnold LL, Wellman CL, Mowery TM. Receptor autoradiographic correlates of deafferentation-induced reorganization in adult primate somatosensory cortex. J Comp Neurol. 2006;497:636–45.

Gavett BE, Stern RA, McKee AC. Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. Clin Sports Med. 2011;3:179–88.
Gill JS, Asgerally A, Simopoulos TT. High-frequency spinal cord stimulation at 10 kHz for the treatment of complex regional pain syndrome: a case series of patients with or without previous spinal cord stimulator implantation. Pain Pract. 2019;19(3):289–94.
Goddeau RP Jr, Silverman SB, Sims JR. Dexmedetomidine for the treatment of paroxysmal autonomic instability with dystonia. Neurocrit Care. 2007;7(3):217–20.
Goetz CG, Pappert EJ. Trauma and movement disorders. Neurol Clin. 1992;10:907–20.
Goetz GC, Stebbins GT. Effects of head trauma from motor vehicle accidents on Parkinson's disease. Ann Neurol. 1991;29:191–3.
Goldman S, Ahlskog JE. Posttraumatic cervical dystonia. Mayo Clin Proc. 1993;68:443–8.
Goldman SM, Tanner CM, Oakes D, Bhudhikanok GS, Gupta A, Langston JW. Head injury and Parkinson's disease in twins. Ann Neurol. 2006;60:65–72.
Gowers WR. A manual of diseases of the nervous system. London: Churchill; 1888. p. 659.
Grandas F, Elston J, Quinn N, Marsden CD. Blepharospasm: a review of 264 patients. J Neurol Neurosurg Psychiatry. 1988;51:767–72.
Hallet M. Pathophysiology of dystonia. J Neural Transm. 2006;70:485–8.
Hallet M. Physiology of psychogenic movement disorders. J Clin Neurosci. 2010;17:959–65.
Harmon RL, Long DF, Shirtz J. Treatment of post-traumatic mid-brain resting-kinetic tremor with combined levodopa/carbidopa and carbamazepine. Brain Inj. 1991;5:213–8.
Hawley JS, Weiner WJ. Psychogenic dystonia and peripheral trauma. Neurology. 2011;77:496–502.
Herbaut AG, Soeur M. Two other cases of unilateral essential tremor induced by peripheral trauma. J Neurol Neurosurg Psychiatry. 1989;52:1213.
Höllinger P, Burgunder J. Posttraumatic focal dystonia of the shoulder. Eur Neurol. 2000;44:153–5.
Holmes G. On certain tremors in organic cerebral lesions. Brain. 1904;27:327–75.
Hord ED, Oaklander AL. Complex regional pain syndrome: a review of evidence-supported treatment options. Curr Pain Headache Rep. 2003;7:188–96.
Hutson CB, Lazo CR, Mortazavi F, Giza CC, Hovda D, Chesselet MF. Traumatic brain injury in adult rats causes progressive nigrostriatal dopaminergic cell loss and enhanced vulnerability to the pesticide paraquat. J Neurotrauma. 2011;28(9):1783–801.
Iacono D, Lee P, Hallett M, Perl D. Possible post-traumatic focal dystonia associated with Tau pathology localized to Putamen-Globus Pallidus. Mov Disord Clin Pract. 2018;5(5):492–8.
Ibrahim N, Martino D, van de Warrenburg BP, Quinn NP, Bhatia KP, Brown RJ, Trimble M, Schrag A. The prognosis of fixed dystonia: a follow-up study. Parkinsonism Relat Disord. 2009;15:592–7.
Impellizzeri D, Campolo M, Bruschetta G, Crupi R, Cordaro M, Paterniti I, Cuzzocrea S, Esposito E. Traumatic brain injury leads to development of Parkinson's disease related pathology in mice. Front Neurosci. 2016;10:458.
Ip CW, Isaias IU, Kusche-Tekin BB, Klein D, Groh J, O'Leary A, Knorr S, et al. Tor1a+/− mice develop dystonia-like movements via a striatal dopaminergic dysregulation triggered by peripheral nerve injury. Acta Neuropathol Commun. 2016;4(1):108.
Iwadate Y, Saeki N, Namba H, Odaki M, Oka N, Yamaura A. Post-traumatic intention tremor–clinical features and CT findings. Neurosurg Rev. 1989;12(Suppl 1):500–7.
Jacob PC, Chand RP. Posttraumatic rubral tremor responsive to clonazepam. Mov Disord. 1998;13:977–8.
Jafari S, Etminan M, Aminzadeh F, Samii A. Head injury and risk of Parkinson disease: a systematic review and meta-analysis. Mov Disord. 2013;28(9):1222–9.
Jankovic J. Post-traumatic movement disorders: central and peripheral mechanisms. Neurology. 1994;44:2006–14.
Jankovic J. Peripherally induced movement disorders. Neurol Clin. 2009a;27(3):821–32.
Jankovic J. Treatment of hyperkinetic movement disorders. Lancet Neurol. 2009b;8:844–56.
Jankovic J, Ashoori A. Movement disorders in musicians. Mov Disord. 2008;14:1957–65.
Jankovic J, Brin M. Therapeutic uses of botulinum toxin. N Engl J Med. 1991;324:1186–94.

Jankovic J, Glass JP. Metoclopramide-induced phantom dyskinesia. Neurology. 1985;35:432–5.
Jankovic J, Pardo R. Segmental myoclonus: clinical and pharmacological study. Arch Neurol. 1986;43:1025–3.
Jankovic J, Van der Linden C. Dystonia and tremor induced by peripheral trauma: predisposing factors. J Neurol Neurosurg Psychiatry. 1988;51:1512–9.
Johnson SL, Hall DM. Post-traumatic tremor in head injured children. Arch Dis Child. 1992;67:227–8.
Jordan BD, Relkin NR, Ravdin LD, Jacobs AR, Bennett A, Gandy S. Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. JAMA. 1997;278:136–40.
Kaas JH, Merzenich MM, Killackey HP. The reorganization of somatosensory cortex following peripheral nerve damage in adult and developing mammals. Annu Rev Neurosci. 1983;6:325–56.
Karl A, Birbaumer N, Lutzenberger W, Cohen LG, Flor H. Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. J Neurosci. 2001;21(10):3609–18.
Keane JR. Galloping tongue: post-traumatic, episodic, rhythmic movements. Neurology. 1984;34:251–2.
Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years follow-up of the randomized controlled trial. Ann Neurol. 2004;55:13–8.
Kenborg L, Rugbjerg K, Lee PC, Ravnskjær L, Christensen J, Ritz B, Lassen CF. Head injury and risk for Parkinson disease: results from a Danish case-control study. Neurology. 2015;84(11):1098–103.
Kim HJ, Lee DH, Park JH. Posttraumatic hemiballism with focal discrete hemorrhage in contralateral subthalamic nucleus. Parkinsonism Relat Disord. 2008;14:259–61.
King RB, Fuller C, Collins GH. Delayed onset of hemidystonia and hemiballismus following head injury: a clinicopathological correlation. J Neurosurg. 2001;94:309–14.
Kivi A, Trottenberg T, Kupsch A, Plotkin M, Felix R, Niehaus L. Levodopa-responsive posttraumatic parkinsonism is not associated with changes of echogenicity of the substantia nigra. Mov Disord. 2005;20:258–60.
Koller WC. Edentulous orodyskinesias. Ann Neurol. 1983;13:97–9.
Koller WC, Wong GF, Lang A. Posttraumatic movement disorders: a review. Mov Disord. 1989;4:20–36.
Krack P, Deuschl G, Kaps M, Warnke P, Schneider S, Traupe H. Delayed onset of “rubral tremor” 23 years after brainstem trauma. Mov Disord. 1994;9:240–2.
Krauss JK. Movement disorders secondary to craniocerebral trauma. Handb Clin Neurol. 2015;128:475–96.
Krauss JK, Jankovic J. Hemidystonia secondary to carotid artery gunshot injury. Childs Nerv Syst. 1997a;13:285–8.
Krauss JK, Jankovic J. Tics secondary to craniocerebral trauma. Mov Disord. 1997b;12:776–82.
Krauss JK, Jankovic J. Head injury and posttraumatic movement disorders. Neurosurgery. 2002;50:927–39.
Krauss JK, Mohadjer M, Braus DF, Wakhloo AK, Nobbe F, Mundinger F. Dystonia following head trauma: a report of nine patients and review of the literature. Mov Disord. 1992;7:263–72.
Krauss JK, Mohadjer M, Nobbe F, Mundinger F. The treatment of posttraumatic tremor by stereotactic surgery. Symptomatic and functional outcome in a series of 35 patients. J Neurosurg. 1994;80(5):810–9.
Krauss JK, Wakhloo AK, Nobbe F, Tränkle R, Mundinger F, Seeger W. Lesion of dentatothalamic pathways in severe post-traumatic tremor. Neurol Res. 1995;17:409–16.
Krauss JK, Trankle R, Kopp KH. Post-traumatic movement disorders in survivors of severe head injury. Neurology. 1996;47:1488–92.
Krauss JK, Seeger W, Jankovic J. Cervical dystonia associated with tumors of the posterior fossa. Mov Disord. 1997a;12:443–7.

Krauss JK, Trankle R, Kopp KH. Posttraumatic movement disorders after mild to moderate head trauma. Mov Disord. 1997b;12:428–31.
Krauss JK, Trankle R, Raabe A. Tremor and dystonia after penetrating diencephalic-mesencephalic trauma. Parkinsonism Relat Disord. 1997c;3:117–9.
Krul JM, Wokke JH. Bilateral subdural hematoma presenting as subacute parkinsonism. Clin Neurol Neurosurg. 1987;89:107–9.
Kulisevsky J, Martí-Fàbregas J, Grau JM. Spasms of amputation stumps. J Neurol Neurosurg Psychiatry. 1992;55:626–7.
Kumar H, Jog M. Peripheral trauma induced dystonia or post-traumatic syndrome? Can J Neurol Sci. 2011;38:22–9.
Kuner R. Central mechanism of pathological pain. Nat Med. 2010;16:1258–66.
Lee MS, Rinne JO, Ceballos-Baumann A, Thompson PD, Marsden CD. Dystonia after head trauma. Neurology. 1994;44:1374–8.
Lenka A, Jankovic J. Tremor syndromes: an updated review. Front Neurol. 2021a;12:684835.
Lenka A, Jankovic J. Sports-related Dystonia. Tremor Other Hyperkinet Mov (N Y). 2021b;11:54.
Li HX, He L, Zhang CC, Eisinger R, Pan YX, Wang T, Sun BM, Wu YW, Li DY. Deep brain stimulation in post-traumatic dystonia: a case series study. CNS Neurosci Ther. 2019;25(11):1262–9.
Loher TJ, Krauss JK. Dystonia associated with pontomesencephalic lesions. Mov Disord. 2009;24:157–67.
Loher TJ, Hasdemir MG, Burgunder JM, Krauss JK. Long-term follow-up study of chronic globus pallidus internus stimulation for posttraumatic hemidystonia. J Neurosurg. 2000;92:457–60.
Mackay DF, Russell ER, Stewart K, MacLean JA, Pell JP, Stewart W. Neurodegenerative disease mortality among former professional Soccer players. N Engl J Med. 2019;381(19):1801–8.
Maclver K, Lloyd DM, Kelly S, Roberts N, Nurmikko T. Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. Brain. 2008;131:2181–91.
Majumdar A, Appleton RE. Delayed and severe but transient Tourette syndrome after head injury. Pediatr Neurol. 2002;27:314–7.
Maki Y, Akimoto H, Enomoto T. Injuries of basal ganglia following head trauma in children. Childs Brain. 1980;7:113–23.
Manjunath N, Jhunjhunwala K, Devi BI, Pal PK. Posttraumatic movement disorders: a clinical and imaging profile of 30 patients. Neurol India. 2019;67(3):738–43.
Marinus J, Moseley GL, Birklein F, Baron R, Maihöfner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol. 2011;10:637–48.
Marsden CD, Obeso JA, Traub MM, et al. Muscle spasm associated with Sudeck's atrophy after the injury. Br Med J. 1984;288:173–6.
Marsden CD, Obeso JA, Zarranz JJ, Lang AE. The anatomical basis of symptomatic hemidystonia. Brain. 1985;108:463–83.
Martínez-Mañas R, Rumià J, Valldeoriola F, Ferrer E, Tolosa E. Thalamic neuro-inhibition in the treatment of post traumatic tremor. Rev Neurol. 2002;34:258–61.
Martino D, Defazio G, Abbruzzese G, Girlanda P, Tinazzi M, Fabbrini G, Aniello MS, Avanzino L, Colosimo C, Majorana G, Trompetto C, Berardelli A. Head trauma in primary cranial dystonias: a multicentre case-control study. J Neurol Neurosurg Psychiatry. 2007;78:260–3.
McKee AC. The neuropathology of chronic traumatic encephalopathy: the status of the literature. Semin Neurol. 2020;40(4):359–69.
McKee AC, Cantu R, Nowinski C, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J Neurol Exp Neuropathol. 2009;68:709–35.
McKee AC, Gavett BE, Stern RA, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. J Neurol Exp Neuropathol. 2010;69:918–29.
Méndez-Rebolledo G, Gatica-Rojas V, Torres-Cueco R, Albornoz-Verdugo M, Guzmán-Muñoz E. Update on the effects of graded motor imagery and mirror therapy on complex regional pain syndrome type 1: a systematic review. J Back Musculoskelet Rehabil. 2017;30(3):441–9.
Mercier C, Reilly KT, Vargas CD, Aballea A, Siriqu A. Mapping phantom movement representations in the motor cortex of amputees. Brain. 2006;129:2202–10.

Mez J, Daneshvar DH, Kiernan PT, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. JAMA. 2017;318(4):360–70.
Meunier S, Garnero L, Ducorps A, et al. Human brain mapping in dystonia reveals both endophenotypic traits and adaptive reorganization. Ann Neurol. 2001;50:521–7.
Miura I, Horisawa S, Kawamata T, Taira T. Successful treatment of focal hand dystonia after cervical whiplash injury by thalamotomy. Surg Neurol Int. 2022;13:387.
Münchau A, Mathen D, Cox T, Quinn NP, Marsden CD, Bhatia KP. Unilateral lesions of the globus pallidus: report of four patients presenting with focal or segmental dystonia. J Neurol Neurosurg Psychiatry. 2000;69:494–8.
Munts AG, van der Plas AA, Voormolen JH, et al. Intrathecal glycine for pain and dystonia in complex regional pain syndrome. Pain. 2009;146:199–204.
Navarro X, Vivo M, Valero-Cabre A. Neural plasticity after peripheral nerve injury and regeneration. Prog Neurobiol. 2007;82:163–201.
Netravathi M, Pal PK, Indira DB. A clinical profile of 103 patients with secondary movement disorders: correlation of etiology with phenomenology. Eur J Neurol. 2012;19(2):226–33.
Netravathi M, Pal PK, Ravishankar S, Indira DB. Electrophysiological evaluation of tremors secondary to space occupying lesions and trauma: correlation with nature and sites of lesions. Parkinsonism Relat Disord. 2010;16(1):36–41.
Nicoletti A, Vasta R, Mostile G, Nicoletti G, Arabia G, Iliceto G, Lamberti P, Marconi R, Morgante L, Barone P, Quattrone A, Zappia M. Head trauma and Parkinson's disease: results from an Italian case-control study. Neurol Sci. 2017;38(10):1835–9.
Nobrega JC, Campos CR, Limongi JC, Teixeira MJ, Lin TY. Movement disorders induced by peripheral trauma. Arq Neuropsiquiatr. 2002;60:17–20.
O'Riordan S, Hutchinson M. Cervical dystonia following peripheral trauma: a case control study. J Neurol. 2004;251:150–5.
Okun MS, Nadeau SE, Rossi F, Triggs WJ. Immobilization dystonia. J Neurol Sci. 2002;201:79–83.
Ostrem JL, Marks WJ Jr, Volz MM, Heath SL, Starr PA. Pallidal deep brain stimulation in patients with cranial-cervical dystonia (Meige syndrome). Mov Disord. 2007;22:1885–91.
Ostrem JL, Racine CA, Glass GA, Grace JK, Volz MM, Heath SL, Starr PA. Subthalamic nucleus deep brain stimulation in primary cervical dystonia. Neurology. 2011;76:870–8.
Owen RL, Grewal SS, Thompson JM, Hassan A, Lee KH, Klassen BT. Effectiveness of Thalamic Ventralis Oralis anterior and posterior nuclei deep brain stimulation for posttraumatic Dystonia. Mayo Clin Proc Innov Qual Outcomes. 2022;6(2):137–42.
Parkinson J. Essay on the shaking palsy. London: Sherwood, Neely and Jones; 1817.
Perlmutter JS, Raichle ME. Pure hemidystonia with basal ganglion abnormalities on positron emission tomography. Ann Neurol. 1984;15:228–33.
Pettigrew LC, Jankovic J. Hemidystonia: a report of 22 patients and review of the literature. J Neurol Neurosurg Psychiatry. 1985;48:650–7.
Rabinsten AA. Paroxysmal autonomic instability after brain injury. Arch Neurol. 2004;61:1625.
Ranjan N, Nair KP, Romanoski C, Singh R, Venketswara G. Tics after traumatic brain injury. Brain Inj. 2011;25:629–33.
Rauschenberger L, Knorr S, Pisani A, Hallett M, Volkmann J, Ip CW. Second hit hypothesis in dystonia: dysfunctional cross talk between neuroplasticity and environment? Neurobiol Dis. 2021;159:105511.
Reese R, Herzog J, Falk D, Lützen U, Pinsker MO, Mehdorn HM, Ebersbach G, Deuschl G, Volkmann J. Successful deep brain stimulation in a case of posttraumatic tremor and hemiparkinsonism. Mov Disord. 2011;26:1954–5.
Reich SG. Painful legs and moving toes. Handb Clin Neurol. 2011;100:37–83.
Remy P, de Recondo A, Defer G, et al. Peduncular 'rubral' tremor and dopaminergic denervation: a PET study. Neurology. 1995;45:472–7.
Richardson JC, Howes JL, Celinski MJ, Allman RG. Kinesigenic choreoathetosis due to brain injury. Can J Neurol Sci. 1987;14:626–8.

Rojas-Medina LM, Esteban-Fernández L, Rodríguez-Berrocal V, Del Álamo de Pedro M, Ley Urzaiz L, Bailly-Baillere IR. Deep brain stimulation in posttraumatic tremor: A series of cases and literature review. Stereotact Funct Neurosurg. 2016;94(6):379–386. https://doi.org/10.1159/000448078

Romanelli P, Brontë-Stewart H, Courtney T, Heit G. Possible necessity for deep brain stimulation of both the ventralis intermedius and subthalamic nuclei to resolve Holmes tremor. Case report. J Neurosurg. 2003;99:566–71.

Rondot P, Bathien N, De Recondo J, Gueguen B, Fredy D, De Recondo A, Samson Y. Dystonia-parkinsonism syndrome from a bullet injury in the midbrain. J Neurol Neurosurg Psychiatry. 1994;57:658.

Rugbjerg K, Ritz B, Korbo L, Martinussen N, Olsen JH. Risk of Parkinson's disease after hospital contact for head injury: population based case control study. BMJ. 2008;337:a2494.

Sa DS, Mailis-Gagnon A, Nicholson K, Lang AE. Posttraumatic painful torticollis. Mov Disord. 2003;18:1482–91.

Sankhla C, Lai EC, Jankovic J. Peripherally induced oromandibular dystonia. J Neurol Neurosurg Psychiatry. 1998;65:722–8.

Scarano V, Jankovic J. Post-traumatic movement disorders: effect on the legal system on outcome. J Forensic Sci. 1998;43:334–9.

Schirinzi T, Grillo P, Di Lazzaro G, Zenuni H, Salimei C, Dams-O'Connor K, Sancesario GM, Mercuri NB, Pisani A. Effects of head trauma and sport participation in young-onset Parkinson's disease. J Neural Transm (Vienna). 2021;128(8):1185–93.

Schott GD. The relationship of peripheral trauma and pain to dystonia. J Neurol Neurosurg Psychiatry. 1985;48:698–701.

Schrag A, Bathia KP, Quinn NP, Marsden CD. Atypical and typical cranial dystonia following dental procedures. Mov Disord. 1999;14:492–6.

Schrag A, Trimble M, Quinn NP, Bhatia KP. The syndrome of fixed dystonia: an evaluation of 103 patients. Brain. 2004;127:2360–72.

Schwartzman RJ. Reflex sympathetic dystrophy. Curr Opin Neurol Neurosurg. 1993;6:531–6.

Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. Neurology. 1990;40:57–61.

Scott BL, Jankovic J. Delayed-onset progressive movement disorders after static brain lesions. Neurology. 1996;46:68–74.

Seidel S, Kechvar-Parast J, Sycha T, Zeitlhofer J. The first case of a "jumping stump" syndrome in a lower limb amputee responding to pramipexole. Eur J Neurol. 2011;18:e45–6.

Siemers E, Pascuzzi R. Posttraumatic tic disorder. Mov Disord. 1990;5:183.

Singer C, Papapetropoulos S. Lower limb post-immobilization dystonia in Parkinson's disease. J Neurol Sci. 2005;239:111–4.

Singer S, Sanchez-Ramos J, Weiner WJ. A case of post-traumatic tic disorder. Mov Disord. 1989;4:342–4.

Slevin JT, Sparks DL, Dempsey RJ, Davis DG, Hunsaker JC 3rd, DeKosky ST. Altered striatal dopaminergic metabolism 36 hours after unilateral trauma to the human mesencephalon. Neurology. 1987;37:322–5.

Snyder AM, Stricker EM, Zigmond MJ. Stress-induced neurological impairments in an animal model of parkinsonism. Ann Neurol. 1985;18:544–51.

Spangenberg S, Hannerz H, Tüchsen F, Mikkelsen KL. A nationwide population study of severe head injury and Parkinson's disease. Parkinsonism Relat Disord. 2009;15:12–4.

Srinivasan S, Lim CCT, Thirugnanam U. Paroxysmal autonomic instability with dystonia. Clin Auton Res. 2007;17:378–81.

Stern RA, Adler CH, Chen K, Navitsky M, Luo J, Dodick DW, Alosco ML, Tripodis Y, Goradia DD, Martin B, Mastroeni D, Fritts NG, Jarnagin J, Devous MD Sr, Mintun MA, Pontecorvo MJ, Shenton ME, Reiman EM. Tau positron-emission tomography in former national football league players. N Engl J Med. 2019;380(18):1716–1725. https://doi.org/10.1056/NEJMoa1900757

Stewart JT. Akathisia following traumatic brain injury: treatment with bromocriptine. J Neurol Neurosurg Psychiatry. 1989;52:1200–1.
Suchowersky O, Calne DB. Non-dystonic causes of torticollis. Adv Neurol. 1988;50:501–8.
Sumitani M, Miyauchi S, Uematsu H, Yozu A, Otake Y, Yamada Y. Phantom limb pain originates from dysfunction of the primary motor cortex. Masui. 2010;59:1364–9.
Supiot F, Gazagnes MD, Blecic SA, Zegers de Beyl D. Painful arms and moving fingers: clinical features of four new cases. Mov Disord. 2002;17:616–8.
Svetel M, Ivanovic N, Marinkovic J, Jovic J, Dragasevic N, Kostic VS. Characteristics of dystonic movements in primary and symptomatic dystonias. J Neurol Neurosurg Psychiatry. 2004;75:329–30.
Tanner CM, Chen B, Wang WZ, Peng ML, Liu ZL, Liang XL, Kao LC, Gilley DW, Schoenberg BS. Environmental factors in the etiology of Parkinson's disease. Can J Neurol Sci. 1987;14(3 Suppl):419–23.
Tarsy D. Comparision of acute- and delayed-onset posttraumatic cervical dystonia. Mov Disord. 1998;13:481–5.
Taylor SS, Noor N, Urits I, Paladini A, Sadhu MS, Gibb C, Carlson T, Myrcik D, Varrassi G, Viswanath O. Complex regional pain syndrome: a comprehensive review. Pain Ther. 2021;10:875–92.
Taylor CA, Saint-Hilaire MH, Cupples LA, Thomas CA, Burchard AE, Feldman RG, Myers RH. Environmental, medical, and family history risk factors for Parkinson's disease: a new England-based case control study. Am J Med Genet. 1999;88:742–9.
Taylor KM, Saint-Hilaire MH, Sudarsky L, Simon DK, Hersh B, Sparrow D, Hu H, Weisskopf MG. Head injury at early ages is associated with risk of Parkinson's disease. Parkinsonism Relat Disord. 2016;23:57–61.
Thenganatt MA, Jankovic J. Psychogenic (Functional) movement disorders. Continuum (Minneap Minn). 2019;25(4):1121–1140. https://doi.org/10.1212/CON.0000000000000755
Thyagarajan D, Kompoliti K, Ford B. Post-traumatic shoulder "dystonia": persistent abnormal postures of the shoulder after minor trauma. Neurology. 1998;51:1205–7.
Topp KS, Byl NN. Movement dysfunction following repetitive hand opening and closing: anatomical analysis in owl monkeys. Mov Disord. 1999;14:295–306.
Tränkle R, Krauss JK. Post-traumatic focal dystonia after contralateral thalamic lesion. Nervenarzt. 1997;68:521–4.
Trosch RM, Ransom BR. Levodopa-responsive parkinsonism following central herniation due to bilateral subdural hematomas. Neurology. 1990;40:376–7.
Troung DD, Duinsky R, Hermanowicx N, Olson WL, Silverman B, Koller W. Posttraumatic torticollis. Arch Neurol. 1991;48:221–3.
Turjanski N, Lees AJ, Brooks DJ. Dopaminergic function in patients with posttraumatic parkinsonism: an 18F-dopa PET study. Neurology. 1997;49:183–9.
Tyvaert L, Krystkowiak P, Cassim F, et al. Myoclonus of peripheral origin: two case reports. Mov Disord. 2009;24:274–7.
Uryu K, Giasson BI, Longhi L, Martinez D, Murray I, Conte V, Nakamura M, Saatman K, Talbot K, Horiguchi T, McIntosh T, Lee VM, Trojanowski JQ. Age-dependent synuclein pathology following traumatic brain injury in mice. Exp Neurol. 2003;184(1):214–24.
van Hilten JJ, Geraedts EJ, Marinus J. Peripheral trauma and movement disorders. Parkinsonism Relat Disord. 2007;13:S395–9.
van Rijn MA, Marinus J, Putter H, van Hilten JJ. Onset and progression of dystonia in complex regional pain syndrome. Pain. 2007;130:287–93.
van Rijn MA, Munts AG, Marinus J, Voormolen JH, de Boer KS, Teepe-Twiss IM, van Dasselaar NT, Delhaas EM, van Hilten JJ. Intrathecal baclofen for dystonia of complex regional pain syndrome. Pain. 2009;143:41–7.
van Rooijen DE, Geraedts EJ, Marinus J, Jankovic J, van Hilten JJ. Peripheral trauma and movement disorders: a systematic review of reported cases. J Neurol Neurosurg Psychiatry. 2011;82:892–8.
Vanek Z, Jankovic J. Dystonia in corticobasal degeneration. Mov Disord. 2001;16:252–7.

Verdugo RJ, Ochoa JL. Abnormal movements in complex regional pain syndrome: assessment of their nature. Muscle Nerve. 2000;101:262–9.

Visnjevac O, Costandi S, Patel BA, Azer G, Agarwal P, Bolash R, Mekhail NA. A comprehensive outcome-specific review of the use of spinal cord stimulation for complex regional pain syndrome. Pain Pract. 2017;17(4):533–45.

Walters AS, Henning WA, Shah SK, Chokroverty S. Painless legs and moving toes: a syndrome related to painful legs and moving toes? Mov Disord. 1993;8:377–9.

Wang A, Jankovic J. Hemifacial spasm: clinical correlates and treatments. Muscle Nerve. 1998;21:1740–7.

Weiner WJ. Controversy: can peripheral trauma induce dystonia? No! Mov Disord. 2001;16:13–22.

Wellman CL, Arnold LL, Garman EE, Garraghty PE. Acute reductions in GABAA receptor binding in layer IV of adult primate somatosensory cortex after peripheral nerve injury. Brain Res. 2002;954:68–72.

Wijemanne S, Jankovic J. Hemidystonia-hemiatrophy syndrome. Mov Disord. 2009;24:583–9.

Williams DB, Annegers JF, Kokmen E, O'Brien PC, Kurland LT. Brain injury and neurologic sequelae: a cohort study of dementia, parkinsonism, and amyotrophic lateral sclerosis. Neurology. 1991;41:1554–7.

Wright RA, Ahlskog JE. Focal shoulder-elevation dystonia. Mov Disord. 2000;15:709–13.

Wu LJ, Jankovic J. Runner's dystonia. J Neurol Sci. 2006;251(1–2):73–6.

Yaltho TC, Jankovic J. The many faces of hemifacial spasm: differential diagnosis of unilateral facial spasms. Mov Disord. 2011;26:1582–92.

Zijlmans J, Booij J, Valk J, Lees A, Horstink M. Posttraumatic tremor without parkinsonism in a patient with complete contralateral loss of the nigrostriatal pathway. Mov Disord. 2002;17:1086–8.

Chapter 14
Tremor in Childhood

Padraic J. Grattan-Smith and Russell C. Dale

Abstract Tremor particularly affects the upper limbs but can involve almost any part of the body including the head, face, eyelids, tongue, vocal cords, and trunk. In a Consensus Statement of the Movement Disorders Society, tremor is defined as "*a rhythmic, involuntary, oscillatory movement of a body part*" (Deuschl et al., Mov Disord 13:2–23, 1998). As with most definitions of movement disorders, there is an immediate problem with the words used, in this case with "*rhythmic*." In Webster's dictionary there are 10 definitions of "*rhythm*" the first being "*movement or procedure with uniform or patterned recurrence of a beat, accent or the like.*" In current clinical practice when there are regular oscillations, the term "tremor" is used with "rhythmic" and "regular" essentially having the same meaning.

Keywords Children · Newborn · Dopamine · Metabolism

Tremor particularly affects the upper limbs but can involve almost any part of the body including the head, face, eyelids, tongue, vocal cords, and trunk. In a Consensus Statement of the Movement Disorders Society, tremor is defined as "*a rhythmic, involuntary, oscillatory movement of a body part*" (Deuschl et al. 1998). As with most definitions of movement disorders, there is an immediate problem with the words used, in this case with "*rhythmic*." In Webster's dictionary there are 10 definitions of "*rhythm*" the first being "*movement or procedure with uniform or patterned recurrence of a beat, accent or the like.*" In current clinical practice when there are regular oscillations the term tremor is used with "rhythmic" and "regular" essentially having the same meaning.

However, rhythm is further defined in Webster's Dictionary as being "*regular or irregular*." Gordon Holmes in his classic paper on tremor stated: "*I would suggest that the term tremor be used to denote a clinical phenomenon consisting in the*

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involuntary oscillation of any part of the body around any plane, such oscillations being either regular or irregular in rate and in amplitude, and due to the alternate action of groups of muscles and their antagonists" (Holmes 1904). The literature on tremor does not always insist on regularity and in the following, we discuss conditions where the word "*tremor*" is used rather than attempt to only deal with those where the movement disorder has been demonstrated to be always regular (There are in turn 26 entries under "*regular*" in Webster's Dictionary but its meaning is usually clear).

Tremor is the commonest movement disorder of adults (Louis and Ferreira 2010). It has been suggested that as many as 23% of the elderly may have essential tremor (Louis et al. 2001a). There is no data on the prevalence of tremor in childhood but in the personal series of Fernandez-Alvarez of children under 18 years, 129 (19%) of 673 cases presented with tremor as the sole or predominant feature. It was seen twice as commonly in boys and the apparent age of onset was typically around 6 years (Fernandez-Alvarez and Aicardi 2001).

In adult medicine discussions about tremor particularly concentrate on two common disorders—essential tremor and Parkinson's disease. The large number of patients suffering from these conditions has meant that there is a vast literature on their pathophysiology and treatment. In contrast, in childhood there are a large number of rare conditions that can produce tremor and in most, little is known about their pathophysiology.

Although there are sophisticated techniques available for its measurement, the assessment of tremor in children remains essentially clinical (Singer et al. 2010a). Singer et al. note: "*Electromyography, accelerometers, and other instruments are sometimes used to quantitate tremors, but the* ***clinical*** *utility of this information, that is, its ability to improve diagnostic and/or therapeutic medical decision making, has not been demonstrated in children.*" However, Canavese, in a retrospective review of 61 children who had a tremor study, found that in 31% the polymyographic features allowed the identification of a clinically unclassified movement disorder (Canavese et al. 2008). Further in 19.6% it disclosed an associated movement disorder which was not clinically evident. It was also useful in supporting the clinical diagnosis of psychogenic movement disorder. It is possible that in future, tremor studies will have a greater role in children.

For the reasons outlined above, in this chapter we take a clinical approach to the problem of the child with a tremor.

14.1 Classification

Tremor is traditionally divided into *resting tremor* and *action tremor*. Using tremor of the upper limbs as an example, with *resting tremor*, the tremor is seen when the arm is totally relaxed. Full relaxation is not always easy to achieve but asking the child to rest the arm on the bed and let it become "loose" may be effective. *Action tremor* is any tremor that is produced by voluntary contraction of muscle. It is

further subdivided into (1) *postural tremor* which occurs when a limb is voluntarily maintained against gravity, for example, when the arms are held out steadily straight out in front of the patient and (2) *kinetic tremor* defined as any tremor that occurs during voluntary movement.

Kinetic tremors can in turn be subdivided. *Intention tremor* worsens as a target is approached, classically in the "finger–nose" test. Again there are problems with terminology. The use of the word *intention* has been criticized as the problem is not one of motive but the performance of a target directed, visually guided movement. *Terminal tremor* has been advocated as an alternative but has not been widely adopted, presumably in part because patients and their families may misinterpret this as indicating a fatal tremor. *Simple kinetic tremor* occurs during voluntary movements that are not goal directed, for example, during pronation/supination movements of the forearm. *Task-specific tremors* occur during or are provoked by a particular action, for example, writing. *Titubation* is the slow head/trunk tremor typically seen with cerebellar disease but also in adults with essential tremor.

Holmes tremor is present both at rest and with intention and often with posture. It can be extremely disabling. With the finger–nose test as the hand returns to the nose there may be extreme oscillations of the hand and the threat of injury to the eyes or face. The term *Holmes tremor* is now preferred to such terms as *rubral* or *midbrain* tremor which were used in the past. It is believed to be caused by involvement of both the nigrostriatal and dentato-rubro-thalamic pathways (Deuschl et al. 1998).

Isometric and orthostatic tremors are conditions that occur mainly in adults and will not be discussed further here.

There are difficulties with the term *dystonic tremor* as the movements are usually not regular. However, the movements although usually jerky may be of large amplitude and mimic a tremor. They present a very different sign to the twisting and sustained postures of dystonia and to subsume them under *dystonic movements* deprives us of a term that is clinically useful. The Consensus Statement restricts the term to the situation where the movements occur in a body part affected by dystonia, for example, torticollis combined with jerky head movements. A difficulty here is deciding whether a posture such as a head tilt or wrist extension is a sign of dystonia or an attempt to reduce the tremor (Elbe and Deuschl 2011). The label of dystonic tremor is most confidently applied when it has the following features: irregularity, high amplitude, posture-dependency, and complexity (i.e., it is multidirectional). Other features which suggest that a tremor is dystonic are its appearance with specific activities such playing a musical instrument and its relief by a geste antagoniste (a physical gesture or a position which reduces or interrupts temporarily dystonia).

Another and more common disorder of childhood that comes into consideration in the differential diagnosis of tremor is a stereotypy. Stereotypies have been defined as *involuntary patterned, repetitive* ***often rhythmic*** (our emphasis) *movements that are goal directed and occur in the same fashion with each repetition* (Singer et al. 2010b). They can appear in multiple different settings such as when the child is bored or excited. Stereotypies may take on many forms but common examples that are rhythmic include hand flapping and body rocking. Some of the

poorly understood complex but rhythmic movement disorders of childhood such as shuddering attacks may be stereotypies. When stereotypies occur in children who are otherwise normal, the child often describes getting a feeling of pleasure or comfort from the movements.

14.2 Examination of the Child with a Tremor

A full and careful neurological and general physical examination should, of course, be performed. Here we concentrate on the assessment of the tremor itself.

Tremor is a visual sign and the examination of tremor consists of initially viewing the child at rest, then with posture and then in motion. With resting and postural tremors, getting the older child to do mental arithmetic is effective in bringing out a quiescent tremor and will often exaggerate a pathological tremor. If the tremor is psychogenic it may disappear with mental arithmetic. Asking the child to hold both index fingers as close to the nose as possible without touching it, with the arms abducted and elbows flexed (the "*wing posture*") can provoke both distal and proximal tremors. Getting the child to drink from a plastic cup, to write and to copy a spiral are useful ways of assessing the disability caused by the tremor. Young children are best observed during play with toys. Most enjoy taking the top on and off a pen and the function of each arm can be assessed by holding the top of a marker pen and asking the child to put the pen in it with one hand. Tremor amplitude is usually inversely proportional to tremor frequency so that slow tremors (e.g., with a frequency of 3 Hz) tend to be coarse and fast tremors (e.g., 12 Hz) tend to be fine.

14.3 Pathophysiology

As discussed above, there is a paucity of data specific to childhood on the pathophysiology of tremor and the authors suggest a review of other chapters in this publication. For completeness, a brief review will be provided to give relevance to the clinical descriptions.

All of us have a tremor which is usually only seen under conditions of stress such as anger or extreme fatigue. This so-called *physiological tremor* is an action tremor that takes the form of an oscillation of the outstretched hands at a frequency of 8–12 Hz. Marsden listed the multiple interacting systems that give rise to physiological tremor (Marsden 1984). These include the ballistocardiogram (the expansion of the intravascular space during systole), biomechanical and physical properties of the muscle, motorneuronal firing, spindle feedback (which influences the synchronization), supraspinal influences, and pharmacological influences (especially via the beta-receptors). Marsden further indicated that the human limbs possess a natural frequency of oscillation and the greater the mass, the lower the frequency. The natural frequency of the finger is approximately 25 Hz whereas that of the

wrist is around 9 Hz and the elbow 2 Hz. Enhanced physiological tremor and essential tremor can appear identical. However, the frequency of physiological tremor decreases with mass loading whereas loading the limb has no effect on centrally derived tremors such as essential tremor (Fahn and Jankovic 2007a).

Manto has discussed the various "loops" in the nervous system that when disordered can give rise to tremor (Manto 2008). These include (1) the loop between motor cortex and basal ganglia, (2) the loop between the cerebellum and the brainstem, especially the Guillain–Mollaret triangle, linking the dentate nucleus of the cerebellum with the contralateral red nucleus and the inferior olive, (3) the loop between the cerebellum, the thalamic nuclei, and the motor cortex (cerebello-thalamo-cortical pathway and cortico-ponto-cerebellar tracts), (4) the peripheral loops, including the afferents from the muscle spindles to the alpha-motoneurons (spinal loop), and (5) loops from the peripheral sensors to the motor cortex (transcortical loop). Most pathological tremors arise from excessive oscillatory activity arising from the so-called "central oscillators" in the brain. This may result from loss of inhibition or changes within the networks that favor the development of excessive synchronized activity.

14.4 An Approach to the Diagnosis of Tremor in Childhood

As discussed above, in adult medicine reviews of tremor disorders particularly concentrate on two common conditions—essential tremor and Parkinsonism. Recent evidence has shown that even with these two disorders, long recognized, and intensively studied, everything is not as straightforward as it once seemed. The issues around essential tremor will be discussed below. What was once regarded as a variant of Parkinson's disease "benign tremulous Parkinsonism" is now thought to be often a form of dystonic tremor without evidence of dopamine deficiency (Schwingenschuh et al. 2010). In childhood, the large number of rare conditions that can produce tremor may result in long and rather confusing lists of potential causes. Here we will approach the problem using the age of the child as the starting point. Clearly, there may be overlap between conditions that appear in infancy and early childhood. Rather than listing all conditions where a tremor can be seen, we will concentrate on conditions where tremor is the predominant feature or where it is an important clue to the underlying diagnosis. We do not limit our review to conditions that have been documented to show regularity of movements.

With the diversity of causes of childhood tremor, it is not possible to formulate broad principles of treatment. Treatment is in general directed at the underlying cause but in the following sections, there is insufficient space to deal with this in any detail.

14.5 The Newborn

"*Jitteriness*" is seen in as many as half of all term infants and as such is the commonest form of tremor in childhood. In most, it settles over a few days. Asphyxiated babies may show this in an extreme form. In jitteriness, the rhythmic oscillatory movements can be provoked by startle and be stopped by gently holding the moving limb or changing its position. The main differential is a clonic seizure where the jerking will continue despite gentle restraint or repositioning. A fundamental difference is that the to and fro movements of jitteriness are of equal amplitude whereas in clonic seizures, the phase of flexion is usually more sustained than that of extension (Scher 1997).

Asphyxiated babies may also develop rhythmic *cycling movements* involving the arms or legs. These can be provoked by stimulation and the more repetitive the stimulation and the greater the number of areas stimulated, the greater the response. These are thought to be abnormal but non-epileptic behaviors "released" by injury to the forebrain structures that normally inhibit them (Mizrahi and Kellaway 1987).

Benign neonatal sleep myoclonus is a non-epileptic form of myoclonus (Coulter and Allen 1982). At times, the myoclonic jerks come in flurries that can be rhythmic and rapid and mimic a tremor. Although all four limbs are often involved, there can also be asymmetry. The movements are only seen in sleep and the baby is otherwise normal helping to differentiate this condition from seizures. A normal electroencephalogram (EEG) is helpful in confirming the clinical diagnosis, especially when the jerks are recorded.

14.6 Infants

There are a relatively small number of causes of tremor in infancy. These are important to identify as treatment has the potential to produce a marked improvement in the neurological status of these children.

14.6.1 Inborn Errors of Dopamine Metabolism

These are rare and the infant is often misdiagnosed as having "cerebral palsy." Typically, the picture is of "dystonia-Parkinsonism" with dopamine deficiency causing akinesia, rigidity, tremor, dystonia, and oculogyric crises. As dopamine is converted to noradrenaline, this is also deficient and results in the additional features of ptosis, miosis, and excessive drooling. This may give the false impression that the child has a neuromuscular disorder.

The tremor of dopamine deficiency is usually slow and coarse. It is not seen in all cases but when present is a most important clue to the diagnosis. It has

been described with tyrosine hydroxylase deficiency (de Rijk-Van Andel et al. 2000), 6-pyruvoyl-tetrahydropterin synthetase deficiency (Factor et al. 1991), an undefined disorder of biopterin synthesis (Snyderman et al. 1987) with aromatic acid decarboxylase deficiency (Korenke et al. 1997) and with sepiapterin reductase deficiency (Neville et al. 2005). In the study of Neville of seven cases of sepiapterin reductase deficiency, two of seven patients had an early onset of "parkinsonian tremor." In a personal case of tyrosine hydroxylase deficiency (Grattan-Smith et al. 2002), the tremor was the first definite sign. It commenced at 2 months of age and over time spread to involve the tongue, head, arms, and legs. It was coarse and presented a dramatic clinical picture (videos accompany the article). It was present when the infant appeared to be at rest and with attempts at movement. A tremor study from the tibialis anterior muscle showed rhythmic muscle bursts at 4 Hz frequency. The tremor responded rapidly to L-dopa therapy. It is of interest that the tremor in this infant first appeared at around 2 months of age. This is the same time sleep spindles first appear in the EEG of infants, representing a sign of thalamo-cortical synchronization. Recent reviews describing 36 patients with tyrosine hydroxylase deficiency (Willemsen et al. 2010) and 78 patients with aromatic acid decarboxylase deficiency (Brun et al. 2010) have not emphasized the presence of tremor but when present it is a very important sign.

14.6.2 Vitamin B12 Deficiency

In 1962, Jadhav reported the syndrome of vitamin B12 deficiency in Indian infants characterized by apathy, developmental regression, involuntary movements, and skin pigmentation (Jadhav et al. 1962). Subsequently there have been multiple similar reports from the "developed" world. The typical story is that the mother has vitamin B12 deficiency due either to her diet or undiagnosed pernicious anemia. The baby is exclusively breast-fed. From around 4 to 8 months, there is progressive developmental regression. The infant may not be anemic but the blood film is often macrocytic. The movement disorder can be present before diagnosis but is more often seen after treatment with vitamin B12 has started. It is commonly described as "choreoathetosis" (Graham et al. 1992) but in some children the movement disorder is more rhythmic (Higginbottom et al. 1978). At times, it takes the form of a violent tremor that can cause the cot to shake (Emery et al. 1997). In a series of three patients, two had pronounced limb shaking thought to be a mixture of tremor and myoclonus with the first infant also having pronounced involvement of the tongue and pharynx (Grattan-Smith et al. 1997). The third infant had persistent movements of the right hand resembling epilepsia partialis continua (EPC) which appeared before treatment was started. Both seizures and movement disorders can occur in vitamin B12 deficiency and it is important to try to separate the two. The violent tremor that appears after the initiation of treatment usually settles over 4–6 weeks. Why it occurs is unknown. In the developing world, the "kwashiorkor shakes" has

been described in severely malnourished children on refeeding (Kahn and Falcke 1956). Again, the cause is unknown.

14.6.3 Head Tremors of Infancy

Head tremors of all ages can be further subdivided into *negative* when the head shakes from side to side and *positive* (or *affirmative*) when the shaking takes the form of a vertical nodding. Some children with *congenital nystagmus* have head shaking movements. It is not clear why these occur but there are usually no diagnostic difficulties in the face of the coarse pendular nystagmus that is usually horizontal. Totally blind children may also have repetitive head movements that may be a form of self-stimulation (Fazzi et al. 1999). The term *bobble-head doll syndrome* was introduced by Benton and subsequent reports have not improved upon the clinical description (Benton et al. 1966). Two children were described with "*to-and-fro bobbing or nodding of the head and trunk. The movement is reminiscent of that seen in dolls with weighted heads resting on a coiled spring.*" Both children had cysts in relation to the third ventricle with associated hydrocephalus. With the first child it was noted that: "*The head and trunk were involved in a slow, 2- to 3-per-second nodding, forward-and-backward tremor which was evident whenever she sat or stood without support. Each excursion of the trunk from the back to forward position or in the reverse was associated with a full cycle of head movement-extension, flexion, and extension.*" The head movements could be inhibited voluntarily for brief periods and disappeared on intended movement and at complete rest (This breaks the rule that the ability to stop a movement with distraction generally means there is no serious underlying pathology). Subsequent reports have confirmed that is typically caused by mass lesions around the third ventricle causing CSF obstruction.

Nellhaus (1983) lists hypomagnesemia, uremia, thyrotoxicosis, citrullinemia, antihistamine drugs, antipsychotic agents, and amphetamine as other causes of head tremor in childhood. He also recalled a child with post-encephalitic Parkinsonism who had a transient head tremor. (In older children, head nodding can also be seen during absence seizures, but the seizure is usually the dominant clinical feature.)

In *spasmus nutans* there is rapid head nodding, nystagmus (often monocular), and head tilt or torticollis. The nystagmus and head shaking typically occur in bursts lasting 5–30 s in association with fixation (Aicardi 1998). Classically described as a benign phenomenon, at times it is caused by an anterior visual pathway glioma (Anthony et al. 1980).

Head Stereotypies Some infants and young children have rhythmic side to side head movements that can persist for years with no other signs present. Sometimes these will be more obvious when the child is otherwise unoccupied and the movements may disappear with intense concentration or if the child is asked to stop the movement. However, this is not always the case. This appears to be an unusual

form of *stereotypy*. Hottinger-Blanc et al. described eight children with onset in the first year of life of an isolated head stereotypy (Hottinger-Blanc et al. 2002). All were of normal intelligence but were clumsy and two had abnormalities of cerebellar development. DiMario (2000) described four children with persistent head tremor with no cause identified. Three of these four children had shuddering attacks prior to the development of the head movements, giving further credence to the possibility that the movements represent a stereotypy (see Sect. 14.6.4).

Because of the number of potentially serious underlying causes, neuroimaging should be considered in children with head tremors.

14.6.4 Shuddering Attacks

In shuddering attacks, the infant often stiffens and the body trembles. The typical description is that it is as though water has been poured down the child's back. A large number of episodes can occur per day. In the initial description (Vanasse et al. 1976), it was thought these attacks might represent an early presentation of essential tremor, but subsequent studies have not supported this. (As they grew older most of the children described in this paper also developed tics.) Shuddering attacks may be another form of stereotypy.

14.7 Childhood and Beyond

A common situation is the child thought to have a tremor at home or school but when examined, there is either nothing to see or there are intermittent, subtle, and not uncommonly irregular finger movements. Investigations such as thyroid function tests, copper and caeruloplasmin, a urine metabolic screen, and neuroimaging are normal. Whether this represents enhanced physiological tremor, the earliest presentation of essential tremor or a mild form of dystonic tremor without other signs of dystonia is unclear. However, it is prudent to follow these children over time.

14.7.1 Enhanced Physiological Tremor

The amplitude of physiological tremor is determined by the degree of synchronization of motor unit discharges modulated by muscle spindle 1a afferents (Fahn and Jankovic 2007a, b). This process is exaggerated during anxiety and exercise and other conditions that enhance peripheral β adrenergic activity. Probably the commonest example of enhanced physiological tremor in childhood is the child

with severe asthma receiving intensive bronchodilator therapy. Other causes include thyrotoxicosis, hypoglycemia, withdrawal syndromes, and a pheochromocytoma. In a recent review, 110 cases of acquired thyrotoxicosis were identified over a 1-year period in the United Kingdom and Ireland (Williamson and Greene 2010). Tremor, identified in 58% of children, was the second most common sign with only goiter (78%) more common. As the data were derived from a surveillance program, no further details of the tremor were provided. Fernandez-Alvarez and Aicardi (2001, p. 44) report that they have seen children with intellectual handicap whose exaggerated physiological tremor was so intense in stressful situations that the tremor was more disabling than the intellectual problems.

14.7.2 Essential Tremor

Essential tremor (ET) is typically a bilateral, largely symmetric postural, or kinetic tremor involving mainly the arms (Deuschl et al. 1998). The head and voice may also be involved. An epidemiological study from Rochester found that the annual incidence of ET in the 0–19 years age group was 2.3 per 100,000 (Rajput et al. 1984). In contrast in the over-80 age group, the annual incidence was 84.3 per 100,000. There is a paucity of literature on ET in the first decade. Reflecting this, we have seen only a small number of children who have the typical features of ET. Further, despite the frequency of ET in adults and its apparently dominant inheritance, genetic studies have failed to identify a single causative gene. It seems likely that it is a heterogeneous condition. This is supported by the clinical variability. Some patients have additional cerebellar signs such as difficulty with tandem gait and the finger–nose test (Elbe and Deuschl 2011). Some adult patients with advanced disease develop a resting tremor without other evidence of Parkinsonism (Deuschl and Elbe 2009). However, this is not seen in the absence of an action tremor.

In the study of Louis of 19 children with ET, the mean age at the time of publication was 12.7 years, and the median age of onset was 7 years (Louis et al. 2001b). All had arm tremor. In most cases tremor was both with posture and with movement, and the latter was usually more pronounced. Problems occurred with hand shaking during tasks requiring precise motor control, drinking from a cup, and writing. Only one patient had head tremor. Four patients had received treatment at some time and this was usually propanolol. Jankovic described 39 patients, with a mean age at evaluation of 20 ± 14 years (Jankovic et al. 2004). The mean age of onset was determined to be around 8 years and there was also a male predominance. Forty-six percent had neurological co-morbidity with 11 patients (28%) having dystonia. Jankovic discussed the problem of referral bias in such studies emanating from units devoted to the study of movement disorders.

In a child suspected of having ET, as well as taking a careful family history, the parents should be examined. ET is typically improved by alcohol intake but this is not specific to ET. Other movement disorders may be alcohol responsive

including myoclonus dystonia, focal dystonias, task-specific dystonias, post-anoxic myoclonus, and tics (Mostile and Jankovic 2010).

It has been suggested that in the adolescent with ET where there is significant impairment (and no history of asthma), propranolol can be started in a dose of 30 mg per day (Keller and Dure 2009). The dose may subsequently need to be increased to 60–80 mg per day. Long acting preparations may have a role.

A number of conditions can produce a tremor that may be mistaken for ET including hydrocephalus, hereditary and motor sensory neuropathies, Wilson's disease, and Klinefelter syndrome (Fernandez-Alvarez and Aicardi 2001). Hyperthyroidism should also be considered.

14.7.3 Drugs and Toxins

Drugs commonly give rise to tremor in adults. The causes include alcohol withdrawal, neuroleptics, lithium, and tricyclic antidepressants (Tolosa et al. 1998). Drugs that cause tremor in both children and adults include salbutamol and other bronchodilators, and valproic acid. The tremor produced by valproic acid appears to be dose related and is similar to essential tremor (Hyman et al. 1979). Abuse of cocaine and other stimulants may produce tremor as well as tics, chorea, and dystonia (Brust 2010). Chronic inhalation of petrol and organic solvents can also cause a tremor as well as other neurological disturbance (Kaelan et al. 1986; Lazar et al. 1983). Lewis reported the case of an elderly couple who suddenly developed a "severe muscle tremors" after consuming a soup contaminated by the fungus *Penicillium crustosum* which produces the mycotoxin penitrem A (Lewis et al. 2005). This is a widely distributed fungus that causes spoilage of a wide range of foods and is therefore a risk for children as well as adults. Serotonin syndrome comes into the differential diagnosis of acute poisonings associated with jerkiness but the movement disorder is generally described as myoclonus (Kipps et al. 2005).

14.7.4 Hydrocephalus

Older children with "arrested" hydrocephalus may present with a tremor similar to essential tremor. The presence of macrocephaly is an important diagnostic clue.

14.7.5 Palatal Tremor

Palatal tremor was previously called palatal myoclonus and is classified into symptomatic and essential forms (Deuschl et al. 1994). Symptomatic palatal tremor is usually seen in adults and results from a stroke or other lesion involving the

dentato-olivary pathway. There may be hypertrophy of the inferior olivary nucleus which can be demonstrated on MRI scans. The palatal movement is produced by contraction of levator veli palatine. There may be widespread jerks involving muscles of many areas including the face and diaphragm which are synchronous with the palatal movements. There are no ear clicks. In essential palatal tremor, the movements result from contraction of tensor veli palatine. Ear clicks are commonly present and the movements are restricted to the palate. There are no abnormalities of the inferior olivary nucleus. Campistol-Plana reported four children with a mean age of 6 years with essential palatal tremor and found there was a good response to piracetam (Campistol-Plana et al. 2006). Some cases of essential palatal tremor appear to be psychogenic.

14.7.6 Holmes Tremor Following Head Injury

Probably first described by Kremer et al. in 1947, the delayed onset of tremor following severe head injury can be a particularly disabling condition. Andrew reviewed eight cases where the mean age at the time of the head injury was 14 years (Andrew et al. 1982). The patients were comatose after the head injury, usually for several weeks. A third nerve palsy suggesting brainstem injury was common. Tremor developed between 1 and 18 months after the initial injury. It was unilateral and often the emergence of tremor coincided with an improvement in the initial weakness of the limb. In five patients the tremor was so severe that the limb was useless. It was present at rest in three patients and in all was made worse by attempts at movement. In six patients it was felt there were also myoclonic jerks. In one patient, the movements were so wild they suggested hemiballismus and another would sit on her hand to control the limb. As well as cranial nerve palsies there were often other signs such as dysarthria. In this series the tremor of each patient improved after stereotaxic thalamotomy. The ventral intermediate nucleus was the primary target but often multiple lesions were required. There have been a number of subsequent case reports suggesting deep brain stimulation can also be effective (Peker et al. 2008). Levetiracetam has also been reported to improve Holmes tremor (Ferlazzo et al. 2008).

14.7.7 Wilson's Disease

Wilson's disease in childhood usually presents with liver failure or a hemolytic anemia and a neurological presentation is rare. Nevertheless as a treatable condition it must be always considered in the differential diagnosis of tremor. It has been said that every patient with Wilson's disease has his or her own unique movement disorder. The classic tremor is the high amplitude proximal tremor seen when the fingers are held close to the nose with the shoulders abducted and elbows flexed—

the so-called "*wing-beating*" tremor. Patients with Wilson's disease may also exhibit a rest tremor, intention tremor, and an action tremor when trying to write or drink from a cup (Hoogenraad 1996).

14.7.8 Hereditary Geniospasm

Hereditary geniospasm (literally chin spasm) or chin quivering is a highly distinctive disorder involving the mentalis muscle of the chin. Typically, there is "up and down" movement of the chin with quivering of the lip. The movements do not have the rhythmicity of tremor but tend to come in irregular bursts. They tend to be worse with anxiety. The movements can be quite strong and may give the impression that they emanate from the jaw. If there is significant social disability from the movements, botulinum toxin injections can quell them. In some families as well as the cosmetic problems severe tongue lacerations from nocturnal tongue biting can be a significant cause of disability (Jarman et al. 1997). The inheritance is autosomal dominant.

14.7.9 Spinal Muscular Atrophy and Neuropathies

Moosa and Dubowitz (1973) citing the works of others who had gone before them emphasized the diagnostic value of the presence of a tremor in children with what we now call Types II and III spinal muscular atrophy (SMA). They described 13 children with SMA and tremor. In only two was the tremor obvious. In the others it represented a subtle but important sign. They found limb tremor to be more common than fasciculations of the tongue, a better known sign of SMA. The tremor was an action tremor present with outstretched hands or noted during the manipulation of toys. Similar movements can also be seen in children with congenital neuropathies (Yiu et al. 2011) and in chronic inflammatory demyelinating neuropathy (Ouvrier et al. 1999). The movements are due to the firing of large motor units in a muscle with decreased numbers of motor units (Riggs et al. 1983) and are a sign of chronic denervation and reinnervation. They are not entirely rhythmic and terms such as *contraction fasciculations* (Denny-Brown and Pennybaker 1938) have been used. Spiro (1970) describing children with SMA, called these movements *minipolymyoclonus*, a term coined by his colleague Dennis Giblin and now confusing as it was subsequently used in the setting of epileptic myoclonus (Wilkins et al. 1985). Riggs suggested *contraction pseudotremor of chronic denervation* might be the best term.

14.7.10 Glut-1 Deficiency

Glucose transporter 1 deficiency is due to a heterozygous mutation in the glucose transporter 1 gene. Early reports defined a syndrome characterized by the onset of seizures early in infancy, often with associated intellectual handicap and microcephaly (De Vivo et al. 1991). Over time, it has become clear that this condition can present with movement disorders including exercise-induced dykinesia, action dystonia, ataxia, tremor, chorea, and myoclonus (Pons et al. 2010). Roubergue and colleagues have described a woman who presented at 11 years of age with a dystonic tremor (Roubergue et al. 2011). Her mother was also found to have a dystonic tremor with onset in her teenage years. Both were heterozygous for a thr137ala missense mutation in the Glut-1 gene. The index case had a generalized action tremor which interfered with writing and the ability to carry a glass of water. Her voice was jerky and "slight postural and action tremor" were observed in the upper limbs. A tremor study supported the diagnosis of dystonic tremor. On careful questioning, both also had action dystonia. Neither agreed to be treated with either carbamazepine or the ketogenic diet. A literature review by Roubergue revealed 12 other cases where tremor was associated with Glut-1 deficiency and in 2, tremor was the only constant symptom.

14.7.11 Segawa Disease

Although typically presenting as leg dystonia with diurnal variation, children of 10 years and older with GTP cyclohydrolase deficiency may have a postural tremor. Segawa observed that a postural hand tremor was present in 14 of 28 gene-proven patients (Segawa et al. 2003). He believes that a Parkinsonian resting tremor does not occur in this condition.

14.7.12 Epilepsia Partialis Continua

In EPC, there is continuous focal jerking of a body part, usually localized to a distal limb, occurring over hours, days, or even years (Cockerell et al. 1996). Sometimes it ceases in sleep. Usually there is sufficient variability in timing and amplitude for the movements to be recognized as not a tremor but there is a report in the adult literature of a man with EPC initially felt to have a Parkinsonian tremor (Al-Hayk and LeDoux 2003). There are many causes of EPC but if it is due to a focal cortical dysplasia, there may be mainly localized jerking and no alteration of consciousness causing potential diagnostic difficulty. Other causes include Rasmussen syndrome, viral encephalitis including measles and POLG mutations (Cardenas and Amato

2010). In these conditions, there is usually alteration of consciousness and intense seizure activity taking the diagnosis away from the possibility of a tremor.

14.7.13 Familial Cortical Myoclonic Tremor with Epilepsy

It is a rare disorder which can be mistaken for essential tremor (van Rootselaar et al. 2005). Although more common in adults, the onset can be as early as 10 years of age. Typically there is no tremor at rest but the tremor appears with posture and movement. In the video of a case shown by van Rootselaar et al. the tremor was mainly present in the fingers and hands. It was high frequency, semirhythmic, and of varying amplitude. It was stimulus sensitive and neurophysiology was consistent with a cortical reflex myoclonus. The condition shows autosomal dominant inheritance. Tremor is usually the first symptom with epilepsy developing over time in around 80% of affected individuals.

14.7.14 Task-Specific Tremors

In 1979, Rothwell et al. described a male who presented at the age of 12 years with jerking of the right forearm on writing (Rothwell et al. 1979). Although both myoclonus and dystonic jerking was considered as possible causes, electrophysiological studies suggested that the jerks were due to short bursts of tremor. It was felt that he suffered from a primary writing tremor (PWT). PWT is the commonest task-specific tremor in adults. It has been subdivided into two types depending on whether tremor appeared during writing alone or while writing and adopting the hand position used in writing (Bain et al. 1995). It is rare in childhood and in our experience a more common situation is the older child with DYT1 dystonia presenting with writing difficulties due to dystonic tremor. Subsequently the dystonia spreads to involve other parts of the body.

14.7.15 Gene Microdeletions and Microduplications

There is emerging evidence that microdeletions or microduplications of whole genes or parts of genes are important causes of neurological and neurodevelopmental syndromes such as autism. Methods such as Comparative Genomic Hybridization microarray are replacing the karyotype as an investigation of the child with autism (Miller 2010). It is becoming increasingly clear that there will also be a role for such techniques in the investigation of children with movement disorders, especially if they are complex and there are associated learning difficulties or intellectual handicap (Bodzioch et al. 2011; Dale et al. 2011).

14.7.16 Psychogenic Tremor

Psychogenic tremors are here discussed last, the traditional position for psychogenic problems in publications by neurologists. However, they are much more common in childhood than many of the conditions discussed above. The features of psychogenic tremor described in adults are also seen in children. It is often present at rest, with posture and with movement (Fahn and Jankovic 2007b). It tends to vary in frequency, amplitude, and location especially if the patient is engaged in conversation. A gross psychogenic tremor may disappear if the child attempts to do mental arithmetic at a level that challenges her or him. Entrainment may also be present, that is, if the examiner moves his or her hand at a certain frequency, the tremor of the patient may change to this same frequency. The subject of psychogenic disorders is huge and beyond the scope of this chapter. A taste of the complexity of the situation is given by the following observation from the Consensus Statement: "*In psychogenic tremor, the tremor may be produced voluntarily, although awareness that the tremor is voluntary may be subconscious*" (Deuschl et al. 1998).

14.7.17 Myogenic Tremor

Myogenic tremor is a new tremor entity, first reported in 2019 and likely originates in the muscle itself (Schaefer et al. 2021). It presents as a high frequency, postural, and kinetic tremor with onset in infancy. Myopathies affecting the contractile elements, in particular myosin and a myosin-associated protein, have been associated with myogenic tremor. The generator of the tremor is presumably located in the sarcomere, with propagation and amplification of sarcomeric oscillatory activity through the CNS reflex loops, similarly to the neuropathic tremor.

References

Aicardi J. Disorders of the ocular motor and visual functions. In: Diseases of the nervous system in childhood. 2nd ed. London: Mac Keith; 1998. p. 667–88.

Al-Hayk K, LeDoux MS. Epilepsia partialis continua mistaken for Parkinson's disease. Mov Disord. 2003;18:107.

Andrew J, Fowler CJ, Harrison MJG. Tremor after head injury and its treatment by stereotaxic surgery. J Neurol Neurosurg Psychiatry. 1982;45:815–9.

Anthony J, Ouvrier RA, Wise GA. Spasmus Nutans, a mistaken identity. Arch Neurol. 1980;37:373–5.

Bain PG, Findley LJ, Britton TC, et al. Primary writing tremor. Brain. 1995;118:1461–72.

Benton JW, Nellhaus G, Huttenlocher P, et al. The bobble-head doll syndrome. Report of a unique truncal tremor associated with third ventricular cyst and hydrocephalus in children. Neurology. 1966;16:725–9.

Bodzioch M, Lapicka-Brodzioch K, Rudzinska M, et al. Severe dystonic encephalopathy without hyperphenylalaninemia associated with an 18-bp deletion within the proximal GCH1 promotor. Mov Disord. 2011;26:337–40.
Brun L, Ngu LH, Keng WT, et al. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. Neurology. 2010;75:64–71.
Brust JCM. Substance abuse and movement disorders. Mov Disord. 2010;25:2010–20.
Campistol-Plana J, Majumdar A, Fernández-Alvarez E. Palatal tremor in childhood: clinical and therapeutic considerations. Dev Med Child Neurol. 2006;48:982–4.
Canavese C, Ciano C, Zorzi G, et al. Polymyography in the diagnosis of childhood onset movement disorders. Eur J Paediatr Neurol. 2008;12:480–3.
Cardenas JF, Amato RS. Compound heterozygous polymerase gamma gene mutation in a patient with Alpers disease. Semin Pediatr Neurol. 2010;17:62–4.
Cockerell OC, Rothwell J, Thompson PD, et al. Clinical and physiological features of epilepsia partialis continua. Cases ascertained in the UK. Brain. 1996;119:393–407.
Coulter DL, Allen RJ. Benign neonatal sleep myoclonus. Arch Neurol. 1982;39:191–2.
Dale RC, Nasti JJ, Peters GB. Familial 7q21.3 microdeletion involving epsilon-sarcoglycan causing myoclonus dystonia, cognitive impairment, and psychosis. Mov Disord. 2011;26(9):1774–5.
de Rijk-Van Andel JF, Gabreels FJ, Van Den Heuvel LP, et al. L-dopa responsive infantile hypokinetic rigid parkinsonism due to tyrosine hydroxylase deficiency. Neurology. 2000;55:1926–8.
De Vivo D, Trifiletti RR, Jacobson RI, et al. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhacia, seizures and developmental delay. NEJM. 1991;325:703–9.
Denny-Brown D, Pennybaker JB. Fibrillation and fasciculation in voluntary muscle. Brain. 1938;61:311–34.
Deuschl G, Elbe R. Essential tremor – neurodegenerative or nondegenerative disease towards a working definition of ET. Mov Disord. 2009;24:2033–41.
Deuschl G, Toro C, Valls-Solé J, et al. Symptomatic and essential palatal tremor. 1. Clinical, physiological and MRI analysis. Brain. 1994;117:775–88.
Deuschl G, Bain P, Brin M, et al. Consensus statement of the movement disorder society on tremor. Mov Disord. 1998;13(suppl 3):2–23.
DiMario FJ. Childhood head tremor. J Child Neurol. 2000;15:22–5.
Elbe R, Deuschl G. Milestones in tremor research. Mov Disord. 2011;26:1096–105.
Emery ES, Homans AC, Colleti RB. Vitamin B12 deficiency: a cause of abnormal movements in infants. Pediatrics. 1997;99:255–6.
Factor SA, Coni RJ, Cowger M, Rosenblum EL. Paroxysmal tremor and orofacial dyskinesia secondary to a biopterin synthesis deficit. Neurology. 1991;41:930–2.
Fahn S, Jankovic J. Tremors diagnosis and management. In: Principles and practice of movement disorders. Philadelphia: Churchill Livingstone; 2007a. p. 451–78.
Fahn S, Jankovic J. Psychogenic movement disorders. In: Principles and practice of movement disorders. Philadelphia: Churchill Livingstone; 2007b. p. 597–611.
Fazzi E, Lanners J, Danova S. Stereotyped behaviours in blind children. Brain and Development. 1999;21:522–8.
Ferlazzo E, Morgante F, Rizzo V, et al. Successful treatment of Holmes tremor by levetiracetam. Mov Disord. 2008;23:2101–3.
Fernandez-Alvarez E, Aicardi J. Movement Disorders with tremor as the main clinical manifestation. In: Movement disorders in children. London: MacKeith Press; 2001. p. 43–62.
Graham SM, Arvela OM, Wise GA. Long term neurological consequences of nutritional B 12 deficiency in infants. J Pediatr. 1992;121:710–4.
Grattan-Smith PJ, Wilcken B, Procopis PG, Wise GA. The neurological syndrome of infantile cobalamin deficiency: developmental regression and involuntary movements. Mov Disord. 1997;12:39–46.
Grattan-Smith PJ, Wevers RA, Steenbergen-Spanjers GC. Tyrosine hydroxylase deficiency: clinical manifestations of catecholamine insufficiency in infancy. Mov Disord. 2002;17:354–9.

Higginbottom MC, Sweetman L, Nylian WL. A syndrome of methylmalonic aciduria, homocystinuria, megaloblastic anemia and neurological abnormalities in a vitamin B 12-deficient breast fed infant of a strict vegetarian. N Engl J Med. 1978;299:317–23.
Holmes G. On certain tremors in organic cerebral lesions. Brain. 1904;27:327–75.
Hoogenraad TU. Major problems in neurology, Vol 30, Wilson's disease, vol. 30. London: WB Saunders; 1996. p. 85.
Hottinger-Blanc PM, Ziegler AL, Deonna T. A special type of head stereotypies in children with developmental (?cerebellar) disorder: description of 8 cases and literature review. Eur J Paediatr Neurol. 2002;6:143–52.
Hyman NM, Dennis PD, Sinclair GA. Tremor due to sodium valproate. Neurology. 1979;29:1177–80.
Jadhav M, Webb JKG, Vaishnava S, Baker SJ. Vitamin B12 deficiency in Indian infants. Lancet. 1962;2:903–7.
Jankovic J, Madisetty J, Vuong KD. Essential tremor among children. Pediatrics. 2004;114:1203–5.
Jarman PR, Wood NW, Davis MT, et al. Hereditary geniospasm: linkage to chromosome 9q13-q21 and evidence for genetic heterogeneity. Am J Hum Genet. 1997;61:928–33.
Kaelan C, Harper C, Viera BI. Acute encephalopathy and death due to petrol sniffing: neuropathological findings. Aust NZ J Med. 1986;16:804–7.
Kahn E, Falcke HC. A syndrome simulating encephalitis affecting children recovering from malnutrition (kwashiorkor). J Pediatr. 1956;49:37–45.
Keller S, Dure LS. Tremor in childhood. Semin Pediatr Neurol. 2009;16:60–70.
Kipps CM, Fung VS, Grattan-Smith P, et al. Movement disorder emergencies. Mov Disord. 2005;20:322–34.
Korenke GC, Christian HJ, Hyland K, et al. Aromatic L-amino acid decarboxylase deficiency: an extrapyramidal movement disorder with oculogyric crises. Eur J Pediatr Neurol. 1997;2–3:67–71.
Lazar RB, Ho SU, Melen O, Daghestani AN. Multifocal central nervous system damage caused by toluene abuse. Neurology. 1983;33:1337–440.
Lewis PR, Donoghue MB, Hocking A, et al. Tremor syndrome associated with fungal toxin: sequelae of food contamination. Med J Aust. 2005;182:582–4.
Louis ED, Ferreira JJ. How common is the commonest adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010;25:534–41.
Louis ED, Ford B, Frucht S, et al. Risk of tremor and impairment from tremor in relatives of patients with essential tremor: a community-based family study. Ann Neurol. 2001a;49:761–9.
Louis ED, Dure LS, Pullman S. Essential tremor in childhood: a series of nineteen cases. Mov Disord. 2001b;16:921–3.
Manto M. Tremorgenesis: a new conceptual scheme using reciprocally innervated circuit of neurons. J Transl Med. 2008;6:71.
Marsden CD. Origins of normal and pathological tremor. In: Findlay LJ, Capildeo R, editors. Movement disorders: tremor. New York: Oxford University Press; 1984. p. 37–84.
Miller DT. Genetic testing for autism: recent advances and clinical implications. Expert Rev Mol Diagn. 2010;10:837–40.
Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. Neurology. 1987;37:1837–44.
Moosa A, Dubowitz V. Spinal muscular atrophy in Childhood. Two clues to clinical diagnosis. Arch Dis Child. 1973;48:386–8.
Mostile MD, Jankovic J. Alcohol in essential tremor and other movement disorders. Mov Disord. 2010;25:2274–84.
Nellhaus G. Abnormal head movements of young children. Dev Med Child Neurol. 1983;25:384–9.
Neville BGR, Parascandalo R, Farrugia R, Felice A. Sepiapterin reductase deficiency: a congenital dopa-responsive motor and cognitive disorder. Brain. 2005;128:2291–6.

Ouvrier RA, McLeod JG, Pollard JD. Chronic inflammatory demyelinating polyradiculoneuropathy. In: Peripheral neuropathy in childhood. 2nd ed. London: MacKeith Press; 1999. p. 55–66.
Peker S, Isik U, Akgun Y, Ozek M. Deep brain stimulation for Holmes' tremor related to a thalamic abscess. Childs Nerv Syst. 2008;24:1057–62.
Pons R, Collins A, Rotstein M, et al. The spectrum of movement disorders in Glut-1 deficiency. Mov Disord. 2010;25:275–81.
Rajput AH, Offord KP, Beard CM, et al. Essential tremor in Rochester, Minnesota; a 45 year study. J Neurol Neurosurg Psychiatry. 1984;47:466–70.
Riggs JE, Gutman L, Schochet S. Contraction pseudotremor of chronic denervation. Arch Neurol. 1983;40:518–9.
Rothwell JC, Traub MM, Marsden CD. Primary writing tremor. J Neurol Neurosurg Psychiatry. 1979;42:1106–14.
Roubergue A, Apartis E, Mesnage V, et al. Dystonic tremor caused by mutation of the glucose transporter gene GLUT1. J Inherit Metab Dis. 2011;34:483–8.
Schaefer J, Saak A, Bönnemann CG, Jackson S. Myogenic tremor - a novel tremor entity. Curr Opin Neurol. 2021;34(5):706–13.
Scher MS. Seizures in the newborn infant. Diagnosis, treatment and outcome. Clin Perinatol. 1997;24:735–72.
Schwingenschuh P, Ruge D, Edwards MJ, et al. Adult onset asymmetric upper limb tremor misdiagnosed as Parkinson's disease: a clinical and electrophysiological study. Mov Disord. 2010;25:560–9.
Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanasine triphosphate cyclohydrolase 1 deficiency (Segawa Disease). Ann Neurol. 2003;54(Suppl 6):S32–45.
Singer HS, Mink JW, Gilbert DL, Jankovic J (eds). Tremor. In: Movement disorders in childhood. Philadelphia: Saunders Elsevier; 2010a. p. 129–138.
Singer HS, Mink JW, Gilbert DL, Jankovic J (eds). Stereotypies. In: Movement disorders in childhood. Philadelphia: Saunders Elsevier; 2010b. p. 56–65.
Snyderman SE, Sansaricq C, Pulomones MT. Successful long term therapy of biopterin deficiency. J Inherit Metab Dis. 1987;10:260–6.
Spiro AJ. Minipolymyoclonus: a neglected sign in childhood spinal muscular atrophy. Neurology. 1970;20:1124–6.
Tolosa E, Koller WC, Gerdhanik OS. Differential diagnosis and treatment of movement disorders. London: Butterworth-Heinemann; 1998. p. 68.
Van Rootselaar A-F, van Schaik IN, van der Maagdenberg AM, et al. Familial cortical myoclonic tremor with epilepsy: a single syndromic classification for a group of pedigrees bearing common features. Mov Disord. 2005;20:665–73.
Vanasse M, Bedard P, Andermann F. Shuddering attacks in children: an early clinical manifestation of essential tremor. Neurology. 1976;26:1027–30.
Wilkins DE, Hallett M, Erba G. Primary generalised epileptic myoclonus: a frequent manifestation of minipolymyoclonus of central origin. J Neurol Neurosurg Psychiatry. 1985;48:506–16.
Willemsen MA, Verbeek MM, Kamsteeg EJ. Tyrosine hydroxylase deficiency: a treatable disorder of brain catecholamine biosynthesis. Brain. 2010;133:1810–22.
Williamson S, Greene SE. Incidence of thyrotoxicosis in children: a national population based study in the UK and Ireland. Clin Endocrinol. 2010;72:358–63.
Yiu EM, Geevasinga N, Nicholson GA, et al. A retrospective review of X-linked Charcot-Marie-Tooth disease in childhood. Neurology. 2011;76:461–6.

Chapter 15
Metabolic Causes of Tremor

Diksha Mohanty and Peter Hedera

Abstract Metabolic causes of tremor include systemic metabolic, neurometabolic, and endocrine abnormalities. These can be diagnosed by identification of specific biochemical abnormalities detected by laboratory assays from serum or cerebrospinal fluid. The recognition of diagnostic biochemical or endocrinological abnormalities causing tremor is important because many conditions have specific treatments available that can correct or mitigate tremor. In this chapter we review most common causes of tremor that can be evaluated by laboratory-based investigation, including recommended biochemical tests, phenomenology of tremor and other neurologic abnormalities, and available therapies beyond symptomatic therapy. We emphasize the treatable causes because the delayed diagnosis may have very negative impact on the prognosis and therapeutic outcomes. We did not include drug and external toxin-induced causes of tremor in this chapter.

Keywords Metabolic cause of tremor · Endocrine cause of tremor · Wilson's disease · Cerebrotendinous xantomatosis · Niemann-Pick disease type C

15.1 Introduction to Metabolic Causes of Tremors

Tremor syndromes are usually diagnosed based on their typical clinical presentation, including the presence of additional neurologic and systemic manifestations. Most common causes of tremor, including Parkinson's disease and essential tremor, are associated with neurodegenerative conditions (see dedicated chapters in this volume). Currently, there are no established biochemical markers that would routinely facilitate the diagnosis in neurodegenerative causes of tremor.

However, another important group of conditions inducing tremor are metabolic causes. These can be linked to specific biochemical abnormalities, which can

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be detected by laboratory assays. The identification of specific biochemical or endocrinological abnormalities causing tremor is important because many times the specific treatments can correct or mitigate tremor, rather than being only limited to symptomatic therapy of tremor.

Etiology of metabolic causes of tremors may be broadly divided into organ dysfunction, endocrinologic abnormalities, electrolyte disturbances, and inborn errors of metabolism. Tremor phenomenology varies based on pathophysiology of disease. This review is focused on systemic metabolic, neurometabolic, and endocrine causes of tremor. We did not include drug and external toxin-induced causes of tremor. Furthermore, we emphasize the treatable causes because the delayed diagnosis may have very negative impact on the prognosis and therapeutic outcomes.

15.2 Hypoglycemia

Hypoglycemia has been defined as an abnormally low plasma glucose concentration, typically below $\leq$70 mg/dL (3.9 mmol/L). This may occur due to an excess of insulin due to insulinomas, functional β-cell disorders, or factitious hyperinsulinemia. Alternatively, it may be caused by a defective glucose counter-regulation pathways such as gluconeogenesis or glycogenolysis, secondary to other metabolic disorders. An initial diagnosis may be established by the Whipple's triad which consists of a low plasma glucose concentration, clinical manifestations of hypoglycemia, and their resolution with administration of glucose. While common in patients with Type 1 and 2 diabetes mellitus, it is commonly encountered in patients who do not have a prior diagnosis of diabetes. Causes include medications, bariatric surgery, critical illnesses, malnutrition, adrenal insufficiency, and non-islet cell tumors. Hypoglycemia can also follow bariatric surgery.

Hypoglycemia presents with autonomic and neuroglycopenic symptoms. Tremors in hypoglycemia are co-existent with other symptoms of autonomic failure such as lightheadedness, sweating and headaches, nausea, vomiting (Zahed et al. 2020). Symptoms are thought to be secondary to activation of regions of the brain such as the medial pre-frontal cortex, following the activation of hypothalamus in hypoglycemia (Cryer 2005). This type of tremor is classified as an enhanced physiologic tremor. It is characterized by symmetric involvement of upper extremities, with low amplitude and high frequency tremor ranging from 8 to 12 Hz (Lenka and Jankovic 2021).

Evaluation of hypoglycemia includes review of medications and laboratory or imaging to establish primary etiology (Bansal and Weinstock 2000). Testing should be timed during development of symptoms or in setting of prolonged supervised fasting. Treatment involves management of determined underlying cause after detailed evaluation. Resolution of tremor occurs with normalization of blood glucose level.

15.3 Hyperthyroidism

Hyperthyroidism may be caused by endogenous or exogenous causes of thyroid hormone production. Endogenous etiologies include autoimmunity such as Graves' disease or hyperplasia of thyroid tissue unregulated by feedback from thyroid-stimulating hormone (TSH). Exogenous modes of hormone production include hormone-producing masses that stimulate TSH-receptors, which in turn upregulates thyroid hormone production. Other etiologies include thyroiditis secondary to radiation or chemical toxicity.

A fine tremor with low amplitude and high frequency is associated with hyperthyroidism. This is classified as an enhanced physiological tremor with symmetric distribution in upper extremities. Tremors are co-existent with other symptoms caused by sympathetic overactivity such as heat intolerance, unintentional weight loss, tachycardia, arrhythmias, anxiety, and sweating (Lazarus et al. 1943). Patients with hyperthyroidism may also experience behavior changes such as restlessness and emotional lability. Graves' disease, the most frequent cause of hyperthyroidism, presents with unique clinical signs such as ophthalmopathy and infiltrative dermopathy. Hyperthyroidism has also been found to exaggerate other pre-existing tremors, such as parkinsonian tremor, by similar mechanisms (Kim et al. 2005). Drug-induced thyrotoxicosis such as that caused by amiodarone or lithium salts may result in a similar tremor (Ishida et al. 2010).

Biochemical diagnosis entails serum concentrations of TSH along with free thyroxine (T4) or triiodothyronine (T3). Further investigation of the cause may include thyroid ultrasonography, radioactive iodine uptake studies, and detection of antibodies against thyroid receptors. Individuals with a normal or high radioiodine uptake are managed by thionamides such as methimazole, which interrupt synthesis of the hormone in the body. When radioiodine uptake is absent, suggesting inflammatory destruction of thyroid tissue due to exogenous production of the hormone, underlying cause must be determined and managed.

15.4 Pheochromocytoma

Catecholamine-secreting tumors in the adrenal medulla are called pheochromocytomas whereas those originating from sympathetic ganglia are paragangliomas, both of which exhibit similar clinical features. They are characterized by paroxysms of hypertension, with headache, sweating, and tachycardia. While most paragangliomas are sporadic, about 40% may be associated with familial disorders with bilateral gland tumors (Neumann et al. 2019). Pheochromocytoma may be associated with multiple endocrine neoplasia type 2 (MEN2), frequently with underlying RET mutation, or von Hippel-Lindau disease (VHL) with a loss-of-function variant in the VHL gene.

Tremor is a common presenting feature of pheochromocytoma, paragangliomas, and other epinephrine-producing neuroendocrine tumors, and are caused by catecholamine excess. These are also classified as enhanced physiologic tremors and occur with a low amplitude and high amplitude as with conditions described above. Tremors are associated with hypertension, which may be sustained or present with rapid swinging of blood pressures, hyperhidrosis, anxiety, palpitations, pallor, or nausea (Geroula et al. 2019).

Biochemical testing consists of detection of elevated catecholamines and metanephrines in 24-hour urine assays and plasma. Localization of tumors may require abdominal (computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography) or dedicated adrenal imaging. Genetic testing may be considered prior to surgical resection where feasible. In appropriate clinical context, evaluation of malignancy may be indicated in the presence of paragangliomas, along with long-term follow-up to identify metastatic disease.

15.5 Hepatic Encephalopathy

Hepatic encephalopathy is a neuropsychiatric complication of liver dysfunction, heralded by onset of disorientation or asterixis. It may also result from surgical transjugular intrahepatic porto-systemic shunting done in setting of refractory ascites or variceal bleeding secondary to underlying hepatic dysfunction. Encephalopathy may range from subtle to overt and may present as any combination of insomnia, hypersomnia, deficit in attention, reaction time, working memory, disorientation, or mood changes. Systemic signs of liver cirrhosis such as muscle wasting, jaundice, ascites, palmar erythema, edema, spider telangiectasias, and fetor hepaticus are clinical clues to diagnosis.

Chronic porto-systemic encephalopathy may present with coarse tremors with co-existent choreoathetoid movements. Asterixis, or flapping tremor or "negative myoclonus," is commonly recognized in mild to moderate grades of this condition, characterized by brief lapses in tone and thus maintained posture. This type of tremor is evident with outstretched and dorsiflexed hands but can affect any muscle group. A "metabolic tremor" may accompany severe hepatic dysfunction which is characterized by tremulousness (Timmermann et al. 2005). Grade IV hepatic encephalopathy presents with comatose states where asterixis is typically absent. Other neurological deficits such as bradykinesia, hyperreflexia, nystagmus, dysarthria, or ataxia may be co-existent. In addition, patients may exhibit a peripheral neuropathy with tremor.

Laboratory testing includes liver biochemical and synthetic function tests along with electrolyte levels. Brain imaging may reveal symmetric high signal within the insula, thalamus, and posterior limbs of the internal capsule, and cingulate gyrus. Diffuse cerebral edema can be seen in severe cases. MRI imaging is useful to rule out alternative etiology. Electroencephalographic activity is abnormal with diffuse

dysfunction in the form of decreased wave frequency and increased wave amplitude. Nerve conduction velocities are useful to establish the peripheral neuropathy.

Management of hepatic encephalopathy warrants treatment of a precipitating cause including medications, dehydration, gastrointestinal bleeding, increased dietary protein, constipation, thromboses in hepatic or portal veins or hepatocellular carcinoma. Medications such as lactulose, rifaximin, zinc are commonly used. Liver transplantation is warranted in cases of advanced cirrhosis with high mortality.

15.6 Hyponatremia

Hyponatremia is an acute and significant reduction in serum sodium concentration associated with lowering of serum osmolality, which results in osmotic cerebral edema. Causes of hyponatremia include renal failure, heart failure, cirrhosis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), or endocrine dysfunction such as severe hypothyroidism or primary adrenal insufficiency. Other causes include a high fluid diet such as "beer potomania" or water intoxication as in primary polydipsia or exercise-related water intake.

Systemic signs of nausea, muscle cramps, and malaise may present in mild to moderate cases. Severe hyponatremia manifests as headache, confusion, lethargy, seizures or may be life-threatening with coma and respiratory arrest at levels lower than 120 mEq/L. While sodium is not known to cause tremors directly, there is evidence of a rest tremor occurring as a long-term sequelae of extra-pontine myelinolysis (Maraganore et al. 1992). There is documented evidence of acute onset of parkinsonian symptoms with masked facies, shuffling gait, and a pill-rolling tremor accompanying this type of rest tremor in individuals with MRI changes following osmotic demyelination after rapid correction (Perikal et al. 2018; Sullivan et al. 2000). In severe hyponatremia, tremor may occur in rare cases associated with confusion, seizures, hallucinations, or hemiparesis (Ellis 1995).

Management consists of evaluation and treatment of underlying cause along with discontinuation of drugs that may contribute, such as thiazide or loop diuretics. Other measures are such as fluid restriction. Other than serum sodium and osmolality, urine sodium and osmolality, TSH, morning levels of serum cortisol may need to be tested. Goal correction rate should be 6 mEq/L/day to avoid osmotic demyelination and resultant central pontine myelinolysis from rapid correction of sodium. Administration of hypertonic saline may be considered in severe cases.

15.7 Hypomagnesemia

Acute magnesium deficiency may be precipitated by extraneous factors such as administration of epinephrine, stress such as extreme cold, injury, or surgery, particularly parathyroidectomy (Flink 1981). It may also occur secondary to low dietary

intake, refeeding syndrome, treatment of diabetic ketoacidosis, and increased renal or gastrointestinal losses. Chronic use of proton-pump inhibitors and alcohol abuse may lower serum concentrations of magnesium. Hypomagnesemia may be associated with polygenic heritability via multiple loci or familial renal magnesium wasting (Meyer et al. 2010). Gitelman (familial hypokalemia-hypomagnesemia) and Bartter (defect in the thick ascending limb of the loop of Henle) syndromes are commonly described forms of familial renal magnesium wasting and are caused by recessive mutations in SLC12A3 and CLCNKB respectively. EAST syndrome is an autosomal recessive disorder with mutation in KCNJ10 gene which presents in infancy with epilepsy, ataxia, sensorineural deafness, and a renal salt-losing tubulopathy, besides intellectual disability (Celmina et al. 2019).

Acute or chronic deficiency may be asymptomatic or present with mild non-specific symptoms such as anorexia or gastrointestinal disturbance. In other cases, it is characterized by hyperreactivity of the nervous system presenting with an action tremor of upper and lower extremities and mandible, myoclonic jerks, fasciculations, or spontaneous vertical downbeat nystagmus (Marse et al. 2020). Chvostek and Trousseau signs have also been described in this condition, which refer to facial twitching upon tapping over the facial nerve and carpopedal spasm upon applying an inflated sphygmomanometer cuff to the upper arm, respectively. In extreme cases, tetany, seizures, psychiatric disturbances, arrhythmias such as ventricular fibrillation which may cause sudden death (Espay 2014). Hypermagnesemia may present with severe asterixis in setting of chronic renal failure with severe toxicity leading to quadriparesis and respiratory insufficiency (Morimatsu et al. 2021).

Management includes intravenous administration of magnesium (4–8 gr per day; a pulse of 1–2 gr may be administered IV diluted in 100 mL of 5% dextrose) and treatment of underlying pathology. Multiple nephrotoxic medications may contribute to a low serum magnesium level and must be reviewed.

15.8 Hypermanganesemia

Manganese is a trace element vital for normal growth and development. “Manganism” is a spectrum of disorders resulting from manganese deposition in striatum, globus pallidus and substantia nigra, which involves motor dysfunction with neuropsychiatric and cognitive features. Acquired causes of elevated serum manganese include high dietary intake (foods rich in Manganese or consumption of well water), total parenteral nutrition or inhalational exposure. Occupational exposure in workers at steel or welding factories (Fell et al. 1996). It may produce asymmetric chorea with neurocognitive decline in multiple domains. A manganese-containing fungicide called maneb has been implicated in the pathogenesis of Parkinson’s disease.

Inborn errors of manganese metabolism have been identified linked to SLC30A10, SLC39A14, and SLC39A8. A homozygous deletion of SLC30A10 which is inherited autosomal recessively produces hypermanganesemia with dys-

tonia 1 (HMNDYT1), with whole-blood manganese concentration >2000 nmol/L. Deficiency of the gene has been shown to affect the basal ganglia in post-mortem studies, along with white matter gliosis and axonal loss of corticospinal tracts. Other systemic involvement in this condition includes blood dyscrasias and hepatomegaly. Clinical presentation includes a four-limb dystonia, dysarthria, gait impairment, fine tremor, and rigidity with impaired fine motor ability in children. Adults with the deletion evidenced parkinsonism but without tremor or dystonia, unresponsive to L-dopa treatment. In severe cases, it may cause spastic paraplegia (Tuschl et al. 1993a). Hypermanganesemia has also been associated with presence of biallelic pathogenic variants of SLC39A14 and is characterized by parkinsonian features including a resting tremor (Tuschl et al. 1993b).

Acquired hypermanganesemia may present with extrapyramidal symptoms such as parkinsonian tremor, dyskinesia, dystonia, or akathisia. Systemic symptoms such as headache or vomiting may be present (Ghosh et al. 2020). MRI imaging may demonstrate symmetrically increased signal intensity in basal ganglia on T1-weighted imaging.

Treatment of HMNDYT1 involves chelation therapy with edetate calcium disodium and tetrabenazine, along with iron supplementation, besides physical rehabilitation. Avoidance of foods rich in manganese such as nuts, saffron, tea, dark chocolate, and seeds is typically advised.

15.9 Primary Hyperparathyroidism and Hypoparathyroidism

Hyperparathyroidism, or elevated serum concentration of intact parathyroid hormone (PTH) is usually detected during evaluation of asymptomatic hypercalcemia. It may also occur in a rare autosomal dominant disorder called familial hypocalciuric hypercalcemia (FHH) occurring with calcium-sensing receptor (CaSR) mutation. Parathyroid tumors may cause primary hyperparathyroidism in sporadic tumors with cyclin D1/PRAD1 mutations or familial tumors as in MEN1 mutations in multiple endocrine neoplasia type 1 syndrome or MEN2A. A familial type of primary hyperparathyroidism (PHPT) may also present isolated from other endocrine disorders and is called familial isolated hyperparathyroidism (FIHP).

PHPT is commonly asymptomatic but may rarely present with acute crisis or a PHPT with normal serum calcium concentration. Clinical manifestations include malaise, depression, cognitive or neuromuscular dysfunction, hypertension, ventricular hypertrophy, skeletal deformities called osteitis fibrosa cystica, and nephrolithiasis. Parathyroid adenomas may be asymptomatic or present as neck mass. A parkinsonian tremor may present along with cognitive decline, proximal muscle weakness, and generalized fatigue, particularly in hypercalcemia (Ishii 2017).

Diagnosis is established by testing serum concentrations of calcium, PTH, 25-hydroxyvitamin D, and 24-hour urine calcium concentration. Candidacy for surgery is determined by severity of renal or cardiac disease. Close observation is adopted for milder forms of disease. There is insufficient data on long-term benefit of bisphosphonate therapy for bone disease. Hypercalcemic crises may be encountered in 1.6–6% of patients undergoing parathyroidectomy and requires emergent management with fluid resuscitation (Phitayakorn and McHenry 2008).

Hypoparathyroidism is caused by PTH deficiency and the resulting biochemical abnormality is hypocalcemia. In the absence of adequate PTH activity, the ionized calcium concentration in the extracellular fluid falls below the reference range. Assay of 25-hydroxy vitamin D is important to exclude vitamin D deficiency as a cause of hypocalcemia. Primary hypoparathyroidism is most commonly induced by iatrogenic causes, such as anterior neck surgeries. Secondary hypoparathyroidism is a physiologic state in which PTH levels are low in response to a primary process that causes hypercalcemia.

Treatment of patients with hypoparathyroidism involves correcting the hypocalcemia by administering calcium and vitamin D. Recombinant human PTH is also used as an adjunctive therapy, together with calcium and vitamin D supplementation.

Most common clinical symptoms include muscle cramps involving the lower back, legs, and feet. Increased neuromuscular irritability from hypoparathyroidism-induced hypocalcemia can be detected at beside by eliciting the Chvostek and Trousseau signs. Parkinsonian signs with hypokinetic-rigid syndrome and typical rest tremor can be seen in patients with hypoparathyroidism because biochemical abnormalities of calcium homeostasis frequently result in the intracranial calcifications. Calcifications with a striato-pallido-dentate distribution are most typical, but more widespread calcification may be also detected (Fig. 15.1). Intracranial calcifications associated with primary hyperparathyroidism are rare.

15.10 Vitamin B12 Deficiency

Vitamin B12 deficiency is a common cause of megaloblastic anemia and is crucial for synthesis of deoxyribonucleic acid (DNA) for normal neurologic functioning. It also plays a vital role in myelination of the nervous system. Vitamin B12 deficiency is defined as a serum level <200 pg/mL; however, neurologic manifestations present at levels below 400 pg/mL (Arıcan et al. 2020).

Etiologies include a number of pathologies of the gastrointestinal system involving the stomach, pancreas or small bowel which impede absorption. Alternatively, it is known to result from dietary deficiency such as in those individuals who follow a strict vegan diet or from use of medications that alter normal absorption such a biguanides (e.g., metformin), proton-pump inhibitors, histamine 2 receptor antagonists, or nitrous oxide during anesthesia. A transcobalamin II deficiency may also be inherited to produce a vitamin B12 deficiency. Infants who are exclusively

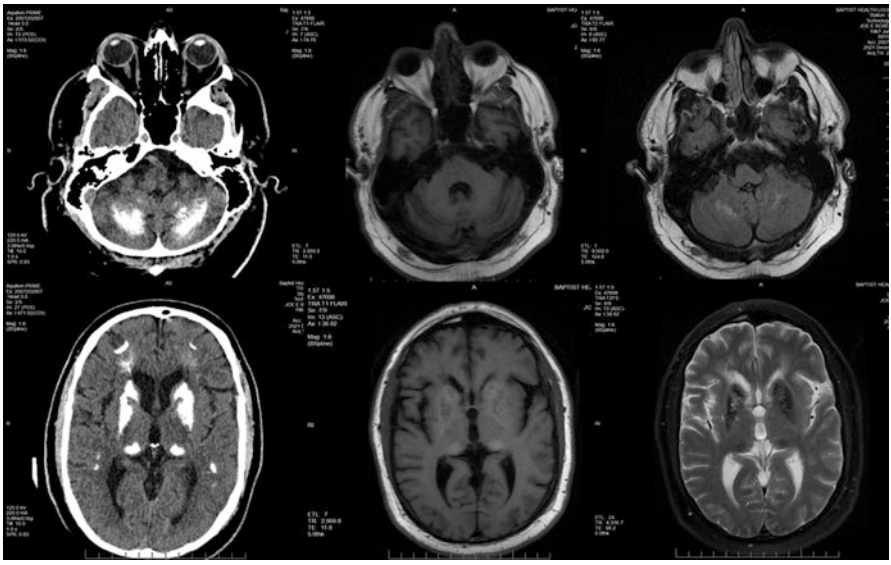

Fig. 15.1 CT (left panels), T1-weighted and T2-weighted MRI (middle and right panels) of a patient with the iatrogenic primary hypoparathyroidism showing widespread calcifications in the basal ganglia and cerebellum

breastfed by mothers with a deficiency of the vitamin can develop vitamin B12 deficiency in early infancy.

In rare cases, this deficiency may be familial and inherited by an autosomal recessive manner. Different stages of the pathway may be involved in such familial conditions, such as intracellular metabolism, genes encoding transcobalamins, biallelic mutations in gene encoding intrinsic factor (IF), known as juvenile cobalamin deficiency, or a biallelic mutation of cubilin (CUBN/AMN) encoding the ileal receptor of the vitamin B12-IF complex which produces the Imerslund-Gräsbeck syndrome.

While uncommon, vitamin B12 deficiency may present with involuntary movements in adults and children. Phenomenology may range from chorea, tremor, myoclonus, dystonia to parkinsonism. A few cases of orthostatic tremor have been reported with vitamin B12 deficiency (Benito-León and Domingo-Santos 2016; Benito-León and Porta-Etessam 2000). These symptoms are known to respond well to treatment with vitamin B12 supplementation (de Souza and Moloi 2014). Infantile tremor syndrome is a clinical entity characterized by anemia, regression of developmental milestones, failure to thrive and coarse tremors that has been found to correlate with dietary vitamin B12 deficiency in some parts of the world. Tremors are prominent in distal extremities and head, with early response to supplementation (Sharawat et al. 2018). Other signs and symptoms may include a "glove and stocking" distribution loss of pain and temperature sensation in extremities, along with varying degrees of neurocognitive impairment.

Initial testing of hemoglobin concentration, along with mean corpuscular volume and vitamin B12 level is necessary. Early investigation into cause of deficiency helps determine duration and dosing of vitamin B12 orally or parenterally.

15.11 Ataxia with Vitamin E Deficiency (AVED)

Vitamin E is a fat-soluble vitamin, and its alpha-tocopherol form acts a free radical scavenger to prevent oxidation of cell membranes. Its bioavailability is dependent on fat metabolism. The recommended daily allowance (RDA) for vitamin E is 15 mg for adults. Alpha-tocopherol levels of less than 0.5 mg/dL typically produce clinical signs and symptoms.

Deficiency of the vitamin is common in setting of fat malabsorption such as pancreatic insufficiency, cholestasis, or impaired absorption as in small bowel disease. In low serum concentrations it may present with spinocerebellar manifestations of ataxia, hyporeflexia, and loss of proprioception and vibration. In early infancy, it may also cause hemolysis.

Tocopherol transfer protein A (TTPA) is the gene encoding transfer protein that enables vitamin E transfer (Di Donato et al. 2010). Mutations in this gene give rise to a syndrome called Ataxia with vitamin E deficiency, which is inherited autosomal recessively and presents with progressive ataxia. The phenotype mimics Friedreich ataxia. It may also cause myoclonus or generalized dystonia, in the setting of strabismus, cardiac arrhythmia, and dementia. A side-to-side dystonic head tremor may present in this condition (Terry et al. 2019). Rare atypical presentations of AVED without ataxia have been described to produce a cervical dystonia and cognitive dysfunction (Becker et al. 2016). Treatment consists of lifelong oral supplementation with d-form of alpha-tocopherol in doses of 800–1500 mg/day for adults and 40 mg/kg/day for children. Early diagnosis and management may help reverse disease process (Sondhi and Sharma 2020). Reports suggest isolated vitamin E deficiency secondary to other causes may present with a large amplitude tremor involving limbs and head, which improve with vitamin supplementation (Lo Barco et al. 2021).

15.12 Abetalipoproteinemia (Basssen-Kronzweig Syndrome)

Abetalipoproteinemia is a rare malabsorption syndrome which presents in early infancy with diarrhea, failure to thrive, intention tremors, and ataxia. It is encountered in less than 1 in 100,000 individuals. There is a complete absence of chylomicrons, very-low density protein (VLDL), and low-density lipoproteins (LDL). Symptoms are produced by impaired vitamin E absorption and are associated with developmental delay. It is caused by a mutation in the microsomal triglyceride

transfer protein (MTTP) which is encoded on chromosome 4q22-24 and is inherited in an autosomal recessive manner. MTTP facilitates transfer of lipids onto apo B.

This disorder may cause diarrhea and occur with deficiency of other fat-soluble vitamins and their deficiency syndromes. Ocular manifestations such as pigmentary retinal degeneration may occur in severe forms. Acanthocytes appear in peripheral blood smear from hydroperoxidation of fatty acids causing hemolysis. Critically low levels of cholesterol and triglycerides commonly help diagnose the condition (Walker and Danek 2021). Hepatic steatosis may present with elevated serum transaminases.

Neurological manifestations occur due to demyelination and consist of proximal muscle weakness, with absent or reduced deep tendon reflexes, a wide-based ataxic gait, reduction of vibration and proprioception in a "glove-and-stocking" pattern. A mild intention tremor has been described. Treatment before 16 months of age helps prevent long-term sequelae and consists of fat-soluble vitamin supplementation (Sondhi and Sharma 2020). Rare associations with ileal adenocarcinoma and spinal cord glioblastoma have been reported (Zamel et al. 2008).

15.13 Cerebral Folate Deficiency (CFTD)

The cerebral folate receptor alpha (FRα) transports 5-methyltetrahydrofolate (5-MTHF) into the brain. 5-MTHF is a precursor of methyl-group donor S-adenosylmethionine which is utilized in numerous metabolic pathways. Low concentrations of 5-MTHF in the brain produces CFTD, which is strongly associated with autism-spectrum disorders (ASD).

Mutation of the FOLR1 gene which encodes the folic acid receptor may can CFTD with onset of symptoms in infancy. FOLR1 gene is located in the long arm of chromosome 11. Presence of folate receptor autoantibodies, mitochondrial diseases, and other congenital abnormalities in folate metabolism also cause CFTD. Classically, it is characterized by developmental delay occurring with ataxia, dyskinesia, truncal hypotonia with spasticity in lower extremities and drop attacks which may present as myoclonic epilepsy. Epileptic seizures are common in this condition and may be generalized tonic-clonic, atonic, or myoclonic type (Ferreira et al. 2016).

CFD may also occur secondary to chronic use of antifolate and anticonvulsant medications and may co-exist with Rett syndrome, Kearns-Sayre syndrome, and dihydropteridine reductase deficiency (Pineda et al. 2006). MRI imaging of the brain reveals leukodystrophy and EEG shows slowing of background activity (Zhang et al. 2020).

Diagnosis is established by abnormally low levels of 5-MTHF in cerebrospinal fluid (≤5 nmol/L) with normal levels in the periphery. High-dose folinic acid (*d,l*-leucovorin) supplementation (2–5 mg/kg/day) is the mainstay of therapy with improvement of ASD symptoms (Sondhi and Sharma 2020). While generally safe and well-tolerated, some instances of mood disturbances, insomnia, and headaches

were reported as adverse effects of treatment with folinic acid (Rossignol and Frye 2021).

15.14 Biotin-Thiamine-Responsive Basal Ganglia Disease (BTBGD)

BTBGD is a childhood disorder of thiamine metabolism caused by an autosomal recessive mutation in SLC19A3 gene, commonly presenting in young children. This gene encodes thiamine transporter-2 and enables transport of thiamine through the blood-brain barrier in the central nervous system. This mutation produces three distinct clinical forms that present at different stages of life—early infancy (early infantile lethal encephalopathy), childhood (BTBGD), and adulthood (late-onset Wernicke-like encephalopathy). Of these, BTBGD is the commonest type and presents between ages 3 and 10. Ataxia is co-existent with encephalopathy with variable regression, recurrent seizures, myoclonic jerks, rigidity, and dystonia. It may also be associated with facial palsy, dysphagia, and ophthalmoplegia. Severe forms may include quadriparesis, coma, or death.

Biochemical diagnosis is achieved by demonstration of low free thiamine levels in the CSF with evidence of lactic acidosis in blood and urine. Urinary levels of organic acids are variable. Serum concentration of thiamine is normal (Saini and Sharma 2021).

Symptoms respond well to early oral replacement of high doses of thiamine (10–40 mg/kg/day) and biotin (5–10 mg/kg/day) and are typically continued for life (Sondhi and Sharma 2020). MRI shows increased signal intensity with bilateral, symmetric involvement of caudate, putamen, thalamus with possible extension into brain stem, cortex, and cerebellum. Notably, there is absence of mammillary body involvement. Brain atrophy is often observed (Wesół-Kucharska et al. 2021). This entity should be suspected in all cases of recurrent unexplained encephalopathy in children and treatment initiated early.

15.15 Niemann-Pick Type C (NP-C)

Niemann-Pick disease type C (NP-C) is an autosomal recessive lysosomal storage disorder of impaired cellular cholesterol trafficking, caused by mutations in two causative genes. The estimated incidence is 1/100,000 live births and about 95% cases have mutations in the *NPC1* gene and about 5% in the *NPC2* gene. Clinical phenotype of NP-C varies with the age of onset. Infantile onset is associated mostly with the visceral presentation, including hepatosplenomegaly. Later onset causes more obvious neurologic problems and younger children typically present with hypotonia and developmental delay, later followed by the development of ataxia,

dysarthria, dysphagia, vertical supranuclear gaze palsy and dystonia. Patients with ataxia commonly exhibit intention tremor but this is always associated with more complex motor abnormalities.

Relatively isolated tremor is more commonly encountered in patients with juvenile and adult onset of NP-C. Cerebellar outflow tremor is a typical tremor phenomenology in these patients. Juvenile and adult onset of NP-C is frequently heralded by psychiatric symptoms with psychotic features and the presence of tremor in these patients may be incorrectly attributed to neuroleptics, which may further delay the diagnosis. Extraocular abnormalities with limited upgaze are useful diagnostic clue (Floyd et al. 2007; Josephs et al. 2004).

NP-C is caused by biallelic mutations, but the heterozygous state has also been implicated in the development of postural and action arm tremor. Carriers may also exhibit subtle extraocular abnormalities, REM sleep behavior, or parkinsonism (Kluenemann et al. 2013).

Clinical features that are suggestive of NP-C should prompt additional laboratory evaluation. Detection of elevated plasma levels of oxysterols, including cholestane-3β,5α,6β-triol (C-triol) and 7-ketocholesterol (7-KC) is sensitive screening test and replaced the need for skin biopsy and Filipin staining of cultured fibroblasts after LDL cholesterol load. Genetic testing should be used to confirm the diagnosis and identify the disease-causing gene and pathogenic variants. Timely diagnosis may facilitate the initiation of miglustat therapy that can partially mitigate the disease progression (Sévin et al. 2007; Patterson et al. 2017).

15.16 Wilson's Disease

Wilson's disease is an autosomal recessive disease caused by biallelic mutations in the *ATP7B* gene. Pathogenic mutations disrupt copper transport, resulting in copper toxicity affecting mostly liver and central nervous system. Clinical symptoms are very heterogenous with variable degrees of hepatic and neuro-psychiatric disturbances. The age of initial symptoms varies widely from the first decade to 4th and 5th decade of life, even though most patients develop symptoms in adolescence to early adulthood. Movement disorder associated with this entity is a combination of early-onset parkinsonism, dystonia, and tremor (Pellecchia et al. 2003).

Tremor can be seen in 25–55% of patients diagnosed with WD and when tremor is prominent, this is also referred to as the pseudo-sclerotic subtype of WD. Prototypical tremor in WD is described as the wing-beating tremor with proximal tremor, appearing when the patient holds semi-flexed outstretched arms. Characteristically, its amplitude increases with a longer duration of posture holding and many patients exhibit severe flapping tremor with large amplitudes. However, many patients may exhibit a typical bilateral and action tremor of 8–12 Hz frequency that can be easily confused with essential tremor.

Patients with otherwise unexplained tremor should undergo further laboratory testing. Diagnosis of WD remains laboratory based, and the successful and prompt

diagnosis requires a high index of suspicion. Plasma level of ceruloplasmin is recommended as the screening step in the diagnosis of WD. A serum ceruloplasmin level less than 20 mg/dL (200 mg/L or 2.83 μmol/L; normal values: 20–40 mg/L) is consistent with the diagnosis. However, even low levels cannot confirm the diagnosis and additional confirmatory tests are needed. Every patient with suspected WD should have 24-hour urine copper assay and this test alone can be diagnostic in most of patients. The 24-hour copper values more than 100 μg/24 hours (1.6 μmol/24 hours) are conventionally considered diagnostic of WD. Almost all patients with neurological involvement present with Kayser-Fleischer rings and slit lamp examination can be also used to support the diagnosis. Genetic testing detecting biallelic mutations in the *ATP7B* gene is confirmatory, although WD can be diagnosed based on laboratory data showing copper overload. MRI of brain may be helpful in diagnosis of WD. It can detect structural abnormalities mostly in basal ganglia with hyperintensity on T2-weighted and FLAIR images in putamen, striatum, and globus pallidus (Fig. 15.2). Hyperintense signal in the midbrain around the red nucleus and substantia nigra may give the appearance of "panda sign." Liver biopsy demonstrates deposits of copper. Copper-chelation (penicillamine, trientine) remains gold-standard of WD therapy for now and zinc salts can be successfully used for maintenance therapy (Hedera 2017). Baclofen, trihexyphenidyl, and levodopa may be useful in case of spasticity or extra-pyramidal signs. Liver transplantation (hepatitis, cirrhosis) may improve neurological dysfunction in some cases not responding adequately to medical therapy. A diet low in copper is recommended: avoidance of mushrooms, chocolate, nuts, liver, shellfish, dried fruits.

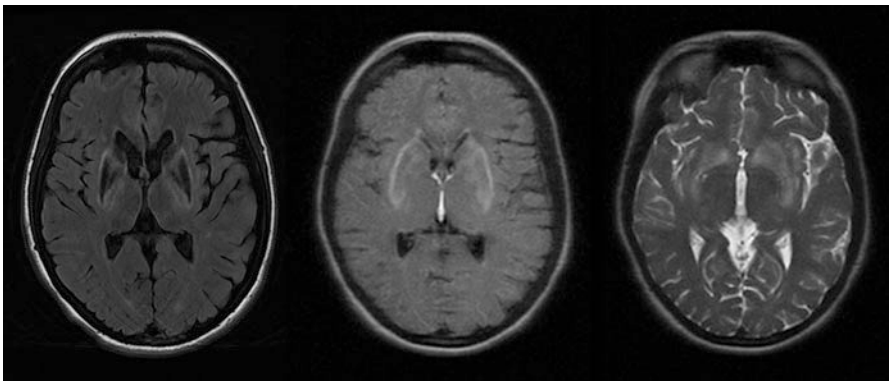

Fig. 15.2 MRI of the brain of three different patients with Wilson's disease showing signal changes in basal ganglia on FLAIR and T2-weighted images

15.17 Segawa Disease

Segawa disease (DYT5 dystonia) is an autosomal-dominant guanosine triphosphate cyclo-hydrolase I (GTPCH-I) deficiency located on the 14q22.1-q22.2 gene. It is a dopa-responsive postural dystonia of a lower extremity that is frequently diagnosed in children between ages 5 and 10. It is characterized by decreased activity of tyrosine hydroxylase in the striatum with reduced dopamine in striatal direct pathways.

Lower extremities are commonly affected; however, it can involve upper extremities or cranio-cervical regions (e.g., torticollis, oromandibular, blepharospasm). A high-frequency postural tremor (8–10 Hz) may present in the upper extremities after age 10. In adult-onset disease, tremor appears first in the hand and is associated with gait abnormalities due to rigidity. Diurnal fluctuation of symptoms is common, with symptomatic improvement in the morning or after sleep. Hyperreflexia with bradykinesia is also noted.

Diagnostic confirmation is obtained by low homovanillic acid in the CSF, and a marked decrease in biopterin and neopterin with normal phenylalanine levels is pathognomonic (Ebrahimi-Fakhari et al. 2019). MRI is normal in these cases. Treatment consists of levodopa 20 mg/kg/day without a decarboxylase inhibitor (Segawa 2009).

15.18 GLUT1 Deficiency Syndrome

Glucose transporter 1 (GLUT1) deficiency syndrome is characterized by early childhood onset. It is caused by a heterozygous de novo mutation of the SLC2A1 gene and presents in infancy with a spectrum of manifestations occurring from low-energy states in the brain due to inadequate supply of glucose.

It presents with epileptic seizures, episodic ataxia, dysarthria, spasticity, chorea, and/or myoclonus. Paroxysms of dyskinesias that are induced by exertion may also be seen. Dystonic tremors have been described with this mutation (Roubergue et al. 2011). Developmental delay with seizures and microcephaly are commonly co-occurring. Paroxysmal rapid and multidirectional eye movements have been noted in a third of the patients which resemble opsoclonus, which are accompanied by syn-directional head movements (Pearson et al. 2017). All symptoms may worsen with fasting or exercise.

Laboratory diagnosis consists of testing for hypoglycorrhachia or reduced (<60 mg/dL) levels of glucose and lactate in CSF. MRI is typically normal. Treatment consists of a ketogenic diet to provide an alternative source of energy and helps rapid resolution of symptoms (Ebrahimi-Fakhari et al. 2019). Triheptanoin, a medium odd-chain triglyceride, is a newer treatment of seizures in this condition.

15.19 Cerebrotendinous Xanthomatosis (CTX)

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive lipid storage disease caused by deficiency of the mitochondrial enzyme sterol 27-hydroxylase, encoded by the *CYP27A1* gene. Defective bile synthesis results in cholestanol and cholesterol accumulation in the central nervous system and other body tissues. Estimated incidence is about 1/10,000 live births.

Initial clinical presentations are systemic, and a typical sequence is infantile diarrhea, followed by cataracts and the development of tendon xanthomas in the childhood or early adulthood. Neuropsychiatric symptoms are typically adult onset, and most patients have mixed phenomenology of parkinsonism, ataxia, dystonia, and myoclonus. Cognitive decline and psychiatric problems frequently co-exist with a movement disorder. More than 50% of patients exhibit signs of cognitive decline and some patients may experience signs of developmental disability since childhood. Tremor seen in CTX patients is either postural in patients who exhibit signs of parkinsonism or cerebellar intention tremor in patients with prominent ataxia.

CTX belongs to a group of treatable neurometabolic conditions and hence, early recognition and diagnosis is important to initiate treatment and slow down the disease progression. The described combination of non-neurologic and neurologic symptoms and signs should prompt laboratory evaluation and neuroimaging studies. Cataracts and xanthomas may not be apparent in some patients who started to exhibit psychiatric and neurologic problems, and a high index of suspicion is needed to diagnose these patients in the early stages. Diagnostic biochemical abnormalities in CTX include high plasma cholestanol concentration, normal-to-low plasma cholesterol concentration, decreased chenodeoxycholic acid, increased concentration of bile alcohols in plasma and urine, and their glyconjugates, and increased concentrations of cholestanol and apolipoprotein B in cerebrospinal fluid. Normal plasma cholestanol concentration is 330 ± 30 μg/dL and patients with CTX typically have more than fivefold elevation of cholestanol levels. Normal-to-low cholesterol levels help to differentiate patients with xanthomas caused by hypercholesterolemia. Genetic testing is helpful to confirm this biochemical diagnosis.

MRI of brain can show T2-weighted hyperintensity in the dentate nuclei in the cerebellum and a variable degree of leukodystrophy in the cerebral and cerebellar white matter. Treatment with chenodeoxycholic acid (CDCA) normalizes bile acid synthesis and normalizes plasma and CSF concentration of cholestanol. This leads to stabilization of clinical course, including neurologic and psychiatric symptoms. Moreover, the observed benefits are better if the therapy is initiated in the early stages of the disease.

15.20 Arginase-1 Deficiency (ARG1D)

Urea cycle disorders are a type of inborn error of metabolism which lead to encephalopathy from accumulation of ammonia. Arginase catalyzes hydrolysis of arginine into ornithine, which is returned into the mitochondria for perpetuation of the cycle and formation of urea.

Arginase deficiency is a distal defect in the cycle and the rarest in this group, with a prevalence of 1 in 350,000 children. The mutation is inherited in autosomal recessive manner. Onset occurs between 2 and 4 years of age. ARG1 is primary found in the liver, red blood cells, and salivary glands, whereas the other isoform ARG2 is found in the kidneys.

Abnormal accumulation of arginine due to ARG1 gene mutation can cause neuropsychiatric symptoms in arginase deficiency characterized by a progressive spastic diplegia, along with developmental delay, seizures, short stature, and intellectual disability. Hyperreflexia and clonus are commonly encountered in ARG1D possibly due to guanidine compounds which inhibit transketolase activity and induce demyelination. Postural and cerebellar tremor and ataxia may present in this disorder. Hyperammonemia is less frequent in ARG1D compared to other urea cycle disorders and not typically an early feature but may need dialysis when it occurs. This is thought to be vital at ammonia levels greater than 250 μmol/L. It is believed that neuro-excitotoxicity is caused by guanidine compounds and arginine which inhibit GABAergic transmission.

Affected individuals are typically identified at neonatal screening by undetectable arginase activity in red blood cells and remains the definitive test for the condition (Sin et al. 2015). Biochemical diagnosis is established by an elevated level of plasma arginine with elevated orotic acid and guanidine compounds in the urine. Imaging findings are non-diagnostic and may present with atrophy of the brain. Diffusion tensor imaging shows non-specific injury to white matter tracts in a few reported cases (Oldham et al. 2010). Dietary restrictions with reduction of arginine and protein intake is the mainstay of management. Other symptomatic management includes treatment of infections, and vitamin supplementation. An acute hyperammonemia crisis may require cessation of protein intake, provision of nutrition with dextrose-containing fluids to limit catabolism and use of nitrogen scavenger compounds (Cornelius et al. 2019).

15.21 Biotinidase Deficiency (BTD)

Biotinidase cleaves biotin which acts as co-enzyme to multiple carboxylases in major cycles of gluconeogenesis, branch chain amino acid catabolism and fatty acid synthesis. The BTD gene located on chromosome 3p25 and is inherited in autosomal recessive fashion to produce a disorder with neurocutaneous involvement. Accumulation products from this deficiency state include lactic acid, alanine, propionate, and

methyl citrate. Global incidence ranges between 1:40,000 and 60,000 live births, with higher incidence in countries like Brazil and Turkey. Typical age of onset ranges from 2 weeks to 2 years but in rare cases may present with delayed onset later in life (Canda et al. 2020).

Biotinidase deficiency presents with ataxia and dystonia with parkinsonian rigidity associated with seizures, rash, developmental delay, optic atrophy, sensorineural hearing loss. Tremor is typically rest or postural. Cutaneous manifestations include hair loss, erythematous plaques over flexors and perioral regions, conjunctivitis, and predisposition to viral and fungal infections. Untreated symptoms may progress to metabolic decompensation, seizures, hypotonia, coma, or death. A late onset of BTD should be suspected in myelopathy with vision loss even despite partial response to corticosteroid therapy.

Newborn screening for this deficiency and prompt oral biotin supplementation (5–20 mg/day) is known to rapidly reverse symptoms except optic and auditory symptoms (Sondhi and Sharma 2020). Laboratory diagnosis can be made by elevated levels of organic and lactic acids, biocytin, and ammonia with a corresponding low biotin level. Colorimetric assays may help assess enzyme activity in plasma with levels lower than 4.4 to 10 nmol/mL/min. Imaging shows cerebral atrophy, ventriculomegaly, basal ganglion calcifications and T2 hyperintensities on MRI with spinal cord involvement noted in late-onset disease. It is important to note that biotin administration can cause a false elevation of T3 and T4 levels with corresponding low TSH levels (Canda et al. 2020; Rajendiran and Sampath 2011).

References

Arıcan P, Bozkurt O, Cavusoglu D, Gencpınar P, Haspolat S, Duman O, et al. Various neurological symptoms with vitamin B12 deficiency and posttreatment evaluation. J Pediatr Neurosci. 2020;15(4):365–9.

Bansal N, Weinstock RS. Non-diabetic hypoglycemia. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al., editors. Endotext. South Dartmouth: MDText.com, Inc. Copyright © 2000–2021, MDText.com, Inc.; 2000.

Becker AE, Vargas W, Pearson TS. Ataxia with vitamin E deficiency may present with cervical dystonia. Tremor Other Hyperkinet Mov (N Y). 2016;6:374.

Benito-León J, Domingo-Santos Á. Orthostatic tremor: an update on a rare entity. Tremor Other Hyperkinet Mov (N Y). 2016;6:411.

Benito-León J, Porta-Etessam J. Shaky-leg syndrome and vitamin B12 deficiency. N Engl J Med. 2000;342(13):981.

Canda E, Kalkan Uçar S, Çoker M. Biotinidase deficiency: prevalence, impact and management strategies. Pediatr Health Med Ther. 2020;11:127–33.

Celmina M, Micule I, Inashkina I, Audere M, Kuske S, Pereca J, et al. EAST/SeSAME syndrome: review of the literature and introduction of four new Latvian patients. Clin Genet. 2019;95(1):63–78.

Cornelius LP, Raju V, Julin A. Arginase deficiency presenting as acute encephalopathy. J Pediatr Neurosci. 2019;14(3):133–6.

Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. Diabetes. 2005;54(12):3592–601.

de Souza A, Moloi MW. Involuntary movements due to vitamin B12 deficiency. Neurol Res. 2014;36(12):1121–8.
Di Donato I, Bianchi S, Federico A. Ataxia with vitamin E deficiency: update of molecular diagnosis. Neurol Sci. 2010;31(4):511–5.
Ebrahimi-Fakhari D, Van Karnebeek C, Münchau A. Movement disorders in treatable inborn errors of metabolism. Mov Disord. 2019;34(5):598–613.
Ellis SJ. Severe hyponatraemia: complications and treatment. QJM. 1995;88(12):905–9.
Espay AJ. Neurologic complications of electrolyte disturbances and acid-base balance. Handb Clin Neurol. 2014;119:365–82.
Fell JM, Reynolds AP, Meadows N, Khan K, Long SG, Quaghebeur G, et al. Manganese toxicity in children receiving long-term parenteral nutrition. Lancet. 1996;347(9010):1218–21.
Ferreira P, Luco SM, Sawyer SL, Davila J, Boycott KM, Dyment DA. Late diagnosis of cerebral folate deficiency: fewer seizures with folinic acid in adult siblings. Neurol Genet. 2016;2(1):e38.
Flink EB. Magnesium deficiency. Etiology and clinical spectrum. Acta Med Scand Suppl. 1981;647:125–37.
Floyd AG, Yu QP, Piboolnurak P, Wraith E, Patterson MC, Pullman SL. Kinematic analysis of motor dysfunction in Niemann-Pick type C. Clin Neurophysiol. 2007;118(5):1010–8.
Geroula A, Deutschbein T, Langton K, Masjkur J, Pamporaki C, Peitzsch M, et al. Pheochromocytoma and paraganglioma: clinical feature-based disease probability in relation to catecholamine biochemistry and reason for disease suspicion. Eur J Endocrinol. 2019;181(4):409–20.
Ghosh R, Dubey S, Chatterjee S, Ghosh M, Ray BK, Benito-León J. Hypermanganesemia induced chorea and cognitive decline in a tea seller. Tremor Other Hyperkinet Mov (N Y). 2020;10:45.
Hedera P. Update on the clinical management of Wilson's disease. Appl Clin Genet. 2017;10:9–19.
Ishida S, Sugino M, Hosokawa T, Sato T, Furutama D, Fukuda A, et al. Amiodarone-induced liver cirrhosis and parkinsonism: a case report. Clin Neuropathol. 2010;29(2):84–8.
Ishii M. Endocrine emergencies with neurologic manifestations. Continuum (Minneap Minn). 2017;23(3, Neurology of Systemic Disease):778–801.
Josephs KA, Matsumoto JY, Lindor NM. Heterozygous Niemann-Pick disease type C presenting with tremor. Neurology. 2004;63(11):2189–90.
Kim HT, Edwards MJ, Lakshmi Narsimhan R, Bhatia KP. Hyperthyroidism exaggerating parkinsonian tremor: a clinical lesson. Parkinsonism Relat Disord. 2005;11(5):331–2.
Kluenemann HH, Nutt JG, Davis MY, Bird TD. Parkinsonism syndrome in heterozygotes for Niemann-Pick C1. J Neurol Sci. 2013;335(1–2):219–20.
Lazarus S, Bell GH, Tremor in Hyperthyroidism. Its value in the diagnosis and assessment of the condition. Glasgow Med J. 1943;140(3):77–86.
Lenka A, Jankovic J. Tremor syndromes: an updated review. Front Neurol. 2021;12:684835.
Lo Barco T, Ghobert AL, Lucca F, Galati G, Proietti J, Cantalupo G. Reversible tremor in an infant with vitamin E deficiency and cystic fibrosis. Lancet. 2021;398(10295):156.
Maraganore DM, Folger WN, Swanson JW, Ahlskog JE. Movement disorders as sequelae of central pontine myelinolysis: report of three cases. Mov Disord. 1992;7(2):142–8.
Marse C, Druesne V, Giordana C. Paroxysmal tremor and vertical Nystagmus associated with hypomagnesemia. Mov Disord Clin Pract. 2020;7(Suppl 3):S61–s2.
Meyer TE, Verwoert GC, Hwang SJ, Glazer NL, Smith AV, van Rooij FJ, et al. Genome-wide association studies of serum magnesium, potassium, and sodium concentrations identify six Loci influencing serum magnesium levels. PLoS Genet. 2010;6(8):e1001045.
Morimatsu M, Ono K, Harada A. Severe asterixis due to hypermagnesemia in chronic renal failure: a case report. Neurol Sci. 2021;42(6):2539–42.
Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and Paraganglioma. N Engl J Med. 2019;381(6):552–65.
Oldham MS, VanMeter JW, Shattuck KF, Cederbaum SD, Gropman AL. Diffusion tensor imaging in arginase deficiency reveals damage to corticospinal tracts. Pediatr Neurol. 2010;42(1):49–52.

Patterson MC, Clayton P, Gissen P, Anheim M, Bauer P, Bonnot O, et al. Recommendations for the detection and diagnosis of Niemann-Pick disease type C: an update. Neurol Clin Pract. 2017;7(6):499–511.

Pearson TS, Pons R, Engelstad K, Kane SA, Goldberg ME, De Vivo DC. Paroxysmal eye-head movements in Glut1 deficiency syndrome. Neurology. 2017;88(17):1666–73.

Pellecchia MT, Criscuolo C, Longo K, Campanella G, Filla A, Barone P. Clinical presentation and treatment of Wilson's disease: a single-centre experience. Eur Neurol. 2003;50(1):48–52.

Perikal PJ, Jagannatha AT, Khanapure KS, Furtado SV, Joshi KC, Hegde AS. Extrapontine Myelinolysis and reversible Parkinsonism after hyponatremia correction in a case of pituitary adenoma: hypopituitarism as a predisposition for osmotic demyelination. World Neurosurg. 2018;118:304–10.

Phitayakorn R, McHenry CR. Hyperparathyroid crisis: use of bisphosphonates as a bridge to parathyroidectomy. J Am Coll Surg. 2008;206(6):1106–15.

Pineda M, Ormazabal A, López-Gallardo E, Nascimento A, Solano A, Herrero MD, et al. Cerebral folate deficiency and leukoencephalopathy caused by a mitochondrial DNA deletion. Ann Neurol. 2006;59(2):394–8.

Rajendiran A, Sampath S. Biotinidase deficiency–clinching the diagnosis rapidly can make all the difference! BMJ Case Rep. 2011;2011:bcr0720114494.

Rossignol DA, Frye RE. Cerebral Folate deficiency, Folate receptor alpha autoantibodies and Leucovorin (folinic acid) treatment in autism spectrum disorders: a systematic review and meta-analysis. J Pers Med. 2021;11(11):1141.

Roubergue A, Apartis E, Mesnage V, Doummar D, Trocello JM, Roze E, et al. Dystonic tremor caused by mutation of the glucose transporter gene GLUT1. J Inherit Metab Dis. 2011;34(2):483–8.

Saini AG, Sharma S. Biotin-Thiamine-responsive Basal Ganglia disease in children: a treatable neurometabolic disorder. Ann Indian Acad Neurol. 2021;24(2):173–7.

Segawa M. Autosomal dominant GTP cyclohydrolase I (AD GCH 1) deficiency (Segawa disease, dystonia 5; DYT 5). Chang Gung Med J. 2009;32(1):1–11.

Sévin M, Lesca G, Baumann N, Millat G, Lyon-Caen O, Vanier MT, et al. The adult form of Niemann-Pick disease type C. Brain. 2007;130(Pt 1):120–33.

Sharawat IK, Kasinathan A, Sankhyan N. Infantile Tremor syndrome: response to B12 therapy. J Pediatr. 2018;196:323-.e1.

Sin YY, Baron G, Schulze A, Funk CD. Arginase-1 deficiency. J Mol Med (Berl). 2015;93(12):1287–96.

Sondhi V, Sharma S. Vitamin-responsive movement disorders in children. Ann Indian Acad Neurol. 2020;23(3):325–31.

Sullivan AA, Chervin RD, Albin RL. Parkinsonism after correction of hyponatremia with radiological central pontine myelinolysis and changes in the basal ganglia. J Clin Neurosci. 2000;7(3):256–9.

Terry C, Forman EB, Gorman KM, King MD. "No-No" Head Tremor-A Nod to the diagnosis. Pediatr Neurol. 2019;100:104.

Timmermann L, Butz M, Gross J, Kircheis G, Häussinger D, Schnitzler A. Neural synchronization in hepatic encephalopathy. Metab Brain Dis. 2005;20(4):337–46.

Tuschl K, Clayton PT, Gospe SM Jr, Mills PB. Dystonia/Parkinsonism, Hypermanganesemia, Polycythemia, and chronic liver disease. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, LJH B, Mirzaa G, et al., editors. GeneReviews(®). Seattle: University of Washington, Seattle Copyright © 1993–2021, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved; 1993a.

Tuschl K, Gregory A, Meyer E, Clayton PT, Hayflick SJ, Mills PB, et al. SLC39A14 deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, et al., editors. GeneReviews(®). Seattle: University of Washington, Seattle Copyright © 1993–2021, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved; 1993b.

Walker RH, Danek A. “Neuroacanthocytosis” - overdue for a taxonomic update. Tremor Other Hyperkinet Mov (N Y). 2021;11:1.

Wesół-Kucharska D, Greczan M, Kaczor M, Pajdowska M, Piekutowska-Abramczuk D, Ciara E, et al. Early treatment of biotin-thiamine-responsive basal ganglia disease improves the prognosis. Mol Genet Metab Rep. 2021;29:100801.

Zahed K, Sasangohar F, Mehta R, Erraguntla M, Qaraqe K. Diabetes management experience and the state of hypoglycemia: National Online Survey Study. JMIR Diabetes. 2020;5(2):e17890.

Zamel R, Khan R, Pollex RL, Hegele RA. Abetalipoproteinemia: two case reports and literature review. Orphanet J Rare Dis. 2008;3:19.

Zhang C, Deng X, Wen Y, He F, Yin F, Peng J. First case report of cerebral folate deficiency caused by a novel mutation of FOLR1 gene in a Chinese patient. BMC Med Genet. 2020;21(1):235.

Chapter 16
Tremor: The Clinical Approach to Reach the Diagnosis

Julian Agin-Liebes and Sheng-Han Kuo

Abstract A systematic approach with a focus on the anatomic location, activating conditions, and phenomenology is needed to accurately diagnose tremor. A detailed history and neurologic exam with an emphasis on certain clinical maneuvers will allow a clinician to formulate a differential diagnosis. Ancillary testing with imaging and electrophysiology may be needed to confirm clinical findings. It may take time to reach a correct diagnosis due to the evolution of tremor symptoms over time. Once a diagnosis is made, a targeted treatment plan can be implemented.

Keywords Tremor · Essential tremor · Parkinson's disease · Task-specific tremor · Focal tremor · Dystonia

16.1 Introduction

The accurate diagnosis of tremor is a challenge, even for the skilled neurologist. Tremor can present in isolation or as part of a syndrome with other associated symptoms. A systematic approach is needed when approaching a patient who comes in for evaluation of tremor. Detailed history, clinical findings, specific exam maneuvers, and ancillary testing may all be needed to reach a diagnosis. The International Parkinson and Movement Disorder Society (IPMDS) has established a framework to approach diagnosing tremors using two main axes, clinical features and etiology (axis 1 and 2 respectively) (Bhatia et al. 2018). This chapter will

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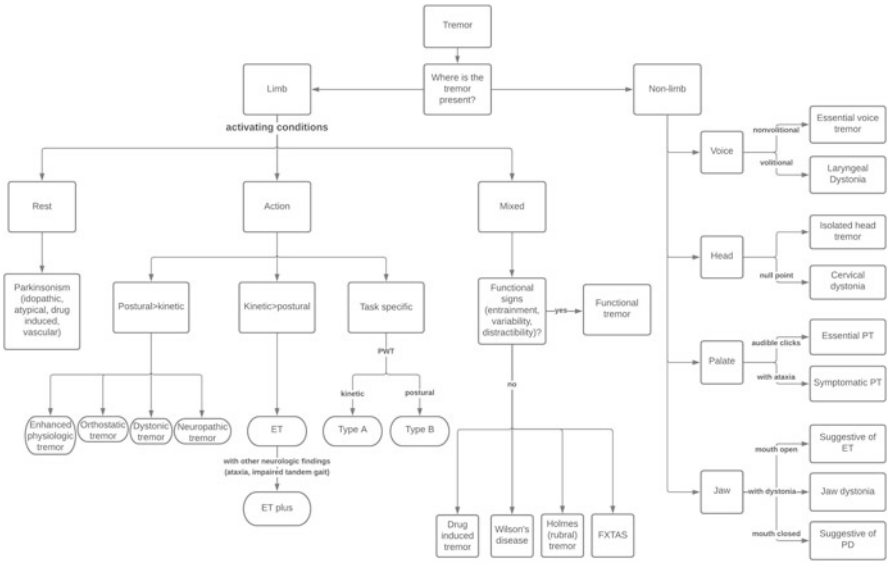

Fig. 16.1 An algorithm for clinical diagnosis of tremor. ET essential tremor, FXTAS fragile X associated tremor/ataxia syndrome, PD Parkinson's disease, PT palatal tremor, PWT primary writing tremor

primarily focus on axis 1 with an emphasis on phenomenology and reaching a differential diagnosis. Treatment options will be covered in other chapters. A diagnostic algorithm has been proposed (Fig. 16.1) that uses the anatomic location as well as activating conditions to reach a diagnosis.

Before one can embark on diagnosing tremor, it is important to first define tremor. Tremor is an involuntary, rhythmic, oscillatory movement of a body part (Bhatia et al. 2018). There is a broad differential diagnosis for tremulous movements and other types of movements such as myoclonus or low-frequency jerky movements seen in epilepsia partialis continua can be mistaken for unilateral tremor (van de Wardt et al. 2020). Since tremor by definition is rhythmic and sinusoidal, myoclonus should be considered if the movements have a "jerky" quality; however, dystonic tremor or Holmes tremor may have a jerky quality as well, complicating the matter. Ancillary tests, such as neuroimaging and electrophysiology, can help clarify the diagnosis when it is not clear from the phenomenology.

16.2 History

As for all neurological disorders, history is a key element to making a diagnosis and is one of the four major categories in axis 1 of the IPMDS classification of tremors. Pertinent historical details include age of onset, temporality, evolution, family history, and alcohol and drug sensitivity. For example, a patient presenting

at the age of 35 with tremor in both hands that has progressively worsened over the past 10 years with a family history of tremor is more consistent with essential tremor (ET) rather than parkinsonism. Additionally, someone who is 70 years old and is suddenly presenting with a unilateral tremor after a hemorrhagic stroke would likely have a Holmes tremor rather than ET. If a tremor has started immediately after an injury or another illness, functional etiology should be considered. These cases illustrate how historical features can provide valuable context to aid in the diagnosis.

16.3 Location

The anatomic distribution of the tremor, particularly whether it is present in a limb, is an important feature in reaching a diagnosis. In our algorithm, the presence of tremor in a limb is the first question that we recommend the clinician should ask or observe as this can help narrow the differential diagnosis. One can further observe whether the tremor is focal (one body part is affected), segmental (two or more contiguous body parts are affected), hemibody (affecting one side of the body) or generalized (affecting both upper and lower body) (Bhatia et al. 2018). Additionally, the evolution of the tremor from one body part to another (typically from a limb to a cranial structure) over time should be noted as this is more indicative of an evolving tremor disorder, rather than an isolated focal tremor.

16.4 Tremor Characteristics

When evaluating for tremor, it is important to note certain features of the tremor itself as well as any associated signs or symptoms. Activating features, whether the tremor is present at rest or action, is one of the most informative pieces of history to help reach the diagnosis and is the next step in our algorithm. Although tremor can present both with rest and action (classified as mixed), this division can be useful when considering the most likely etiology of the tremor. To best elicit this information, it is recommended start by asking the patient open-ended questions: "Could you please describe your tremor?" and "When do you notice your tremor?," followed by more specific questions: "Does your hand shake when you are drinking from a cup?" (Louis 2019). Additionally, the regularity and frequency of tremor should be observed. The regularity refers to the consistency of the tremor and can be described as fine, coarse or jerky. The frequency is the number of oscillations per second and it can be separated by low frequency (<4 Hz), mid-frequency (4–7 Hz), and high frequency (>7 Hz) (Edwards and Deuschl 2013). Lastly, identifying if tremor is isolated or associated with other neurologic signs is essential to the diagnosis. This can be elicited from the exam by looking for features such as bradykinesia, dystonic posturing, ataxia, or peripheral neuropathy. By identifying these tremor characteristics, a clinician will better be able to reach the correct diagnosis.

16.5 Exam

A comprehensive neurologic exam with specific maneuvers can help determine the anatomic location(s) of the tremor and assess for activating conditions that will help reach the diagnosis. When evaluating for tremor in the upper limbs, the positioning of the hands is important to differentiate whether tremor occurs primarily at rest, action, or with a certain posture. Examining rest tremor requires that the patient be at rest and relaxed, which can be challenging in the setting of a doctor's office. When the patient is in a seated position, the hands should be observed with arms hanging over the arm rests or on their lap (Figs. 16.2 and 16.3). When positioned on the lap, they should be in a mid-pronated position to better see the full amplitude of the tremor. If the patient is unable to be relaxed when in the seated position, having the patient lie down in a supine position is the best way to observe a rest tremor by eliminating gravitational force and muscle co-contraction (Zach et al. 2015).

In contrast, action tremor should be examined when the arms are in motion. To evaluate for kinetic tremor, the patient should touch their nose and then touch the examiner's finger at least three times. The examiner's hand should be far enough away so that the patient's elbow is fully extended when they reach the examiner's fingertip. With this maneuver, one can assess if there is an intention component that will manifest as an increased amplitude of the tremor when the patient is about to approach the target and once the patient touches the target, the tremor may stop (Campbell and DeJong 2013). Along the way to the target, there may be little or no tremor. This unique type of tremor characteristic is called intention tremor. On the other hand, if the amplitude does not change as the patient approaches the target, this would be classified as simple kinetic tremor (van de Wardt et al. 2020).

Fig. 16.2 Hands on the lap in a mid-pronated position to examine for rest tremor

Fig. 16.3 Hands hanging over the sides of a chair to examine for rest tremor

When assessing for a postural component the patient should have their arms extended, initially with palms down, and hold it for at least 10 seconds and then position the arms in a wing-beating position with the elbows flexed and the fingers spread out (Figs. 16.4 and 16.5). Additionally, the patient should also position their arms so that their thumbs are pointed upwards as well as pointed downwards to see where tremor is most prominent. The frequency, amplitude, and regularity of tremor should be observed in each of these positions. If tremor emerges immediately after the patient changes positions from the hands in a rest position to arms outstretched, it would be more suggestive of ET. If there is a delay and tremor re-emerges after several seconds (sometimes as long as 60 seconds), it would be more consistent with tremor seen in PD, and the tremor is called a re-emergent tremor. If there is abnormal posturing of the hands when hands are outstretched or a jerky, irregular quality to the tremor, one should suspect a dystonic tremor.

Despite all the different examination positions described, tremor may not always be evident and additional maneuvers can be performed to elicit tremor. If rest tremor is suspected, maneuvers to increase tremor amplitude include cognitive coactivation (naming the months of the year in reverse), motor coactivation with another limb (toe tapping on the contralateral side of the tremor) (van de Wardt et al. 2020) as well as walking with the arms fully relaxed. If tremor amplitude reduces while performing cognitive and motor tasks of the opposite limb, functional tremor should be considered. The amplitude of rest tremor almost always reduces or transiently goes away during voluntary movements with the limb that is affected by the tremor (Bhatia et al. 2018). Rest tremor suppression can be achieved by having patients

Fig. 16.4 Hands in an outstretched position to assess postural tremor and re-emergent tremor

Fig. 16.5 A wing beating position with elbows flexed and fingers spread out to examine for postural tremor

make quick ballistic movements or extension of the wrist and then subsequently see tremor re-emerge as the patient rests (Zach et al. 2015).

When an action tremor is suspected, the patient should be observed pouring water between two cups, preferably over a sink or with towel on the lap if there happens to be spillage. If there is tremor in the hands when performing this task, one can assess the severity of tremor as well as if there is any asymmetry, which can have

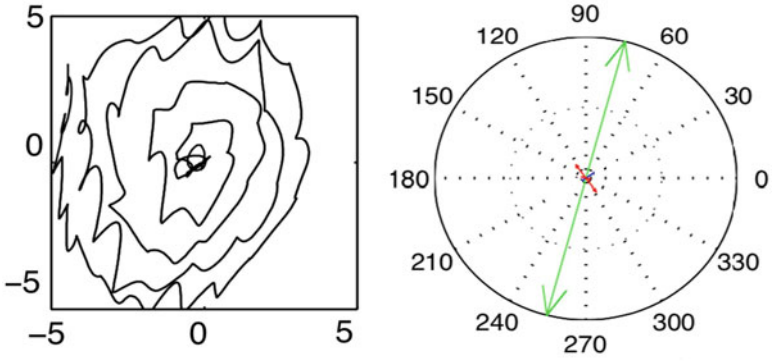

Fig. 16.6 A drawing of an Archimedes spiral from a patient with ET demonstrating an axis from approximately 75°–255°. (Image courtesy of Seth Pullman, MD)

functional implications for the patient especially if it is primarily in the dominant hand.

Writing is another tool to help assess upper limb tremor. Tasks that are typically performed are a writing sample and drawing of the Archimedes spiral. When the patient writes, it should be several sentences long. This is particularly useful in patients with a primary writing tremor where the writing becomes more tremulous only after writing for an extended period of time. The size of the handwriting should also be assessed. If micrographia is present, the handwriting will be small and at times hard to decipher. This is suggestive of PD. If the writing is tremulous and large, it may be suggestive of ET or other tremor disorders.

When drawing an Archimedes spiral, the examiner should look at the size of the spiral and the presence of an axis. When the patient is drawing the spiral, it is important that the hand be elevated above the paper and it should not be supported. If the lines of the spiral are small, close together, and have overlapping lines, this would be suggestive of PD. In patients with ET, the spiral will demonstrate an axis, which is a result of the distal flexion-extension tremor movements. For right-hand spiral drawings, the axis is typically in the 8–2 o' clock direction while those that are drawn with the left hand are in the 10–4 o'clock axis (Fig. 16.6). In dystonic tremor, the axis is usually multidirectional. If there is variability within repeated spiral drawings, specifically if there are changes when drawing the spiral in a clockwise direction compared to a counterclockwise direction, this is suggestive of functional tremor (Alty et al. 2017).

Assessment of tremor in the lower extremities requires that the patient's legs be off the floor in addition to seeing them stand. If there is a suspicion for rest tremor of the leg, the patient should sit on an exam table with legs dangling or lying down for the leg to be completely at rest. Cognitive or motor coactivation techniques mentioned above can be used to help bring out tremor. Patients with ET rarely have leg tremor, but to assess for it, the leg can be lifted up and as the foot approaches the examiner's finger and intention tremor may be visible. If

there is unsteadiness when a patient stands that is relieved upon walking, orthostatic tremor of the legs should be considered. When examining the patient, sometimes a palpable thrill may be felt when touching the legs. A stethoscope may even be used to auscultate the gastrocnemius where a continuous thumping sound may be heard, which is termed the "helicopter sign." The stance may also be wider to compensate for the unsteadiness. The tremor may not be visible to the eye, especially if it is low amplitude and high frequency. Surface electromyography (EMG) or accelerometry may be needed to assist in diagnosis and should record rhythmic activity in the 13–18 Hz range.

Non-limb tremor, such as voice, head, neck, and jaw tremor, may occur in isolation or concurrently with limb tremor and should be assessed during the exam. If the patient has a head or neck tremor, one should have the patient hold their head in different positions in the horizontal and vertical plane to see if there is any change or cessation of tremor. If there is cessation, this is considered a null point and would suggest cervical dystonia. The examiner should pay special attention to the presence of laterocollis, anterocollis, or retrocollis, which would also be suggestive of dystonia. Additionally, the patient may have a "geste antagoniste" or a sensory trick that may improve the tremor and is suggestive of dystonic tremor. One example is having the patient touch their cheek or the neck to see if there is any change. The patient should also be examined lying down since tremor seen in the neck of patients with ET is a postural tremor and should go away when the patient is supine and the head is fully at rest.

When assessing vocal tremor, the patient should produce a sustained phonation, such as "ahh" or "eee," for as long as the patient can hold. The examiner should assess if there is a sinusoidal quality to the voice. This may not be noticed at the beginning of the task, but become apparent as the patient holds the sound for a longer period of time. Additionally, attention should be paid to the neck as the patient makes a phonation. There may be up and down movement of the larynx, which may indicate tremor in the extrinsic laryngeal muscles and may be amenable to botulinum toxin therapy (Finnegan et al. 2009). Voice tremor can be a manifestation of ET or spasmodic dysphonia, which is laryngeal dystonia. Clinically, it can be very difficult to differentiate the etiology of the voice tremor and there is no particular exam maneuver to help differentiate the two etiologies.

When evaluating jaw tremor, it should be observed whether it occurs when the mouth is open or closed. Jaw tremor in patients with ET is seen more when the mouth is open (such as when speaking) and in PD it is seen when the mouth is closed (Louis 2019). If it is seen in isolation, it is more likely to be dystonic in origin.

In addition to the assessment for tremor, other neurologic signs should be assessed as well. When rest tremor is noted, signs of parkinsonism such as bradykinesia and rigidity should be evaluated. For action and postural tremor, cerebellar signs such as impaired tandem gait and dysmetria may also be present and suggestive of ET plus. Reflexes should also be assessed since patients with neuropathy, which would have reduced or absent reflexes, can be an etiology of tremor.

In the following section, we will discuss the phenomenology of tremor categorized by their activating conditions.

16.6 Rest Tremor

16.6.1 PD and Other Parkinsonian Disorders

PD is the most common etiology for rest tremor, but other etiologies need to be considered during the evaluation. Rest tremor occurs when an affected body part is fully supported against gravity and is diminished or absent with voluntary muscle contractions and movements (Jankovic 2022). In PD, the classical tremor is at rest, asymmetric, more prominent distally with a frequency of 4–6 Hz and has a "pill rolling quality" if it is present in the hand (van de Wardt et al. 2020). The phenomenology of "pill rolling" is thumb flexion and this is important because few other conditions have this feature, namely drug-induced parkinsonism, or atypical parkinsonism. If there is thumb extension, this is more characteristic of dystonic tremor (Zach et al. 2015). Tremor can also be present in the jaw, and this is present when the patient is at rest with the mouth closed and goes away when the patient is talking (Louis 2019). Although rest tremor may be the most notable tremor in patients with PD, kinetic and postural tremor should also be assessed. Kinetic and postural tremor was observed in about 50% of PD patients across three different cohort studies (Gupta et al. 2020). Other associated signs accompanying the tremor include bradykinesia and rigidity.

Although PD represents the majority of patients who have rest tremor, clinical, historical as well as phenomenological features can help differentiate it from other etiologies of rest tremor. Atypical parkinsonism syndromes such as multiple system atrophy (MSA) tend to have more of a jerky quality than in PD and lack the "pill rolling" aspect that is seen in PD (van de Wardt et al. 2020). Patients who have a history of being treated with dopamine-blocking agents or anti-emetics, such as metoclopramide, may also present with an asymmetric rest tremor and it is important to review current and past medications (Edwards and Deuschl 2013). Additionally, vascular parkinsonism or lesions within the basal ganglia can lead to rest tremor and imaging can help diagnose these abnormalities.

16.7 Action Tremor

The differential diagnosis for a patient who presents with tremors that are prominent with movement is much broader than for rest tremor and key clinical features can help differentiate between the different etiologies.

16.7.1 ET

ET is the most common cause of tremor with a prevalence of 8.6% in certain geographic regions (Welton et al. 2021). Although it is the most common tremor that clinicians of all disciplines may encounter, it is frequently misdiagnosed ranging from 37% (Jain et al. 2006) to 50% (Schrag et al. 2000). The 2018 IPMDS consensus guidelines classify ET as an isolated tremor syndrome of the bilateral upper extremities seen during action without other neurological signs such as dystonia, ataxia, or parkinsonism. It can be associated with tremor in other locations such as the head, voice, or lower limbs and occurs with at least 3 years duration (Bhatia et al. 2018). Tremor in ET is not always symmetric and one study showed marked asymmetry or unilaterality in about 4% of patients studied, though this is thought to be an underestimation of the prevalence (Phibbs et al. 2009). ET patients often have tremor while performing activities such as eating, drinking, or writing, which can be assessed with finger to nose, the water pouring test, and drawing an Archimedes spiral. Additionally, a family history of tremor and alcohol responsiveness can be helpful clues pointing to ET, but are not specific for ET and can also sometimes be seen in dystonic tremor (Shanker 2019).

ET patients have a kinetic component to their tremor and a postural component may or may not be present (Shanker 2019). About half of patients will also have an intention component to their tremor where there will be worsening as they approach the target (Louis 2019). When present in the upper extremities, postural tremor is usually most notable in the wrists, with flexion-extension movements. The postural component, whether the hands are in an outstretched or in wing beating position, tends to be out of phase, which has functional implications. If a patient holds an object with two hands, tremors in each of the hands cancel each other out to some degree making it easier to hold the object without the tremor interfering (Louis 2019).

Tremor in ET that originally started in the arms can spread to different body parts such as the neck, head, voice, or jaw; however, other causes of tremor should also be considered when encountering cranial tremor. The prevalence of cranial tremor is higher in women than men (Hardesty et al. 2004). About 25% of patients with head tremor due to cervical dystonia have tremor in their hands that is phenomenologically similar to ET (Jankovic et al. 1991) and suggest that there may be an association between dystonia and ET. Voice tremor in ET typically manifests as increased effort while speaking and worsens under stressful conditions or activities requiring concentration (Barkmeier-Kraemer 2020). As mentioned earlier, jaw tremor in ET is typically present when the mouth is open.

Other neurological signs, such as impaired tandem gait, cognitive impairment, and dystonic posturing can be found in patients who have phenomenology suggestive of ET. According to the IPMDS, the presence of these neurologic signs would classify these patients as having ET plus (Bhatia et al. 2018). There is considerable debate about this new entity, especially with regard to epidemiological studies and how to classify patients (Louis 2020; Lenka and Jankovic 2021). Some

of the diagnostic criteria for ET plus contradict the diagnosis of ET, particularly the presence of questionable dystonic posturing, which adds a layer of confusion to what is already a difficult diagnosis. The addition of ET plus to the consensus criteria shows that our understanding of ET is evolving, but it may make it more challenging to accurately diagnose these patients and subsequently study them.

16.7.2 Enhanced Physiologic Tremor

Enhanced physiologic tremor is defined by the IPMDS consensus statement as a symptomatic upper extremity action tremor that is potentially reversible if the cause is found and treated (Bhatia et al. 2018). Enhanced physiological tremor manifests when maintaining a posture, rather than during action, and is often symmetric. It is usually not visible because of its low amplitude and high frequency (>12 Hz) (Lenka and Jankovic 2021). It can be exacerbated by increased sympathetic activity and excessive caffeine consumption. Hyperthyroidism, anxiety, and vigorous exercise are other examples that can make enhanced physiological tremor more visible. Enhanced physiological tremor sometimes can be visualized (if not already seen by eye) with the patient maintaining their arms outstretched and placing a piece of paper on top to make it more obvious. Compared to ET, there is no obvious tremor seen on the finger-to-nose maneuver (Louis 2019). Diagnosis of enhanced physiological tremor is usually made clinically, and one needs to ensure that all other etiologies of tremor are excluded. If objective testing is needed, accelerometers and EMG can be used to confirm the presence of a tremor. Specifically, weight loading will dampen the tremor frequency, measured by accelerometers or EMG, in enhanced physiological tremor but not in ET (Zhang et al. 2017).

16.7.3 Dystonic Tremor

Tremor that is present in patients with dystonia may occur in the body part affected by dystonia or in another part of the body not affected by dystonia, which would be considered a tremor associated with dystonia. There is a wide range of prevalence of tremor in dystonia ranging from 11% to 87% in patients diagnosed with adult onset primary dystonia (Defazio et al. 2015). Tremor in dystonia tends to occur when the patient maintains a posture or during action, with a minority of patients having rest tremor. The tremor may affect the head, upper limbs or voice (Defazio et al. 2015). Dystonic tremor can be difficult to differentiate from tremor in ET given their propensity to present when the patient maintains a posture and with action. Dystonic tremor tends to have more twisting and jerky movements. Dystonic tremor may also not be completely rhythmic or oscillatory, which begs the question whether it is actually a tremor or tremulous (Louis 2019). Additionally, the patient may have

dystonic posturing with arm extension or torticollis associated with neck tremor, which may lead one to suspect dystonic tremor as opposed to ET.

Voice tremor can be a manifestation of ET or spasmodic dysphonia, which is a form of laryngeal dystonia. Voice tremors due to laryngeal dystonia have adductor and abductor types depending on the movement of the vocal cords when making a sound. Adduction laryngeal dystonia sounds more strangulated with intermittent voice stoppages, while abduction laryngeal dystonia has intermittent breathy breaks (Albanese and Sorbo 2016). In contrast, with essential voice tremors there is vertical oscillation of the larynx, tremor articulators, and the respiratory muscles. Dystonic voice tremor is often task specific and only present when speaking, while essential voice tremor is also present during non-volitional respiration (Barkmeier-Kraemer 2020).

When examining patients with dystonic tremor, it is important to identify the presence of a null point and a "geste antagnoiste" as these are specific for dystonia. Hand tremor that is dystonic in etiology may be difficult to differentiate from ET and abnormal posturing of the hands, lack of clear axis when drawing a spiral and jerky irregularity would suggest dystonia as the etiology (Lenka and Jankovic 2021).

16.8 Mixed Tremor

While most tremor types are either activated primarily at rest or with action, there are certain etiologies of tremor that have a varied phenomenology and activating conditions.

16.8.1 Drug-Induced Tremor

There are many drugs that can cause a wide range of tremor. Most drugs either cause rest tremor or postural and kinetic tremor (and sometimes both). When getting the history from a patient, it is necessary to obtain a medication history and determine if there is a temporal relationship between tremor and the offending medications. Other considerations include excluding medical or metabolic causes, determining if there is a dose-response relationship, and seeing that there is a lack of tremor progression over time (Morgan et al. 2017). Several different classes of medications can cause tremors or worsen tremors that are already present, including dopamine-blocking agents, anti-arrhythmic agents, anti-seizure agents, and chemotherapeutics to name a few (Table 16.1).

Psychiatric and dopamine-blocking agents are the most commonly encountered etiologies of drug-induced tremor. Lithium salts are frequently associated with tremor with variability ranging from 4% to 65% (Gelenberg and Jefferson 1995). Lithium-induced tremor typically appears in the hands, is similar to enhanced physiological tremor, and is in the 8–12 Hz range. Lithium-induced tremor for most

Table 16.1 Common medications causing drug-induced tremors and their associated activating conditions

Medication	Activating condition
Amiodarone, procainamide	Action/postural >>> rest
Amitriptyline	Action/postural
Beta adrenergic agonists	Action/postural
Caffeine, nicotine, amphetamines	Action/postural
Dopamine receptor blocking agents (haloperidol, tetrabenazine, metoclopramide)	Action/postural = rest
Immunosuppressants (cyclosporine, tacrolimus)	Action/postural tremor
Lithium salts	Action/postural
Selective serotonin reuptake inhibitors (fluoxetine), tricyclic agents	Action/postural >>> rest
Valproic acid	Action/postural >>> rest
Vidarabine	Action/postural

patients is not debilitating. Rarely, it can present as rest tremor with parkinsonism, which can improve with reduction of the lithium dose (Morgan et al. 2017). Neuroleptic-induced tremor presents as rest tremor that is typically associated with parkinsonism. Drug-induced parkinsonism can affect up to 60% of patients treated with typical neuroleptics depending on the dose, duration of treatment, and age of the patient among other factors (Sethi 2001). Neuroleptic-induced tremor usually occurs in the arm and can be unilateral or bilateral. There may also be a re-emergent component to the tremor. It can be difficult to differentiate between drug-induced parkinsonism and PD. Typically drug-induced parkinsonism is reversible, but it can take several weeks to months to improve. If a patient continues to have parkinsonism after cessation of dopamine-blocking agents, it is thought that the patient has underlying parkinsonism that was unmasked by the neuroleptic exposure (Morgan and Sethi 2005). Tardive tremor can occur after chronic use of neuroleptics and what sets it apart from neuroleptic-induced tremor is that the tremor improves with increasing doses of neuroleptics or dopamine-depleting therapy. The phenomenology of the tremor is also different with a larger amplitude than what is seen in parkinsonian tremor (Morgan and Sethi 2005).

16.8.2 Neuropathic Tremor

Patients with peripheral neuropathy have been observed to have tremor and thus called neuropathic tremor, which should be considered in neuropathy patients in the absence of another movement disorder. Tremor occurs in the same limb that has the peripheral neuropathy, and the development of tremor and neuropathy should be temporally linked (Louis 2016). Typically, neuropathic tremor is postural and/or kinetic tremor and has a frequency of 3–6 Hz in the arm and hand muscles (Bhidayasiri and Tarsy 2012). The affected limb may also have weakness as well

as reduced or absent reflexes. Although postural tremor is the most common, rest tremor has also been noted. In a series of 89 patients from Poland, 51% of neuropathic tremor patients had rest tremor (Wasielewska et al. 2013). Demyelinating neuropathies have a higher predilection for developing tremor than other types of neuropathies (Bhidayasiri and Tarsy 2012). Patients with Charcot Marie Tooth also have a high prevalence of tremor, with one study showing that 40% of patients had tremor (Cardoso and Jankovic 1993), and postural tremor of the hands is most common characteristic of neuropathic tremor (Lenka and Jankovic 2021).

16.8.3 Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

FXTAS is a neurodegenerative disease that typically presents with an action or intention tremor followed by cerebellar ataxia. The heterogeneity of the FXTAS clinical symptoms, which also include parkinsonism, executive dysfunction, and neuropathy, can make it a challenge to diagnose, especially early in the disease. FXTAS patients usually present in their 60s with the first symptom of tremor, typically 2 years preceding ataxia symptoms (Cabal-Herrera et al. 2020). Tremor in FXTAS tends to be mild and about half of patients do not notice their tremor, but it is noticed by other family members when eating, drinking, or writing (Jacquemont et al. 2003). A minority of FXTAS patients have head tremor, truncal titubation, and voice tremor. Up to 60% of FXTAS patients have parkinsonism, manifesting as rest tremor, masked facies, and bradykinesia. If there is a clinical picture of a mixed tremor with parkinsonism and cerebellar ataxia, FXTAS should be on the differential diagnosis (Cabal-Herrera et al. 2020). Another differential diagnosis for cerebellar ataxia and parkinsonism is MSA (Biancalana et al. 2005). When there is a suspicion for FXTAS, genetic testing should be performed, looking for a CGG repeat expansion in the *FMR1* gene with the expansion size ranging from 55 to 200 repeats. More severe disease phenotypes are associated with larger CGG repeat expansions. Additionally, specific MRI findings such as FLAIR hyperintensities in the splenium of the corpus callosum, symmetric T2 hyperintensities in the middle cerebellar peduncles, and white matter lesions with cerebral atrophy can help support the diagnosis as well.

16.8.4 Holmes Tremor

Holmes tremor is a mixed tremor type that is characterized by rest, postural, and action tremor with a low frequency (<5 Hz) at both proximal and distal limbs (Bhatia et al. 2018). Holmes tremor is caused by an insult (usually vascular in origin) to the brainstem (typically the midbrain) or the thalamus. Holmes tremor

can occur weeks to years after the injury. Clinically, it tends to affect the proximal upper extremities in an asymmetric fashion (Lenka and Jankovic 2021). Holmes tremor can be severe with a very prominent postural and kinetic component that can make the limb extremely difficult to use. A recent case series demonstrated two distinct phenotypes, midbrain Holmes tremor, and thalamic Holmes tremor. The midbrain type presents as a syndrome with rest, postural, and kinetic components and sometimes mild dystonic posturing. The thalamic type presents as a syndrome with more prominent dystonia, choreoathetosis, and sometimes pseudo-athetosis, due to joint position sense deficits (Nsengiyumva et al. 2021). In addition to the clinical presentation, imaging can help confirm the diagnosis, typically showing an infarct or hemorrhage in the midbrain or the thalamus.

16.8.5 Wilson's Disease

Patients with Wilson's disease present with a wide range of neurologic symptoms with tremor being the initial neurologic feature in about half of patients (Pfeiffer 2016). Wilson's tremor can be variable in the location of tremor (proximal or distal limbs) and activating conditions (can be rest or action/posture at times) and Wilson's tremor usually has a young age of onset (less than 40 years of age). The classic presentation is a proximal postural tremor in the wing beating position (Louis 2016). Since Wilson's disease has varied tremor phenomenology, the associated neurologic symptoms such as dystonia (particularly risus sardonicus) and parkinsonism as well as nonneurologic signs (Kayser Fleischer rings, psychosis, and cirrhosis) are helpful to make the diagnosis. Ancillary testing with MRI may show T2 and FLAIR hyperintensities bilaterally in the basal ganglia as well as in the midbrain.

16.9 Focal Tremor

Focal tremor is tremor that occurs in non-limb body parts and presents as an isolated tremor in the absence of another movement disorder diagnosis. We will discuss voice, head, palatal, and jaw tremor in this section. Signs of other movement disorders such as ET and PD need to be assessed before a diagnosis of a focal tremor can be made.

16.9.1 Voice Tremor

Voice tremor can be a manifestation of ET or PD, but it can also present in isolation. There are differing theories regarding the etiology of isolated voice tremor; whether it is a type of isolated ET or an isolated laryngeal dystonia (Barkmeier-Kraemer

2020; Patel and Frucht 2015). Patients with voice tremor have fluctuations in the pitch and loudness of their voice and are sometimes associated with intermittent pauses. As mentioned before, during the exam the patient should maintain sustained phonation of vowels to assess for voice fluctuations. If there are any changes related to respiration, this would suggest ET since respiration is not task specific. A laryngoscopy may be needed to visualize the vocal cords and see if there is oscillation, which can help determine the underlying etiology of voice tremor.

16.9.2 Head Tremor

Isolated head tremor is commonly seen in the context of ET or cervical dystonia, and there are data to support that isolated head tremor can be the initial presentation for either of these etiologies. A study of 241 first-degree relatives of ET patients and controls showed that 21% vs. 2% have isolated head tremor supporting that many isolated head tremor cases may be related to ET (Louis et al. 2018). Additionally, a longitudinal study of 20 patients with isolated head tremor found that 75% of them showed features of cervical dystonia, including torticollis and laterocollis, after 5 years (Ferrazzano et al. 2021). Clues for cervical dystonia as the etiology of head tremor include the feeling of a pulling sensation in the neck, while a family history of ET may suggest ET as the etiology. The phenomenology of head tremor due to ET may be "yes-yes," "no-no," or "round-round" (Robakis and Louis 2016). In cervical dystonia, head tremor may appear to be more irregular or jerky and there are postural abnormalities (Chen et al. 2020). Isolated head tremor occurs more frequently in women for both ET and cervical dystonia (Merola et al. 2019). As mentioned earlier, identification of a null point or geste antagoniste would suggest cervical dystonia whereas cessation of the head tremor when lying down would suggest ET as a diagnosis. Diagnosis is made on a clinical basis and there is no specific lab or imaging finding that would help support the diagnosis. Serial examinations over time will likely clarify the etiology of the head tremor.

16.9.3 Palatal Tremor

Palatal tremor is a rare focal tremor with rhythmic oscillations of the soft palate. There are two types of palatal tremor, essential and symptomatic. Essential palatal tremor is produced by contractions of the tensor veli palatini muscle and is usually associated with audible clicks. Symptomatic palatal tremor is caused by contractions of the levator veli palatini and is associated with other neurologic findings, particularly ataxia and pendular nystagmus (Deuschl et al. 1994). The frequency of essential palatal tremor has a wider range from 1 to 7 Hz, while symptomatic palatal tremor tends to be uniformly slower ranging from 1.5 to 3 Hz (Lenka and Jankovic 2021). Clinical history can help differentiate the two

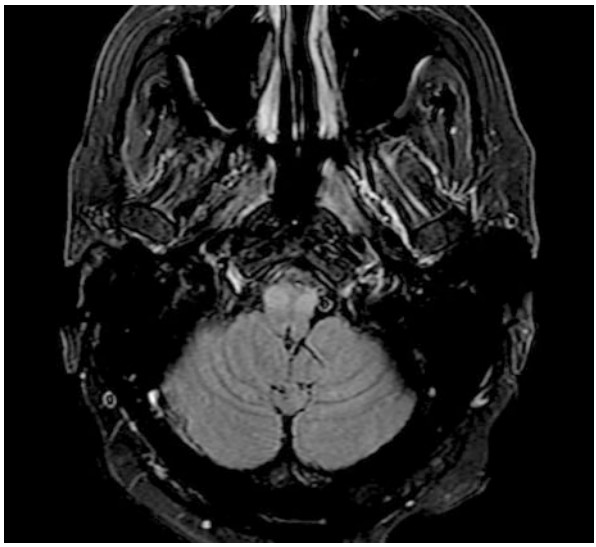

Fig. 16.7 Symmetric hypertrophic degeneration of the inferior olives seen on the T2 FLAIR sequence of MRI

etiologies, particularly ear clicking which is only seen in essential palatal tremor. Additionally, in essential palatal tremor, there will be complete cessation of the tremor during sleep. In contrast, symptomatic palatal tremor persists during sleep, but the frequency may slow down (Lenka and Jankovic 2021). On exam, palatal tremor is visible when the patient opens their mouth and has their tongue rest on the floor of the mouth. For essential palatal tremor there will be no other exam findings aside from the tremor, whereas in symptomatic palatal tremor, there will be ataxia and nystagmus, indicative of damage to the Guillain-Mollaret triangle. On MRI one may see hypertrophic degeneration of the inferior olives (Fig. 16.7). Essential palatal tremor will not have MRI findings and it is not clear what the etiology is, but it has been reported that it may be functional in origin (Vial et al. 2020).

16.9.4 Jaw Tremor

Jaw tremor is frequently recognized as an associated feature of parkinsonism, sometimes ET and rarely in isolation. The phenomenology of jaw tremor is typically "up and down" and less frequently "side to side" (Schneider and Bhatia 2007). Patients with jaw tremor may present with teeth chattering and jaw clenching. A case series of seven patients with jaw tremor found that three had dystonic jaw tremor and four other patients had tremor with associated dystonia in other body parts, among which one patient even had improvement by holding her hand under her chin (Schneider and Bhatia 2007). When seen in isolation, the etiology of jaw tremor is thought to be dystonic, but bradykinesia, rest tremor as well as postural and kinetic tremor should be assessed to see if it could be related to parkinsonism

or ET. A medication history should also be obtained as it has also been reported to develop after neuroleptic treatment (Ebersbach et al. 1997).

16.9.5 Orthostatic Tremor

Orthostatic tremor is high frequency (13–18 Hz) tremor in the legs that is present during standing that can occur in isolation, termed primary orthostatic tremor, or with other neurologic symptoms such as parkinsonism and ataxia, termed orthostatic tremor plus (Bhatia et al. 2018). Patients with orthostatic tremor will describe unsteadiness upon standing still that is relieved immediately upon sitting or lying down. Typically, patients are unable to stand still for more than a minute without leaning on something or sitting. Patients may compensate by widening their base and clawing the floor with their toes (Jones and Bain 2011). Orthostatic tremor is usually relieved with walking. An entity of slow orthostatic tremor, where the frequency is less than 13 Hz, has been described in case reports. Patients with slow orthostatic tremor present similarly as classical orthostatic tremor and may even experience more gait unsteadiness and falls compared to patients who have frequencies >13 Hz (Rigby et al. 2015). It is unclear whether slow orthostatic tremor should be categorized as a separate disease or it may be considered as a broader spectrum of orthostatic tremor with previously under-recognized tremor frequency. The gold standard for diagnosis of orthostatic tremor is electrophysiology with the median frequency ranging from 6 to 7 Hz with tremor bursts ranging from 50 to 150 ms (Hassan and Caviness 2019). About two-thirds of patients with orthostatic tremor will have a coexisting neurological disorder with parkinsonism, ataxia, and dystonia, which should also be considered.

16.10 Task-Specific Tremor

Task-specific tremor is a form of action tremor that only occurs when a person is performing a certain task. The tasks that induce tremor are varied from writing, playing musical instruments (particularly string and wind instruments), sports, and even tasks related to an occupation such as a painter using a brush. Primary writing tremor is the most common of the task-specific tremor. This section will focus on the clinical approach to diagnosing primary writing tremor as other types of task-specific tremors are more rare. Any patient who comes in with a task-specific tremor should be followed longitudinally to observe for other neurological signs. A case series described 11 patients with different task-specific tremors who went on to develop PD years after the initial task-specific tremor onset (Koneru and Ondo 2021).

16.10.1 Primary Writing Tremor

Primary writing tremor is a task-specific tremor that occurs only when a person is writing or a person is in the position of writing. There is considerable overlap with writer's cramp, which is a type of dystonia, and ET with much debate on whether primary writing tremor is a separate entity or related to the aforementioned disorders (Bain 2011). Primary writing tremor tends to occur in the sixth decade of life and is sometimes preceded by trauma to the affected hand. In contrast, writer's cramp tends to have an earlier age of onset. There are two types of primary writing tremor, classified as type A and type B (Bain 2011). Type A primary writing tremor occurs when the person begins to write and type B primary writing tremor starts when the person assumes the position as if they are going to write. Typically primary writing tremor occurs in the dominant hand, and tremor is not typically progressive, has a frequency of 5–7 Hz, and can be either pronation-supination or flexion-extension (Datta et al. 2021). When the person with primary writing tremor writes, the writing speed is slower and the tremor may worsen the longer the patient writes.

16.10.2 Functional Tremor

Functional tremor is one of the most common functional movement disorders, representing more than 50% of patients (Schwingenschuh and Deuschl 2016). Diagnosis of functional tremor poses a challenge since there are no standard criteria for diagnosis. It is important that the diagnosis is based on the positive findings rather than a diagnosis of exclusion (Lenka and Jankovic 2021). The onset of functional tremor is usually abrupt and may be associated with a prior trauma (surgery, accident, infection, or other concurrent illness).

Clinical exam is key to diagnosing functional tremor based on the variability, distractibility, entrainability, coherence, and suggestibility of tremor. Variability means a change in frequency, amplitude, direction (switching from pronation/supination to flexion/extension), or anatomic location (moving from hand to leg) of the tremor. Tremor variability is observed during history taking as well as exam with motor or distraction tasks. Although variability is a feature of functional tremor, it is not specific and can also be seen in other types of tremor, such as dystonic tremor, which can also have variable amplitudes and frequencies. Distractibility means that functional tremor can be suppressed when the patient is distracted. Methods to distract patients include mental coactivation with tasks such as counting backwards from 100 or reciting the months of the year backwards. In contrast, other types of tremor, such as the rest tremor in PD, usually have an increase of tremor amplitude with distraction. Another common method to bring out distractibility is to tap one's fingers out of order and to observe the changes of functional tremor in other body parts (Thenganatt and Jankovic 2014). Entrainability of functional tremor is when the frequency of the tremor matches the frequency of a repetitive movement on the

contralateral side of the body. This can be done by having a person tap their fingers or flex and extend their wrist on the opposite side of the tremor and the tremor will match the frequency of the movements (Thenganatt and Jankovic 2014). Coherence can be assessed when tremor in different parts of the body happens simultaneously. When there is coherence, the frequency of tremor in one body part matches the frequency of another body part. Most ET patients will have noncoherent tremor in different limbs whereas approximately half of patients with a functional tremor have coherence between the two limbs (Raethjen et al. 2004). Suggestibility can be tested to see if tremor can be altered with application of an external stimulus, such as a tuning fork. Changes in tremor amplitude, either increasing or decreasing, with the application of a stimulus may suggest functional tremor. This task may not be suited for all patients and caution should be used when performing this test. Patients may feel deceived after the suggestibility test is done, and if there is an immediate change after the suggestibility test is performed, the patient should be informed of the results right away. Suggestibility can help support the diagnosis of tremor but may not be necessary to test to achieve a diagnosis of functional tremor. Psychiatric evaluation does not show overt signs of hysteria in most cases. However, depression, functional somatic or psychosomatic conditions are relatively common.

Electrophysiology studies can help with a diagnosis of functional tremor when it is unable to be diagnosed on clinical exam and history alone. As mentioned before, entrainment and coherence are features suggestive of functional tremor, but they may not be grossly visible to the examiner's eye and can be confirmed with polymyography, time frequency, and frequency domain measures (O'Suilleabhain and Matsumoto 1998). These tools can also help identify the presence of coherence of tremor as well (Brown and Thompson 2001). The coactivation sign designates a simultaneous activation of agonist and antagonist muscles of a given joint. This sign is often observed at the onset of tremor: there is a tonic coactivation phase of the wrist flexor and extensor muscles about 250–300 ms before the reciprocal alternating tremor bursts evolve. Although these tests are useful to support the diagnosis of functional tremor, they are not widely available outside of a tertiary care center.

16.11 Conclusion

The diagnosis of tremor can be challenging, but a systematic approach that focuses on the location of the tremor, activating features and phenomenology can help clinicians to accurately diagnose tremor disorders (Fig. 16.1). Special attention should be paid to the clinical context and the evaluation of associated neurologic signs. When the diagnosis cannot be made with clinical history and exam findings alone, ancillary testing such as imaging and electrophysiology may be needed. Once a diagnosis is made, the clinician will be able to make informed decisions regarding treatment, to relieve what can ultimately be a very disabling disease.

References

Albanese A, Sorbo FD. Dystonia and tremor: the clinical syndromes with isolated tremor. Tremor Other Hyperkinet Mov (N Y). 2016;6:319.

Alty J, Cosgrove J, Thorpe D, Kempster P. How to use pen and paper tasks to aid tremor diagnosis in the clinic. Pract Neurol. 2017;17(6):456–63.

Bain PG. Chapter 50 - Task-specific tremor. In: Weiner WJ, Tolosa E, editors. Handbook of clinical neurology. 100. Elsevier; 2011. p. 711–8.

Barkmeier-Kraemer JM. Isolated voice tremor: a clinical variant of essential tremor or a distinct clinical phenotype? Tremor Other Hyperkinet Mov (N Y). 2020;10.

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33(1):75–87.

Bhidayasiri R, Tarsy D. Movement disorders: a video atlas. New York: Humana: Springer distributor; 2012. xv, 249 p.

Biancalana V, Toft M, Le Ber I, Tison F, Scherrer E, Thibodeau S, et al. FMR1 premutations associated with fragile X-associated tremor/ataxia syndrome in multiple system atrophy. Arch Neurol. 2005;62(6):962–6.

Brown P, Thompson PD. Electrophysiological aids to the diagnosis of psychogenic jerks, spasms, and tremor. Mov Disord. 2001;16(4):595–9.

Cabal-Herrera AM, Tassanakijpanich N, Salcedo-Arellano MJ, Hagerman RJ. Fragile X-associated tremor/ataxia syndrome (FXTAS): pathophysiology and clinical implications. Int J Mol Sci. 2020;21(12):4391.

Campbell WW, DeJong RN. DeJong's the neurologic examination / William W. Campbell. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. xii, 819 p.

Cardoso FE, Jankovic J. Hereditary motor-sensory neuropathy and movement disorders. Muscle Nerve. 1993;16(9):904–10.

Chen Q, Vu JP, Cisneros E, Benadof CN, Zhang Z, Barbano RL, et al. Postural directionality and head tremor in cervical dystonia. Tremor Other Hyperkinet Mov (N Y). 2020;10.

Datta A, Batra N, Pandey S. Primary writing tremor: current concepts. Ann Indian Acad Neurol. 2021;24(3):319–26.

Defazio G, Conte A, Gigante AF, Fabbrini G, Berardelli A. Is tremor in dystonia a phenotypic feature of dystonia? Neurology. 2015;84(10):1053–9.

Deuschl G, Toro C, Valls-Sole J, Zeffiro T, Zee DS, Hallett M. Symptomatic and essential palatal tremor. 1. Clinical, physiological and MRI analysis. Brain. 1994;117(Pt 4 (4)):775–88.

Ebersbach G, Tracik F, Wissel J, Poewe W. Tardive jaw tremor. Mov Disord. 1997;12(3):460–2.

Edwards MJ, Deuschl G. Tremor syndromes. Continuum (Minneap Minn). 2013;19(5 Movement Disorders):1213–24.

Ferrazzano G, Belvisi D, De Bartolo MI, Baione V, Costanzo M, Fabbrini G, et al. Longitudinal evaluation of patients with isolated head tremor. Parkinsonism Relat Disord. 2021;94:10–2.

Finnegan EM, Hoffman HT, Hemmerich AL, Van Daele DJ. Clinical practice: spasmodic dysphonia and vocal tremor. Perspect Voice Voice Disord. 2009;19(2):66–73.

Gelenberg AJ, Jefferson JW. Lithium tremor. J Clin Psychiatry. 1995;56(7):283–7.

Gupta DK, Marano M, Zweber C, Boyd JT, Kuo SH. Prevalence and relationship of rest tremor and action tremor in Parkinson's disease. Tremor Other Hyperkinet Mov (N Y). 2020;10:58.

Hardesty DE, Maraganore DM, Matsumoto JY, Louis ED. Increased risk of head tremor in women with essential tremor: longitudinal data from the Rochester Epidemiology Project. Mov Disord. 2004;19(5):529–33.

Hassan A, Caviness J. Slow orthostatic tremor: review of the current evidence. Tremor Other Hyperkinet Mov (N Y). 2019;9.

Jacquemont S, Hagerman RJ, Leehey M, Grigsby J, Zhang L, Brunberg JA, et al. Fragile X premutation tremor/ataxia syndrome: molecular, clinical, and neuroimaging correlates. Am J Hum Genet. 2003;72(4):869–78.

Jain S, Lo SE, Louis ED. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? Arch Neurol. 2006;63(8):1100–4.
Jankovic JHMOMSCCFSGJGFS. Principles and practice of movement disorders. 2022.
Jankovic J, Leder S, Warner D, Schwartz K. Cervical dystonia: clinical findings and associated movement disorders. Neurology. 1991;41(7):1088–91.
Jones L, Bain PG. Orthostatic tremor. Pract Neurol. 2011;11(4):240–3.
Koneru V, Ondo WG. Task specific tremor subsequently developing into Parkinson's disease: case series. Mov Disord Clin Pract. 2021;8(1):111–3.
Lenka A, Jankovic J. Tremor syndromes: an updated review. Front Neurol. 2021;12:684835.
Louis ED. Diagnosis and management of tremor. Continuum (Minneap Minn). 2016;22(4 Movement Disorders):1143–58.
Louis ED. Tremor. Continuum (Minneap Minn). 2019;25(4):959–75.
Louis ED. "Essential tremor plus": a problematic concept: implications for clinical and epidemiological studies of essential tremor. Neuroepidemiology. 2020;54(2):180–4.
Louis ED, Meyers JH, Cristal AD, Patel A, Tinaz S, Pullman SL, et al. Transient, isolated head tremor in "unaffected" individuals: is essential tremor an even more prevalent disease than we suppose? Front Neurol. 2018;9:570.
Merola A, Dwivedi AK, Shaikh AG, Tareen TK, Da Prat GA, Kauffman MA, et al. Head tremor at disease onset: an ataxic phenotype of cervical dystonia. J Neurol. 2019;266(8):1844–51.
Morgan JC, Sethi KD. Drug-induced tremors. Lancet Neurol. 2005;4(12):866–76.
Morgan JC, Kurek JA, Davis JL, Sethi KD. Insights into pathophysiology from medication-induced tremor. Tremor Other Hyperkinet Mov (N Y). 2017;7:442.
Nsengiyumva N, Barakat A, Macerollo A, Pullicino R, Bleakley A, Bonello M, et al. Thalamic versus midbrain tremor; two distinct types of Holmes' tremor: a review of 17 cases. J Neurol. 2021;268(11):4152–62.
O'Suilleabhain PE, Matsumoto JY. Time-frequency analysis of tremors. Brain. 1998;121(Pt 11):2127–34.
Patel A, Frucht SJ. Isolated vocal tremor as a focal phenotype of essential tremor: a retrospective case review. J Clin Mov Disord. 2015;2:4.
Pfeiffer RF. Wilson disease. Continuum (Minneap Minn). 2016;22(4 Movement Disorders):1246–61.
Phibbs F, Fang JY, Cooper MK, Charles DP, Davis TL, Hedera P. Prevalence of unilateral tremor in autosomal dominant essential tremor. Mov Disord. 2009;24(1):108–11.
Raethjen J, Kopper F, Govindan R-f BB, Volkmann J, Deuschl G. Two different pathogenetic mechanisms in psychogenic tremor. Neurology. 2004;63(5):812–5.
Rigby HB, Rigby MH, Caviness JN. Orthostatic tremor: a spectrum of fast and slow frequencies or distinct entities? Tremor Other Hyperkinet Mov (N Y). 2015;5:324.
Robakis D, Louis ED. Head tremor in essential tremor: "yes-yes", "no-no", or "round and round"? Parkinsonism Relat Disord. 2016;22:98–101.
Schneider SA, Bhatia KP. The entity of jaw tremor and dystonia. Mov Disord. 2007;22(10):1491–5.
Schrag A, Munchau A, Bhatia KP, Quinn NP, Marsden CD. Essential tremor: an overdiagnosed condition? J Neurol. 2000;247(12):955–9.
Schwingenschuh P, Deuschl G. Chapter 19 - Functional tremor. In: Hallett M, Stone J, Carson A, editors. Handbook of clinical neurology. 139. Elsevier; 2016. p. 229–33.
Sethi KD. Movement disorders induced by dopamine blocking agents. Semin Neurol. 2001;21(1):59–68.
Shanker V. Essential tremor: diagnosis and management. BMJ. 2019;366:l4485.
Thenganatt MA, Jankovic J. Psychogenic tremor: a video guide to its distinguishing features. Tremor Other Hyperkinet Mov (N Y). 2014;4:253.
van de Wardt J, van der Stouwe AMM, Dirkx M, Elting JWJ, Post B, Tijssen MA, et al. Systematic clinical approach for diagnosing upper limb tremor. J Neurol Neurosurg Psychiatry. 2020;91(8):822–30.

Vial F, Akano E, Attaripour S, McGurrin P, Hallett M. Electrophysiological evidence for functional (psychogenic) essential palatal tremor. Tremor Other Hyperkinet Mov (N Y). 2020;10:10.

Wasielewska A, Rudzinska M, Tomaszewski T, Banaszkiewicz K, Wojcik-Pedziwiatr M, Dec-Cwiek M, et al. Tremor in neuropathies of different origin. Neurol Neurochir Pol. 2013;47(6):525–33.

Welton T, Cardoso F, Carr JA, Chan LL, Deuschl G, Jankovic J, et al. Essential tremor. Nat Rev Dis Primers. 2021;7(1):83.

Zach H, Dirkx M, Bloem BR, Helmich RC. The clinical evaluation of Parkinson's tremor. J Parkinsons Dis. 2015;5(3):471–4.

Zhang J, Xing Y, Ma X, Feng L. Differential diagnosis of Parkinson disease, essential tremor, and enhanced physiological tremor with the tremor analysis of EMG. Parkinsons Dis. 2017;2017:1597907.

Chapter 17
Signal Processing

James McNames

Abstract Signal processing transforms sensor data into metrics or plots that are meaningful for clinical and scientific applications. A wide variety of signal processing methods have been applied in the analysis of tremor. Most of these employ some form of spectral analysis because tremor is a quasi-periodic signal with a dominant rhythm, and the power is concentrated in the frequency domain. There are many methods of spectral analysis, but three are predominantly used for tremor: power spectral density (PSD) estimation, coherence analysis, and spectrograms. These methods are powerful but contain conceptual and practical pitfalls that can be avoided if one has a firm grasp of the underlying principles and limitations. This chapter gives a summary of these principles and provides recommendations for effective application of these methods.

17.1 Introduction

As described in the previous chapter and other recent reviews, many instruments have been developed to measure tremor using a variety of technologies (Vescio et al. 2021). These instruments include accelerometers, gyroscopes, magnetometers, audio, video, tablets, lasers, motion capture systems, contactless sensors, electromyography, electromagnetic systems, microelectrode recordings, local field potentials, and many others. Each of these instruments produces one or more continuous signals that are obtained from one or more points in or on the body. No instrument has become accepted as a gold standard for quantifying tremor. All instruments have some disadvantages, and new instruments are continuing to be developed.

Signal processing algorithms for tremor are usually applied in sequential stages of processing. The initial stages of processing are usually specific to the instrument.

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For example, signal processing of accelerometer signals sometimes includes a processing stage to reduce the effects of gravity, which can otherwise cause rotational oscillations to appear as large accelerations (McGurrin et al. 2021; Veltink et al. 1995; Elble 2005; Mamorita et al. 2009; Šprdlík et al. 2011). Electromyograms are typically rectified and demodulated (Journée et al. 1983). Action potentials are extracted from microelectrode recordings and converted into spike trains (Wilson and Emerson 2002; Kim and McNames 2007). Motion capture systems based on markers often contain periods of occlusion that require some form of interpolation (Das et al. 2011).

In advanced applications, further processing may be applied after extraction of the relevant signal metrics to perform a diagnosis or to combine multiple measurements, possibly from multiple tasks and instruments, into overall scores similar to those provided by clinical rating scales (Heldman et al. 2011). These integration methods are typically well-known statistical methods for classification or regression.

Until recently signal processing methods were applied to recordings after the recordings were complete. This is suitable for clinical and laboratory assessments. However, there are a growing number of applications that require the detection and estimation of tremor in real time for a variety of technologies that perform some type of tremor suppression (Riviere et al. 1998; Zhou et al. 2021).

There are also a growing number of devices that are designed to measure tremor continuously during normal daily activities (Yuan et al. 2021; AlMahadin et al. 2021; San-Segundo et al. 2020). This can be much more challenging than recordings that are collected under controlled conditions in a clinic or laboratory because there are many other types of rhythmic activities of daily living that may resemble tremor such as brushing teeth. Typically, these methods apply traditional analysis method design for stationary signals to short segments. This is often called a sliding window approach.

There has also recently been a growth in methods based on machine learning (Yuan et al. 2021; Tong et al. 2021; Ma et al. 2022; Wang et al. 2021; Channa et al. 2021; San-Segundo et al. 2020). Typically, these methods extract a variety of parameters from sliding window segments and then use the parameters as inputs for the machine learning algorithms.

The chapter focuses on spectral analysis of tremor signals. These methods can be used to process one or more signals obtained from one or multiple instruments. However, these methods cannot be applied to instruments that only provide intermittent information such as electronic pegboards and tests that use buttons since these instruments do not provide continuous signals (Synnott et al. 2011). We assume the signals have been sampled at a known sample rate (f_s) with an appropriate anti-alias filter applied prior to sampling. Anti-alias filters are analog low-pass filters that prevent high-frequency signals from appearing as lower frequency signals after sampling. An overview of instruments and signal processing methods for tremor can be found in Grimaldi and Manto (2010) and Vescio et al. (2021).

17.2 Power Spectral Density Estimation

Most of the signal processing algorithms are either for the purpose of signal analysis, which usually provide insights through a visual display, or for the purpose of extracting metrics from the signal for a specific application, such as the estimation of tremor amplitude. Power spectral density estimation is the most common type of analysis employed for tremor signals.

17.2.1 Statistical Preliminaries

Most of the signal processing algorithms are developed within a statistical framework. This enables us to define and estimate important properties, such as confidence intervals that enable us to interpret our results. However, a statistical framework requires some assumptions and an understanding of the fundamentals of random signals. This section briefly summarizes some of the important fundamentals and ideas about properties of random signals and statistical estimators. This framework and these ideas are discussed in much greater detail elsewhere (Priestley 1981; Manolakis et al. 2005).

Within this framework, each signal is treated as a sequence of random numbers with some type of statistical relationship. Because the signal values are random, our interest and characterization of the signals focuses on statistical properties of the signal that are assumed to be static.

The statistical framework usually rests on two key assumptions. First, we assume that the signal is stationary, which means the statistical properties of the signal do not change over time. In most cases, we only need to assume that the signal is wide sense stationary, which means that the mean

$$\mathrm{E}[x(n)] = \mathrm{E}[x(n+m)] \tag{17.1}$$

and autocorrelation

$$\mathrm{E}[x(n+\ell)x(n)] = \mathrm{E}[x(n+\ell+m)x(n+m)] = r(\ell) \tag{17.2}$$

do not change with time. Here, $\mathrm{E}[\cdot]$ is used to denote the expectation

$$\mathrm{E}[x] = \int_{-\infty}^{\infty} x p(x)\,\mathrm{d}x \tag{17.3}$$

where $p(x)$ is the probability density function of the random variable x. The expectation can be thought of as a statistical average over the ensemble of possible values. If a signal is wide sense stationarity, then the variance

$$\text{var}[x(n)] = \sigma_x^2 \tag{17.4}$$

is also constant.

Our second assumption is called ergodicity. This means that if the signal were recorded many times under similar circumstances that the statistical properties would not change from recording to recording, and that the properties obtained from overages over time would converge to the statistical averages, or expected values. For example, if a signal is ergodic, the time average converges to the statistical mean

$$\lim_{N\to\infty} \frac{1}{2N+1} \sum_{n=-N}^{N} x(n) = \text{E}[x(n)] \tag{17.5}$$

Signal processing uses a finite recording of N samples $\{x(n)\}_{n=0}^{N-1}$ and estimates some of the statistical properties. Because our estimate is calculated from a random signal, the estimate itself will be a random variable. For example, let us define the true tremor amplitude as a. Our estimate of the amplitude, $\hat{a}$, will be some function of the recording

$$\hat{a} = f\left[\{x(n)\}_{n=0}^{N-1}\right] \tag{17.6}$$

The bias of this estimate is defined as

$$b(\hat{a}) = a - \text{E}[\hat{a}] \tag{17.7}$$

and the variance is defined as

$$\sigma^2(\hat{a}) = \text{E}\left[\left(\hat{a} - \text{E}[\hat{a}]\right)^2\right] \tag{17.8}$$

Ideally, we would like our estimate to be unbiased, $b(\hat{a}) = 0$, and have as little variance as possible. In practice, it is difficult to find an estimator with these properties, and the algorithm designer usually must make decisions that involve a tradeoff between bias and variance.

17.2.2 Definition

A stationary random signal is usually characterized by the autocorrelation (17.2) or the power spectral density (PSD). They are related by the discrete-time Fourier transform (DTFT)

$$R_x(\omega) = \sum_{\ell=-\infty}^{\infty} r_x(\ell)\text{e}^{-j\omega\ell} \tag{17.9}$$

where $j = \sqrt{-1}$, ω is the discrete-time frequency in units of radians per sample, and $R_x(\omega)$ is the PSD of interest. It can be shown that for real-valued signals the PSD is an even function of frequency

$$R_x(\omega) = R_x(-\omega) \tag{17.10}$$

and that the PSD is a periodic function of frequency

$$R_x(\omega) = R_x(\omega + 2\pi) \tag{17.11}$$

As a consequence of these two properties, the PSD is completely represented over the frequency range of $0 \leq \omega \leq \pi$ and so in most of the applications only this frequency range is displayed or analyzed.

17.2.3 Relating Continuous- and Discrete-Time Representations

In most of the applications, discrete-time signals are sampled from continuous-time signals with appropriate anti-aliasing. Usually, the continuous-time power spectral density is of interest, so it is important to know how the discrete-time and continuous-time PSDs are related. The continuous-time PSD is defined as

$$P_x(f) = \int_{-\infty}^{\infty} r_x(\tau) \mathrm{e}^{-j2\pi f \tau} \, \mathrm{d}\tau \tag{17.12}$$

where f is the frequency in units of hertz and $r_x(\tau)$ is the continuous-time autocorrelation. Over the frequency range of $0 \leq f < f_\mathrm{s}/2$, the continuous-time PSD is related to the discrete-time PSD as follows:

$$P_x(f) = \frac{1}{f_\mathrm{s}} R_x\left(\frac{2\pi f}{f_\mathrm{s}}\right) \text{ for } 0 \leq f \leq \frac{f_\mathrm{s}}{2} \tag{17.13}$$

The units of $P_x(f)$ are the square of the units of the signal per hertz. For example, if the tremor signal is obtained from an accelerometer with units of $\mathrm{m/s^2}$, then the units of $P_x(f)$ would be $(\mathrm{m/s^2})^2/\mathrm{Hz}$. Note that although the PSD is only plotted for positive frequencies, the signal power is related to the PSD by integrating over both positive and negative frequencies by Parseval's theorem

$$\mathrm{E}[x^2(t)] = \int_{-\frac{f_\mathrm{s}}{2}}^{\frac{f_\mathrm{s}}{2}} P_x(f) \, \mathrm{d}f \tag{17.14}$$

17.2.4 Autocorrelation Versus Power Spectral Density (PSD)

The autocorrelation and PSD are equivalent representations of the second-order statistical properties of signals. One can be obtained from the other, and they form a Fourier transform pair. For tremor analysis, the PSD is a more common and useful characterization because tremor is approximately periodic, $x(t) \approx x(t+T)$, and periodic signals have their power concentrated at frequencies that are integer multiples of the fundamental signal period, which are called harmonics. Thus, the PSD will generally contain a few peaks at frequencies that can be readily interpreted as integer multiples of the tremor frequency, whereas the autocorrelation will contain oscillations that spread out across a broad range of lags ℓ. Thus, it is more difficult to accurately estimate the relevant properties of tremor signals from the autocorrelation than it is the PSD.

17.2.5 Types of PSD Estimation

There are three broad types of PSD estimators that are best understood by statistical model of the random process that each is based on. Parametric estimators are usually based on a statistical model in which white noise is filtered by an unknown linear system. The estimation problem is then reduced to estimating the parameters of the linear system and the power of the white noise process. These methods are accurate when the model is appropriate, but this is not a suitable model for quasi-periodic signals and this type of PSD estimation is seldom applied to tremor signals.

Harmonic PSD estimators are based on a statistical model in which the signal is represented as a sum of sinusoids and white noise. The methods estimate the amplitude, phase, and frequency of each sinusoidal component. These methods are rarely used for tremor signals because the amplitude, phase, and frequency of tremor fluctuate over time.

Nonparametric methods do not employ an explicit statistical model but assume that the PSD is a smooth, continuous function of frequency. They are used widely for estimating the PSD of tremor signals. The application of these methods requires a number of algorithm design decisions that affect properties of the PSD estimate and how it is interpreted. The remainder of this section describes nonparametric methods in detail.

17.2.6 Periodogram

The simplest nonparametric estimator is the periodogram

$$\hat{R}_x(\omega) = \frac{1}{N}\left|\sum_{n=0}^{N-1} x(n)\mathrm{e}^{-j\omega n}\right|^2 \tag{17.15}$$

It can be shown that mathematically this is equivalent to estimating the autocorrelation with

$$\hat{r}_x(\ell) = \frac{1}{N} \sum_{n=0}^{N-1-|\ell|} x(n + |\ell|)x(n) \tag{17.16}$$

and then calculating the DTFT of $\hat{r}_x(\ell)$ with (17.9).

17.2.7 Hazards of the Fast Fourier Transform (FFT)

It is important to note that although the signal is sampled at discrete times for only N samples, the PSD is estimated over a continuum of frequencies $0 \leq \omega < \pi$. The Fast Fourier Transform (FFT) is often used to calculate nonparametric estimates of the PSD and only evaluates the DTFT at N discrete frequencies. Specifically, the FFT is a fast algorithm to calculate the Discrete Fourier Transform

$$X(k) = \sum_{n=0}^{N-1} x(n) \mathrm{e}^{-jkn\frac{2\pi}{N}} \tag{17.17}$$

which is equivalent to evaluating the DTFT at frequencies $\omega = k\frac{2\pi}{N}$ for $k = 0, 1, \ldots, N$.

The algorithm attains the greatest computational efficiency when the recording length is an integer power of 2. If the recording contains N samples, then the FFT produces estimates at $N/2+1$ frequencies over the range $0 \leq \omega \leq \pi$. For recordings of short duration, this can result in a sparse representation of the PSD with wide frequency spacing. The limitation of the FFT to recordings with the number of samples equal to an integer multiple of 2 and the sparse representation of the PSD can both be overcome by simply appending zeros to the end of the signal before applying the FFT. This enables one to create a padded signal that is an integer power of 2 and enables the fast evaluation of the PSD with a dense representation at many frequencies. Zero padding is a well-known and simple method, but it often overlooked and not applied in the analysis of tremor signals. This results in PSD estimates that appear to be sharp and jagged due to the combination of sparse representation of the PSD and piecewise linear interpolation that is often used in plots.

Figure 17.1 shows an example of the hazard of insufficient zero padding. The top plot shows a spike train (bottom, gray) obtained from a 10 s microelectrode recording sampled at 22.05 kHz from a patient with Parkinson's disease during stereotactic neurosurgery. The blue signal shows the spike density after decimating the signal by 484 to a decimated sample rate of 45.6 Hz. The bottom plot shows the periodogram without zero padding and piecewise linear interpolation (red) and

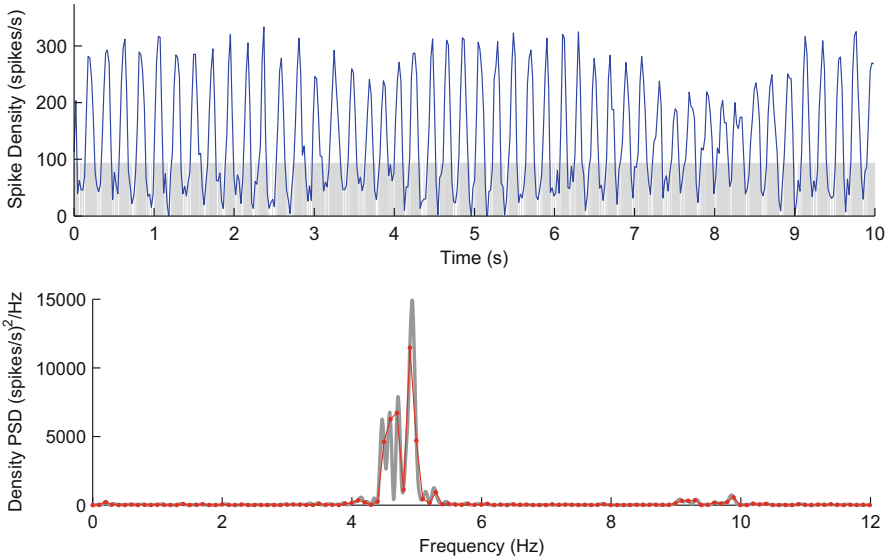

Fig. 17.1 The top figure shows a spike train (gray) and the estimated spike density (blue) of a spike train. The bottom figure shows the periodogram with (thick gray) and without (thin red) zero padding. This example demonstrates the distortions caused by insufficient zero padding and piecewise linear interpolation

the periodogram with zero padding such that the padded signal contained $2^{13} + 1$ samples. The periodograms agree exactly at the estimated frequencies, but the estimate without zero padding is badly distorted by coarse sampling and piecewise linear interpolation.

17.2.8 Signal Windowing

The primary limitation that prevents us from estimating the true PSD perfectly from (17.9) is that our recordings are finite and only comprised of N samples. Mathematically, the effect of observing the signal for only N samples can be modeled as multiplying the signal of interest $s(n)$ with a window $w(n)$

$$x(n) = w(n)s(n) \tag{17.18}$$

where the window has a finite duration

$$w(n) = 0 \text{ for } n < 0 \text{ and } n \geq N \tag{17.19}$$

It can be shown that the PSD of $x(n)$ is related to the PSD of $s(n)$ as follows:

$$\mathrm{E}\left[\hat{R}(\omega)\right] = \frac{1}{2\pi}\int_{-\pi}^{\pi} R_x(u)\frac{1}{N}R_w(\omega - u)\,\mathrm{d}u \tag{17.20}$$

where

$$R_w(\omega) = \sum_{\ell=-(N-1)}^{N-1} r_w(\ell)\mathrm{e}^{-j\omega\ell} \tag{17.21}$$

and

$$r_w(\ell) = \sum_{n=0}^{N-1-|\ell|} w(n+|\ell|)w(n) \tag{17.22}$$

Conceptually, one can understand windowing as a weighted averaging of adjacent frequencies, as represented mathematically by (17.20). One can interpret the effect of windowing as smoothing or blurring the PSD estimate. This causes some bias in the estimate and particularly near sharp features in the spectrum such as peaks. The shorter the recording is, the more difficult it is to distinguish adjacent frequencies. As a rule of thumb, one should aim to ensure the signal duration is sufficiently long to capture ten or more cycles at the lowest frequency of interest. Tremor rarely approaches frequencies below 2 Hz (Deuschl et al. 2001). Thus, recording durations should be at least 5 s in duration and preferably much longer.

Figure 17.2 shows an example of the periodogram applied to the signal in Fig. 17.1. White noise was added to the signal such that the signal-to-noise ratio is approximately 1. The example illustrates that the estimate is smoother and more biased for shorter recording durations, but the variance of the estimate is unaffected by the signal duration. This is the primary limitation of the periodogram.

It is important to keep the effect of windowing in mind when interpreting PSD estimates, particularly when comparing recordings of different durations. Even if the statistical properties of the signals are identical, the recording with a shorter duration will produce an estimate that is smoother. This means any peaks at frequencies corresponding to tremor will be shorter and broader in the shorter duration recording. The effect of windowing is also important to keep in mind when calculating the tremor frequency or amplitude from PSD estimates.

Intuitively, one would expect that a rectangular window

$$w_{\mathrm{r}}(n) = \begin{cases} 1 & 0 \le n \le N-1 \\ 0 & \text{Otherwise} \end{cases} \tag{17.23}$$

would be the best choice. However, windows that are tapered can generate better performance, though this depends on the application. Virtually, all time-domain

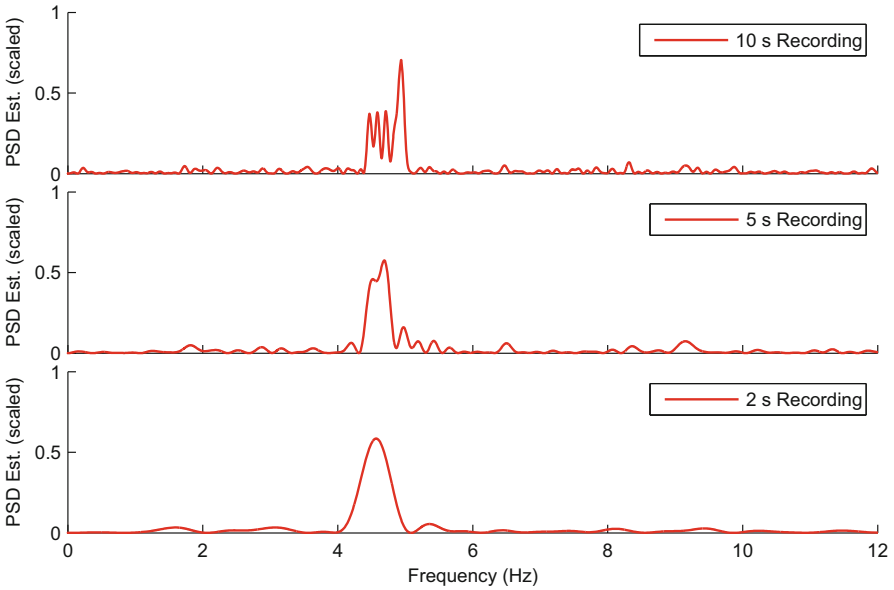

Fig. 17.2 Example of the periodogram applied to the signal from the previous example for recording durations of 10 s (top), 5 s (middle), and 2 s (bottom). White noise was added to better show the variance of the PSD estimates. Longer signal durations produce PSD estimates that have greater resolution (less bias), but the same variance

windows of interest are symmetric and smooth functions of time. As long as the window is scaled such that

$$\sum_{n=0}^{N-1} w(n)^2 = N \tag{17.24}$$

the periodogram is asymptotically unbiased.

The Fourier transform of the windows contains oscillations as shown in Fig. 17.3. The windows give the most weight to adjacent frequencies and some weight to the entire range of frequencies. The primary tradeoff in selection of a window is between the width of the main lobe and the height of the sidelobes. A wider main lobe creates a smoother estimate with more averaging of adjacent frequencies and generally results in smaller sidelobes, as shown in the bottom of Fig. 17.3. A narrower main lobe results in higher sidelobes which can give significant weighting to distant frequencies. Rectangular windows have the narrowest main lobe, but the highest sidelobes. Most of the software packages used for signal processing of tremor signals provide a variety of windows to choose from. More guidance on the selection of windows can be found in Oppenheim and Schafer (1999), Manolakis et al. (2005). The window selected should always be reported as part

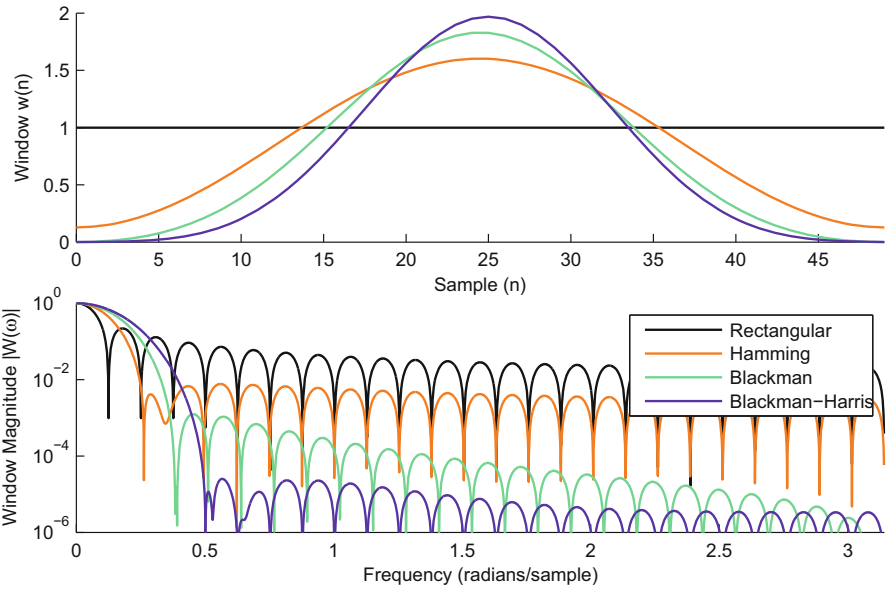

Fig. 17.3 The top plot shows examples of four types of common data windows as a function of time. The windows were scaled to satisfy (17.24). The bottom plot shows the magnitude of the same four windows as a function of frequency. To illustrate the tradeoff between the main lobe width and the sidelobe height, the windows were scaled to have the unity gain at $\omega = 0$

of the methodology. As discussed in Sect. 17.2.11, this decision is generally less critical than selecting the extent of smoothing.

17.2.9 PSD Smoothing

Although the periodogram is a simple estimator, it is not statistically consistent and should not be used to estimate the PSD of tremor signals. A consistent estimator is one that converges to the true PSD as the recording duration increases, $N \to \infty$. The variance of the periodogram at any given frequency remains constant as the recording duration increases, though longer recordings decrease bias and smoothing due to the windowing effect. In most of the applications, the high variance of the periodogram is unacceptable for applications involving the estimation of tremor.

17.2.9.1 The Welch–Bartlett Method

There are two popular nonparametric methods to estimate the PSD. One approach divides the entire recording into segments, possibly with some overlap, calculates

a periodogram for each segment, and creates a final estimate as the average of the segment periodograms. This approach is sometimes called the Welch–Bartlett method (Manolakis et al. 2005). It is both easy to implement and understand, and it is the most common method used to estimate the PSD of tremor signals (Pigg et al. 2020).

The primary tradeoff between bias and variance is determined by the segment length, L. Shorter segment lengths result in larger averages that reduce variance, but at the expense of smoothing the PSD estimates, which causes bias.

The user must also specify the extent to which the segments overlap. Increasing the overlap results in more PSD segments to average, which decreases variance without increasing bias, although at the expense of additional computation. A large degree of overlap can substantially increase the computation without significantly decreasing the bias because the estimated PSDs from segments with a lot of overlap are correlated and contain a lot of the same information. In practice, 50% overlap is often used. This is considered a point of diminishing return, where more overlap does not decrease variance sufficiently for the additional computation that is required.

17.2.9.2 The Blackman–Tukey Method

The second nonparametric method calculates the estimated signal autocorrelation, applies a correlation window, and calculates the DTFT of the windowed autocorrelation estimate to produce the PSD estimate. Specifically, the autocorrelation is estimated with

$$\hat{r}_x(\ell) = v(\ell)\frac{1}{N}\sum_{n=0}^{N-1-|\ell|} x(n+|\ell|)x(n) \tag{17.25}$$

where $v(\ell)$ is the correlation window. The estimated PSD is calculated from (17.9). To prevent bias, $v(\ell)$ is scaled such that $v(0) = 1$. We assume that $v(\ell)$ has a duration of L samples, $v(\ell) = 0$ for $|\ell| \geq L$ and $L < N$. Note that the effect of this windowing is to bias the autocorrelation estimate toward zero. This multiplication of the autocorrelation and window in the time-domain results in a convolution, or filtering, of the periodogram PSD with the Fourier transform of the window. This has the effect of smoothing the PSD estimate, which reduces the variance at the expense of bias.

This method is sometimes called the Blackman–Tukey method (Manolakis et al. 2005). It can be shown that when the Welch–Bartlett method is applied with the maximum overlap, which minimizes the variance of the estimate, it becomes equivalent to the Blackman–Tukey method (Priestley 1981), though the Blackman–Tukey method is more efficient computationally. The Blackman–Tukey method generally produces estimates with less variance for an equivalent degree of smoothing and

is computationally efficient, particularly if the FFT is used to compute both the autocorrelation estimate and the DTFT of the windowed autocorrelation.

The variance of the PSD estimated from the Blackman–Tukey method is approximately

$$\text{var}\left\{\hat{R}_x(\omega)\right\} \approx R_x^2(\omega)\frac{\sum_{\ell=-(L-1)}^{L-1} v^2(\ell)}{N} \tag{17.26}$$

Thus, the estimated PSD variance at a given frequency is proportional to the square of the true PSD, proportional to the energy of the correlation window, and inversely proportional to the recording duration.

Approximate confidence intervals for the Blackman–Tukey method can be obtained from the following:

$$\frac{\hat{R}_x(\omega)}{\frac{1}{\nu}\chi_\nu^{-2}(1-\alpha/2)} < R_x(\omega) < \frac{\hat{R}_x(\omega)}{\frac{1}{\nu}\chi_\nu^{-2}(\alpha/2)} \tag{17.27}$$

where $\chi^{-2}(1-\alpha/2)$ is the inverse cumulative distribution function of a χ^2 distribution with ν degrees of freedom and α specifies the level of confidence. A typical value of $\alpha = 0.05$ generating a 95% confidence interval. The degrees of freedom ν are approximated as

$$\nu = \frac{2N}{\sum_{\ell=-(L-1)}^{L-1} v^2(\ell)} \tag{17.28}$$

Both estimates of the variance and confidence intervals are based on approximations that assume that the bias is small due to a large recording duration and that $L \ll N$. In practice, this assumption is often not satisfied and the variance estimate and confidence intervals should be treated with due caution, particularly near peaks in the estimated PSD.

17.2.9.3 Smoothing Spectral Peaks

Fundamentally, both nonparametric PSD estimators, and other less common nonparametric PSD estimators, effectively smooth the PSD estimates as compared to the periodogram. If the true PSD is a smooth function of frequency and the recording is of sufficient duration, this smoothing can significantly reduce variance without creating significant bias. However, if the PSD contains sharp features such as peaks caused by nearly sinusoidal signal components, the bias can be significant and detrimental. Figure 17.4 shows some examples of this tradeoff with a tremor signal.

Tremor signals share some of the properties of periodic signals, but the amplitude, phase, and frequency of the harmonic components are not constant over time. When estimating the PSD from a given recording, these have the effect of

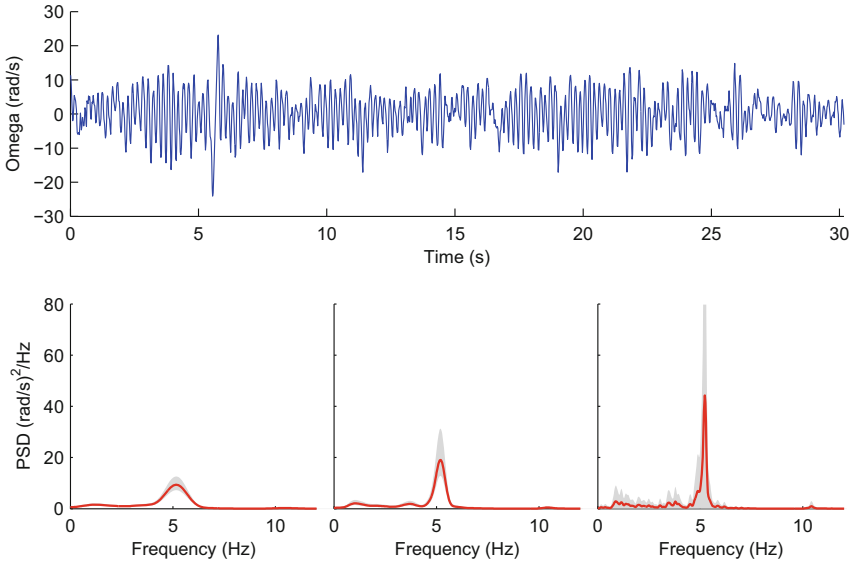

Fig. 17.4 The top plot shows a 30 s recording from a gyroscope placed on the wrist of a person with Parkinson's disease in an unmedicated, practically defined off state. The bottom plots show the PSD estimated with the Blackman–Tukey method. The PSD estimated was calculated with a rectangular signal window and a Blackman correlation window. 95% confidence intervals are shown in gray. The correlation window durations were 2 s (bottom left), 5 s (bottom middle), and 20 s (bottom right)

broadening the peaks in the estimated PSD as compared to a sinusoidal peak. Thus, the spectral peaks are not sharp, and some degree of smoothing is justified to reduce the variance of the estimated PSD.

17.2.10 Interpreting the Power Spectral Density

It is well known that any periodic signal with fundamental period T can be represented as a sum of sinusoids with frequencies at integer multiples of $1/T$. Periodic signals that are smooth have their power concentrated in low frequencies and periodic signals with sharp features, such as impulse trains, have more power at high frequencies.

Tremor signals are called quasi-periodic because they do not meet the strict definition of a periodic signal due to slow changes in amplitude, phase, and frequency. Tremor signals tend to be smooth, and most of the signal power is contained in 2–3 harmonics.

17.2.11 Recommendations and Tradeoffs

There are four decisions that the user must make to apply a nonparametric method of spectral estimation. First, the amount of zero padding should be adequate to permit a dense evaluation of the spectral estimate over the frequency range of interest. The PSD of tremor is rarely plotted for frequencies higher than 20 Hz. Generally, sufficient zero padding should be used to evaluate the PSD at 200–2000 different frequencies. Mathematically, the length of the padded signal should be at least

$$N \geq n_{\mathrm{p}} \frac{f_{\mathrm{s}}}{f_{\max}} \tag{17.29}$$

where n_{p} is the minimum number of frequencies used in the plot, f_{s} is the sample rate, and $f_{\max}$ is the maximum frequency displayed.

Second, the user must select a signal window. If the recording duration is sufficiently long, say >30 s, then little bias is incurred by the smoothing of the PSD estimate caused by the signal window, and then one should prioritize minimizing sidelobe leakage with a sidelobe of no more than 0.1% of the peak amplitude (60 dB). The Blackman window is a simple window that achieves this. If the recording duration is short, say $\leq$ 30 s, a rectangular window is recommended to reduce bias due to smoothing.

Third, the user must select a PSD estimator. The Blackman–Tukey method generally has better statistical properties than the Welch–Bartlett method and is recommended. With modern computers and the computational efficiency gained from use of the FFT, the differences in computational demands of these two methods are not significant, and the Blackman–Tukey method is often more efficient. Because of excessive variance, the periodogram is not recommended.

Fourth, the user must decide how much smoothing to apply. For the Welch–Bartlett method, this is determined primarily by the segment duration. For the Blackman–Tukey method, this is determined primarily by the correlation window duration. This is the most critical decision because it is the primary means to control the tradeoff between bias and variance of the estimate. Generally, the duration should be sufficient to include at least 5–20 cycles of the slowest expected frequency component. For most of the tremor signals, a duration of 5–10 s is recommended.

17.2.12 Power Spectral Density Statistics

Although the statistical properties of PSD estimates are well understood, the statistical properties of metrics calculated from the estimated PSD are not. For example, in many applications, the tremor frequency is calculated as the frequency at which the PSD is maximized, though the statistical properties of this estimator are not known.

The amplitude of the tremor is difficult to estimate from the PSD because the amplitude of the tremor is spread across a range of frequencies due to windowing and smoothing effects and is usually spread across 2–3 harmonics. Although it is a common practice to estimate the tremor amplitude as the height of the peak of the PSD, this practice is not recommended. The recording duration, window selection, amount of zero padding, and degree of PSD smoothing can all have a significant impact on the height of peaks in the estimated PSD, as illustrated in Fig. 17.4. The peak amplitude can also be affected by the degree of fluctuation in the frequency of the tremor.

A better estimate of tremor amplitude can be obtained by calculating the total power over the range of frequencies covered by each of the harmonic peaks. However, this approach is also imperfect because it does not distinguish between the tremor signal and noise over these frequencies and because it can be difficult to accurately estimate the beginning and end of each peak in the PSD. Some efforts have been made to overcome these limitations (Bartolić et al. 2009; McGurrin et al. 2021).

17.3 Coherence Analysis

Coherence is analogous to measuring correlation as a function of frequency. This type of analysis for tremor started to become popular in the 2000s (Deuschl et al. 2001), even though this type of analysis has been known in the time series analysis and signal processing literature since the 1930s.

Consider two ergodic, jointly stationary random signals $x(n)$ and $y(n)$. Coherency is defined as

$$\mathscr{G}_{yx}(\omega) = \frac{\left|R_{yx}(\omega)\right|}{\sqrt{R_x(\omega)R_y(\omega)}} \tag{17.30}$$

where $R_x(\omega)$ and $R_y(\omega)$ are the PSDs as defined in (17.9). $R_{yx}(\omega)$ is the joint power spectral density of $x(n)$ and $y(n)$, which is defined as

$$R_{yx}(\omega) = \sum_{\ell=-\infty}^{\infty} r_{yx}(\ell)\mathrm{e}^{-j\omega\ell} \tag{17.31}$$

where $r_{yx}(\ell)$ is the cross correlation

$$r_{yx}(\ell) = \mathrm{E}\left[y(n+\ell)x(n)\right] \tag{17.32}$$

The coherency is analogous to a Pearson correlation coefficient as a function of frequency. The magnitude-squared coherence (MSC), or simply coherence, is defined as $\mathscr{G}^2_{xy}(\omega)$. The coherence is analogous to a coefficient of determination.

Coherence has many interesting and useful properties. Like the coefficient of determination, coherence is bounded such that $0 \leq \mathscr{G}_{xy}^2(\omega) \leq 1$, and it is invariance to the scale of the signals. If $y(n)$ is the output of an arbitrary linear system with $x(n)$ as an input signal, then $\mathscr{G}_{xy}^2(\omega) = 1$ for all ω. If the signals are uncorrelated such that $r_{xy}(\ell) = 0$ or if the signals are zero mean and statistically independent, then $\mathscr{G}_{xy}^2(\omega) = 0$ for all ω. The coherence is a symmetric function of frequency, so like PSDs, it is only calculated for positive frequencies over the range $0 \leq \omega \leq \pi$.

Like the coefficient of determination, the coherence can be interpreted as the fraction of signal variation that could be explained by an optimal linear dynamic model applied to the other signal. For example, a coherence of 0.5 at a frequency ω_o indicates that half of the variation of $R_y(\omega_o)$ can be explained by estimating $y(n)$ with an optimal linear model that processes $x(n)$.

17.3.1 Coherence Estimation

Coherence may be estimated using either of the nonparametric methods discussed earlier. However, the statistical properties of the estimate is only well established for the Welch–Bartlett method under the assumption that the random signals are Gaussian, the segments are statistically independent, and there is no spectral leakage or bias from windowing effects (Carter 1987; Amjad et al. 1997; Wang and Tang 2004). It is common practice to assume these conditions are approximately met when the Welch–Bartlett method is used with non-overlapping signal segments. However, the assumption of independence is especially questionable for signals with strong spectral peaks, such as tremor, with autocorrelations and cross-correlations that decay slowly with time. Thus, in practice, the assumptions are not satisfied and the statistical properties of coherence estimates should be viewed and interpreted with due caution.

As a practical example, suppose we have a stationary 30 s tremor recording. A typical tremor recording duration may range from 10 to 60 s. Kinetic and postural tremor are difficult to maintain consistently for longer periods due to subject fatigue. If we assume a minimum expected tremor frequency of 2 Hz and we wish to select a segment duration of at least 10 cycles of the lowest frequency, then our segment duration is 5 s. If we use the Welch–Bartlett method with non-overlapping segments to strengthen compliance with our assumption of independent segments, then we have merely 6 independent segments to work with. The exact 95% confidence intervals, given the aforementioned assumptions, are shown in Fig. 17.5 (Wang and Tang 2004). The confidence intervals are narrow for large values and values very close to zero, but at intermediate values the confidence intervals are very large. As expected, the intervals become narrower as the number of intervals becomes larger but still cover a substantial range even when 24 intervals are used, which corresponds to a recording duration of 120 s.

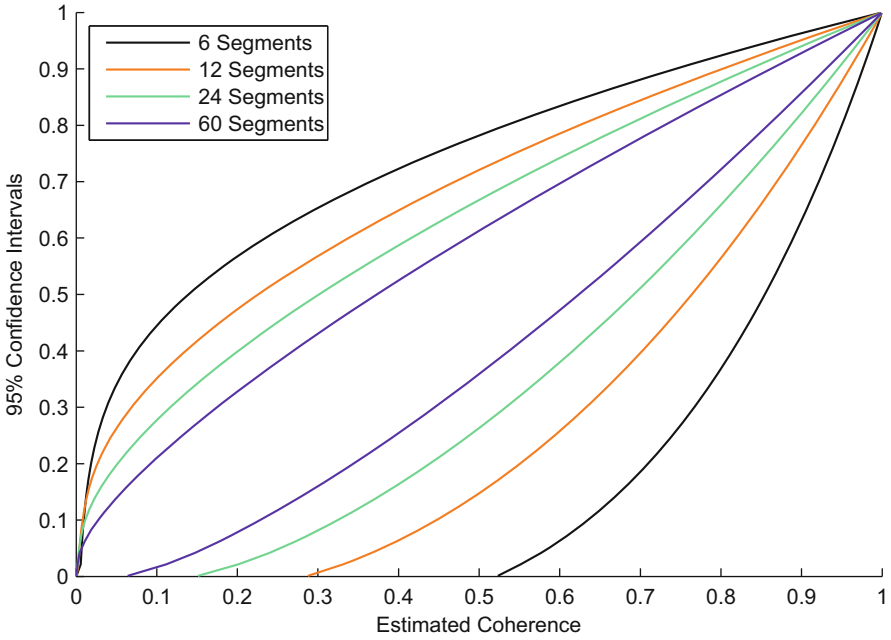

Fig. 17.5 Exact confidence intervals as a function of estimated coherence

There are additional, less well-known hazards and tradeoffs when working with coherence. Random signals with strong spectral peaks and low noise, as often occurs with tremor, can suffer from strong bias due to spectral leakage. The fluctuations in power densities at the tremor harmonics cause induced fluctuations at adjacent frequencies due to the spectral leakage, which can artificially elevate the estimates of coherence at these frequencies and particularly in signals with low noise levels. This problem can be reduced, but not completely eliminated, by selecting a window with a small sidelobe leakage.

Figure 17.6 shows three pairwise coherence estimates from three signals collected from gyros mounted on the wrists of a subject with Parkinson's disease in an unmedicated, practically defined off state. At the time of the recording, the subject was performing a categorical naming task designed to activate the disease symptoms. The first two signals were obtained from gyros mounted in orthogonal directions from the right wrist. The third signal was obtained from the right wrist. As expected, the coherence between the two signals obtained from the right wrist was coherent at the tremor frequency. The two coherence estimates between the gyro signals on the right wrist and the signal on the left wrist were not coherent. Note the large fluctuations in coherence at frequencies other than the tremor frequency. These illustrate the high variance of the coherence estimate.

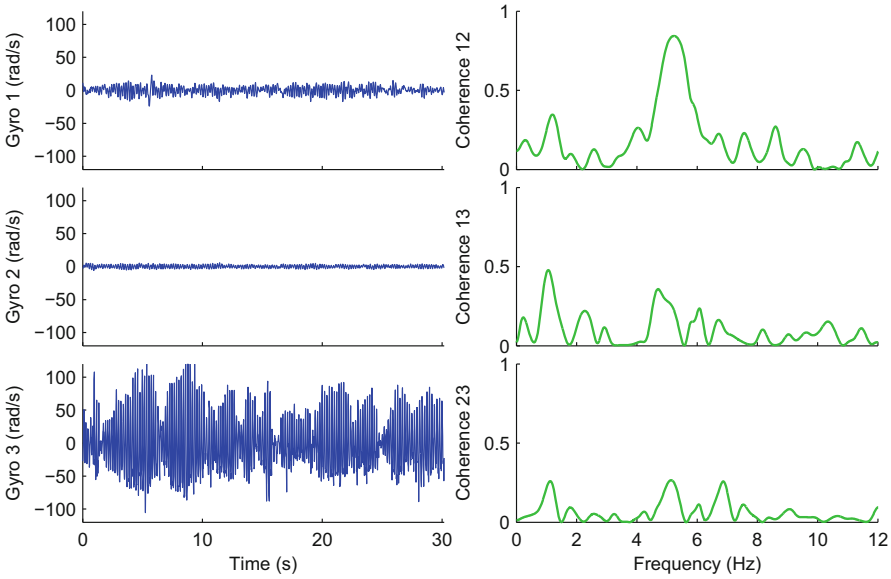

Fig. 17.6 The plots on the left show the signals from three gyroscopes. Two of the gyroscopes were mounted on the right wrist with sensor axes at 90° angles (Gyro 1 and Gyro 2). Gyro 3 was mounted on the left wrist. The three plots on the right show the coherence estimated with the Blackman–Tukey method with a rectangular signal window and a Blackman correlation window with a duration of 5 s. The estimated PSD from Gyro 1 is shown in Fig. 17.4. This example illustrates that the signals from the gyroscopes on the right wrist were coherent at the tremor frequency (≈ 5.2 Hz), but the signals from the left and right wrists were not

17.4 Spectrogram

In short, recordings obtained under carefully controlled conditions where the subject is not performing voluntary movements, it may be reasonable to assume the signal is stationary as described in Sect. 17.2.1. However, in many cases, this assumption does not hold. In particular, kinetic tremor can occur during very brief intervals that are timed with a particular activity. Both the frequency and amplitude of tremor can change over time. This is especially true in long-term recordings that are obtained, while the subjects go about their normal daily activities.

In these situations, it is more suitable to analyze the signal such that the tremor is *locally* stationary. This approach uses a sliding window to analyze windowed segments of the signal:

$$x_s(n, n_s) = w(n - n_s)x(n) \tag{17.33}$$

where $x_s(n, n_s)$ is the windowed signal segment, $w(n - n_s)$ is a symmetric data window such that $w(-n) = w(n)$, and n_s is the time at which the data window is centered. Any data window could be used so long as it has a finite duration,

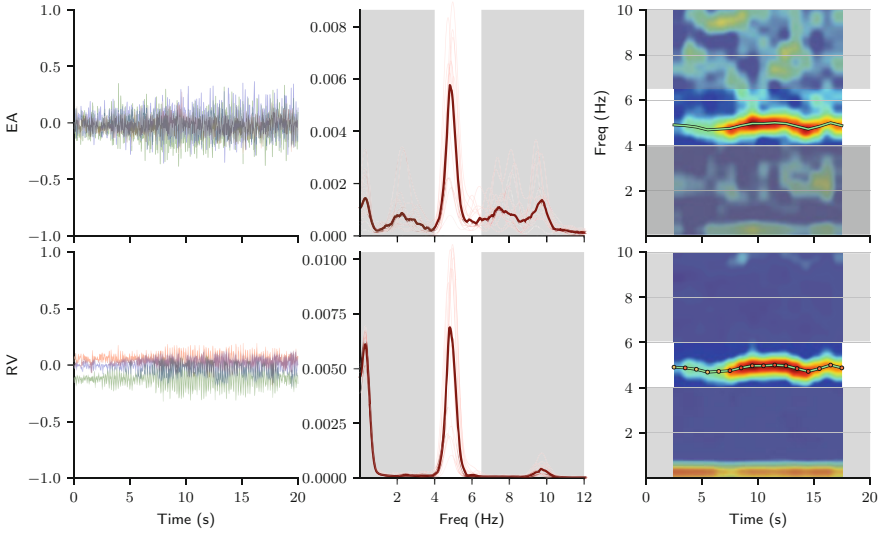

Fig. 17.7 The top row shows the analysis of acceleration in an Earth reference frame and the bottom row shows the analysis of the rotational velocity. The left column shows the time-domain signals, the middle column shows the PSDs, and the right column shows the spectrograms. This illustrates that the amplitude and frequency of tremor may change over time and that this may not be apparent in the time-domain plots and PSD estimates

but typically a tapered window is used such as one of the windows described in Sect. 17.2.8. The same type of spectral analysis can then be performed on each windowed segment to create a series of PSD estimates that vary over time. These are typically displayed with as an image where a range of colors is used to indicate how the signal power is distributed across time and frequency.

Figure 17.7 shows two examples obtained from an inertial measurement unit on the left wrist of a seated subject with essential tremor holding their hands extended in front of them for 20 s. The top row shows the analysis of acceleration estimated in a global reference frame that removes the effects of gravity from the accelerometer (McGurrin et al. 2021). The bottom row shows the analysis of the rotation velocity measured with a gyroscope. The left column shows three signals corresponding to the three sensor axes for acceleration (top left) and rotational velocity (bottom left). The middle column shows the estimated PSD. The PSDs from each axis were added together to create a single overall PSD that is invariant to the orientation of the sensor. In both examples, there is a single prominent peak that is typically interpreted as the tremor frequency and the area under this peak indicates the tremor amplitude. The white region indicates the range of tremor frequencies that are expected for this subject.

The third column shows the spectrograms of these signals. This was calculated using a sliding window estimate using the Blackman–Tukey method. This was based on a Blackman data window with a duration of 4 s and a Blackman autocorrelation

window with a duration of 3.5 s. Following best practices, zero padding was applied to each segment to ensure adequate resolution and display the image across 512 frequencies. Similarly, the sliding window was moved in steps of 3 ms to ensure adequate resolution across the 20 s signal duration. Note that the spectrogram is truncated because with a 4 s data window, the analysis cannot begin until 2 s after the start of the recording and must end 2 s before the end of the recording. The spectrogram also includes a line that shows the tremor frequency estimated as the frequency of the peak at each time point.

This example demonstrates that even during a short recording period where the subject is trying to remain still, both tremor frequency and amplitude are changing over time. This is not readily apparent in either time-domain plots or PSD analysis, but these properties are clear in the spectrograms. This also means the frequency and amplitude of tremor are more accurately represented and thought of as stochastic processes that change over time, rather than as constants.

The window duration is the most important parameter when computing spectrograms. The window duration should be long enough to represent 5–15 fundamental periods of the slowest frequency of interest. Most tremor occurs at frequencies above 3 Hz, so tapered windows with a duration of 3–5 s are usually suitable for tremor. Longer windows provide greater frequency resolution but may over-smooth the time-domain variation. Conversely, shorter windows may result in over-smoothing in the frequency domain producing very broad peaks that make it more difficult to accurately estimate the tremor frequency. Additionally, ample zero padding and small step sizes for the sliding window should be used to ensure the spectrogram can be displayed as a high-resolution image.

17.5 Discussion and Summary

Many types of signal processing algorithms have been developed for the analysis and characterization of tremor signals for a variety of applications (Grimaldi and Manto 2010). The methods described in this chapter are not comprehensive but provide a foundation for the three most common types of analysis that are applied to tremor signals. All three methods are powerful and widely used but require informed decisions to ensure the analysis is accurate and interpreted appropriately.

References

AlMahadin G, Lotfi A, McCarthy M, Breedon P. Task-oriented intelligent solution to measure Parkinson's disease tremor severity. J Healthcare Eng. 2021;2021:9624,386. https://doi.org/10.1155/2021/9624386.

Amjad AM, Halliday DM, Rosenberg JR, Conway BA. An extended difference of coherence test for comparing and combining several independent coherence estimates: theory and application to the study of motor units and physiological tremor. J Neurosci Methods. 1997;73(1):69–79.

Bartolić A, Šantić M, Ribarič S. Automated tremor amplitude and frequency determination from power spectra. Comput Methods Programs Biomed. 2009;94(1):77–87. http://doi.org/10.1016/j.cmpb.2008.10.007.

Carter GC. Coherence and time delay estimation. Proc IEEE. 1987;75(2):236–55.

Channa A, Ifrim RC, Popescu D, Popescu N. A-WEAR bracelet for detection of hand tremor and bradykinesia in Parkinson's patients. Sensors. 2021;21(3). http://doi.org/10.3390/s21030981. https://www.mdpi.com/1424-8220/21/3/981.

Das S, Trutoiu L, Murai A, Alcindor D, Oh M, De la Torre F, Hodgins J. Quantitative measurement of motor symptoms in Parkinson's disease: a study with full-body motion capture data. In: 33rd Annual International Conference of the IEEE EMBS, 2011, p. 6789–92.

Deuschl G, Raethjen J, Lindemann M, Krack P. The pathophysiology of tremor. Muscle Nerve. 2001;24(6):716–35.

Elble RJ. Gravitational artifact in accelerometric measurements of tremor. Clin Neurophysiol. 2005;116(7):1638–43. http://doi.org/10.1016/j.clinph.2005.03.014.

Grimaldi G, Manto M. Neurological tremor: sensors, signal processing and emerging applications. Sensors. 2010;10:1399–422.

Heldman DA, Jankovic J, Vaillancourt DE, Prodoehl J, Elble RJ, Giuffrida JP. Essential tremor quantification during activities of daily living. Parkinsonism Relat Disord. 2011;17(7):537–42. http://doi.org/10.1016/j.parkreldis.2011.04.017.

Journée HL, van Manen J, van der Meer JJ. Demodulation of e.m.g.s of pathological tremours. Development and testing of a demodulator for clinical use. Med Biol Eng Comput. 1983;21(2):172–5.

Kim S, McNames J. Automatic spike detection based on adaptive template matching for extracellular neural recordings. J Neurosci Methods. 2007;165(2):165–74. http://doi.org/10.1016/j.jneumeth.2007.05.033.

Ma C, Li D, Pan L, Li X, Yin C, Li A, Zhang Z, Zong R. Quantitative assessment of essential tremor based on machine learning methods using wearable device. Biomed Signal Process Control. 2022;71:103,244. https://doi.org/10.1016/j.bspc.2021.103244. https://www.sciencedirect.com/science/article/pii/S1746809421008417.

Mamorita N, Iizuka T, Takeuchi A, Shirataka M, Ikeda N. Development of a system for measurement and analysis of tremor using a three-axis accelerometer. Methods Inf Med. 2009;48(6):589–94. http://doi.org/10.3414/ME9243.

Manolakis DG, Ingle VK, Ingle V, Kogon SM. Statistical and adaptive signal processing: spectral estimation, signal modeling, adaptive filtering and array processing. London: Artech House; 2005.

McGurrin P, McNames J, Wu T, Hallett M, Haubenberger D. Quantifying tremor in essential tremor using inertial sensors–validation of an algorithm. IEEE J Transl Eng Health Med. 2021;9:1–10. http://doi.org/10.1109/JTEHM.2020.3032924.

Oppenheim AV, Schafer RW. Discrete-time signal processing. 2nd ed. Upper Saddle River, NJ: Prentice Hall; 1999.

Pigg AC, Thompson-Westra J, Mente K, Maurer CW, Haubenberger D, Hallett M, Charles SK. Distribution of tremor among the major degrees of freedom of the upper limb in subjects with essential tremor. Clin Neurophys. 2020;131(11):2700–12. https://doi.org/10.1016/j.clinph.2020.08.010. https://www.sciencedirect.com/science/article/pii/S1388245720304624.

Priestley MB. Spectral analysis and time series. Cambridge: Academic Press; 1981.

Riviere C, Rader R, Thakor N. Adaptive cancelling of physiological tremor for improved precision in microsurgery. IEEE Trans Biomed Eng. 1998;45:839–46. https://doi.org/10.1109/10.686791

San-Segundo R, Zhang A, Cebulla A, Panev S, Tabor G, Stebbins K, Massa RE, Whitford A, de la Torre F, Hodgins J. Parkinson's disease tremor detection in the wild using wearable accelerometers. Sensors. 2020;20(20). https://doi.org/10.3390/s20205817. https://www.mdpi.com/1424-8220/20/20/5817.

Šprdlík O, Hurák Z, Hoskovcová M, Ulmanová O, Růžička E. Tremor analysis by decomposition of acceleration into gravity and inertial acceleration using inertial measurement unit. Biomed Signal Process Control. 2011;6(3):269–79. https://doi.org/10.1016/j.bspc.2010.09.004. https://www.sciencedirect.com/science/article/pii/S1746809410000741. ITAB 2009.

Synnott J, Chen L, Nugent CD, Moore G. WiiPD — an approach for the objective home assessment of Parkinson's disease. In: 33rd Annual International Conference of the IEEE EMBS; 2011, p. 2388–99.

Tong L, He J, Peng L. CNN-based PD hand tremor detection using inertial sensors. IEEE Sensors Lett. 2021;5:1–4. https://doi.org/10.1109/LSENS.2021.3074958.

Veltink PH, Engberink EGO, Van Hilten BJ, Dunnewold R, Jacobi C. Towards a new method for kinematic quantification of bradykinesia in patients with Parkinson's disease using triaxial accelerometry. In: IEEE 17th Annual Conference Engineering in Medicine and Biology Society, vol. 2; 1995, p. 1303–4. https://doi.org/10.1109/IEMBS.1995.579693.

Vescio B, Quattrone A, Nisticò R, Crasà M, Quattrone A. Wearable devices for assessment of tremor. Front Neurol. 2021;12. https://doi.org/10.3389/fneur.2021.680011. https://www.frontiersin.org/article/10.3389/fneur.2021.680011.

Wang S, Tang M. Exact confidence interval for magnitude-squared coherence estimates. IEEE Signal Process Lett. 2004;11(3):326–9. https://doi.org/10.1109/LSP.2003.822897.

Wang X, Garg S, Tran SN, Bai Q, Alty J. Hand tremor detection in videos with cluttered background using neural network based approaches. Health Inf Sci Syst. 2021;9(1):30. https://doi.org/10.1007/s13755-021-00159-3.

Wilson S, Emerson R. Spike detection: a review and comparison of algorithms. Clin Neurophysiol. 2002;113;1873–81.

Yuan H, Liu S, Liu J, Lin H, Yang C, Cai X, Zeng L, Li S. Detection and quantification of resting tremor in Parkinson's disease using long-term acceleration data. Math Probl Eng. 2021;2021;5669,932. https://doi.org/10.1155/2021/5669932.

Zhou Y, Ibrahim A, Hardy KG, Jenkins ME, Naish MD, Trejos AL. Design and preliminary performance assessment of a wearable tremor suppression glove. IEEE Trans Biomed Eng. 2021;68:2846–57. https://doi.org/10.1109/TBME.2021.3080622.

Chapter 18
Diffusion Imaging in Tremor

Johannes C. Klein

Abstract Diffusion-weighted magnetic resonance imaging (DWI) of the brain is a magnetic resonance technique that probes the motion of free water undergoing spontaneous diffusion in living tissue. Unlike conventional, structural MRI, DWI provides insights into the microscopic composition, integrity and orientation of structures in the human brain. DWI and its derivative measures enable the study of the microstructure of the brain and its white-matter connectivity. These non-invasive measures offer a window into the neuropathology of tremor, and the underlying tremor disorders.

In Parkinson's disease (PD), changes in diffusion-derived parameters such as mean diffusivity (MD) and fractional anisotropy (FA) have been reported in the substantia nigra and its connections to the striatum when compared to control subjects, suggesting that these imaging measures are sensitive to the degeneration of the nigral dopaminergic neurons and their striatal projections. In essential tremor (ET), a link between diffusion-derived measures and the severity of tremor has been shown.

DWI-derived diffusion tractography (DT) enables the study of connectional targets that mediate the effects of deep brain stimulation (DBS) for tremor, and carries the promise to help guide stereotaxic surgical targeting in the future. DT has also provided insight into the motor circuits putatively affected by accidental, tremor-causing brain lesions.

In conclusion, DWI is a promising tool in the study of tremor disorders. Further research is needed to determine if DWI may be useful to plan stereotaxic surgery for tremor.

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18.1 Introduction

In recent years, diffusion-weighted magnetic resonance imaging (DWI) has complemented established imaging techniques for studying the human brain in health and disease. DWI is an MR technique that probes the motion of free water undergoing spontaneous diffusion in the living tissue. Unlike conventional, structural MRI, this method provides insight into the microscopic composition, integrity and orientation of structures in the human brain (Le Bihan 2003).

Water diffusion in the brain is hindered by the presence of microscopic barriers, such as cell membranes, intracellular materials, or myelin sheaths. Water diffuses more readily along those barriers than across them, resulting in anisotropic, i.e., directed diffusion (Fig. 18.1a). DWI is sensitive to this diffusion process, allowing for measurements of diffusion restriction in any desired direction of diffusion within the brain with the use of special gradients.

From these measurements, quantitative indices of the microstructural composition of the tissue can be derived. Most commonly, the tensor model is applied to infer on local microstructure, giving information on the directionality, the shape and the overall restriction of the diffusion process. For tensor estimation, DWI must sample a minimum of six directions of diffusion in the brain. However, the information obtained with such a low number of diffusion directions is inadequate for reliable estimation of the tensor's parameters. DWI must obtain higher angular resolution of diffusion directions to generate stable estimates of the diffusion tensor (Jones et al. 1999), resulting in longer scanning times and higher load on the gradient hardware.

From the diffusion tensor, we can derive quantitative, scalar measurements informing us about the structure and integrity of the tissue under scrutiny. The most commonly used measurements are fractional anisotropy (FA), a measure of the

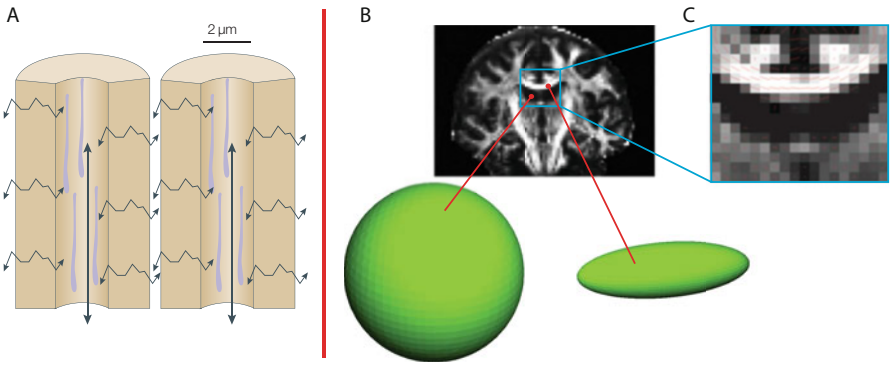

Fig. 18.1 Water diffuses more readily along cellular barriers in the brain than across them, resulting in anisotropic diffusion (**a**). (**b**) illustrates example tensors with isotropic diffusion in CSF, and highly anisotropic diffusion in the callosal fibres. (**c**) shows the principal diffusion direction obtained from the tensor field. ((**a**) Reprinted with kind permission by Nature Publishing Group (Le Bihan 2003))

directionality of diffusion, and mean diffusivity (MD), a quantitative measurement of the overall amount of diffusion with typical values around 0.5–2 · 10^{-3} mm^2/s in brain tissue. MD can be further decomposed into axial diffusivity (AD) and radial diffusivity (RD), describing the magnitude of diffusion along and across the diffusion tensor's main direction (and therefore putatively along and across the main fibre direction), respectively. FA is dimensionless and can take values between 0 and 1, where 0 denotes perfectly isotropic, or undirected, diffusion, while a value of 1 refers to a theoretical, perfectly anisotropic (line-shaped) diffusion process.

Figure 18.1b illustrates example tensors: In CSF, there are no structures hindering the diffusion process, and the tensor takes a spherical shape with an FA value of 0. In the callosal body, densely packed and highly collinear fibres traverse, connecting the two hemispheres of the brain. These axons form a coherent barrier to the diffusion process, and it is easy to imagine that the principal direction of free water diffusion must follow the path of these axons. Consequently, the tensor observed inside and close to the callosal body takes the shape of a cigar, with an FA value around 0.7. As constituents of MD, AD will be high and RD will be low in this case. The detail on the right (Fig. 18.1c) shows the principal diffusion direction obtained from the tensor field and overlaid as red lines onto the FA image. Intuitively, the arrangement of the principal diffusion directions corresponds well with the known architecture of callosal fibres, and tractography methods aim to replicate the underlying fibre anatomy.

Crucially, diffusion imaging probes microstructural properties of the tissue under study, complementing the macroscopic information available through conventional MRI techniques. It is particularly useful in white matter, which contains parallel bundles of axons that lend strong anisotropy to the diffusion signal observed. In grey matter, the presence of cell bodies and the lower volume proportion of directed nerve fibres means that the diffusion process will encounter a more heterogeneous set of diffusion barriers. Thus, FA in white matter is generally higher than in grey matter. In the context of tremor disorders, these measurements allow for the assessment of disintegrity of both central motor pathways and their grey matter terminations.

In addition to the quantitative measurements just outlined, we can exploit the directionality of the diffusion process to infer on underlying neural connections. Diffusion tractography generally follows the pathway of least hindrance of free water diffusion through the brain, exploiting the fact that water diffuses more readily along cellular barriers, such as axons, than across them. Algorithms based on the tensor model generally follow the principal direction of diffusion, resulting in a simple, deterministic pathway. However, there are many different fibre systems interdigitating throughout the brain. Pathways can fan out or contract, they can touch or cross, and it is easy to imagine that a single tensor cannot provide a complete model for the complicated fibre geometry encountered in the brain. Probabilistic tractography approaches were developed to overcome some of these limitations, using both the tensor model and more data-driven approaches (e.g. (Behrens et al. 2003; Parker and Alexander 2003)).

The information given by tractography is not complete, and the evidence provided by tractography studies does not reach the same level of confidence that

is associated with classical tract-tracing studies (Johansen-Berg and Rushworth 2009). However, invasive tract-tracing studies are unavailable in humans for obvious reasons. Diffusion tractography estimates the pathway of axons in the brain from non-invasive MR imaging, enabling the reconstruction of white matter pathways in the living human brain. It is the only modality to do so, and thus our most valuable tool in the assessment of white matter pathology in living subjects.

18.2 Methodological Considerations

Standard voxel-wise analysis techniques for brain imaging are readily adaptable for use with diffusion imaging. These involve spatial registration of individual brains, deforming individual images to match a pre-specified template, smoothing the results and then performing voxel-wise statistical tests to assess group differences. Diffusion images pose certain inherent problems with this approach. Spatial registration is driven largely by interfaces between white and grey matter structures, or interfaces between the brain and the cerebrospinal fluid compartment, where image contrast is high. White matter has very low intrinsic contrast on diffusion images, and thus, it is 'dragged along' when registration takes place. Unfortunately, this also means that spatial registration algorithms driven by structural imaging alone cannot align white matter pathways satisfactorily, and we cannot guarantee that a voxel in standard space coordinates centres on the same white matter tract in all study subjects. Recently developed registration approaches combine information from structural imaging and diffusion-derived maps to drive registration via both 'between tissue'-type contrasts visible on structural imaging, and white matter directionality information derived from diffusion imaging. This enables the registration of grey and white matter structures in a single process (Lange et al. 2020), with a more faithful alignment of major white matter tracts.

Tract-based spatial statistics, or TBSS, aims to address the white matter registration problem differently (Smith et al. 2006): TBSS derives a skeletonised representation of white matter, and projects the nearest maximum FA values onto this skeleton in each individual study subject. This way, TBSS isolates dominant fibre pathways from the brain, and residual variability after spatial registration is reduced. Note that this type of analysis is confined to white matter structures only.

18.3 Diffusion Tensor Imaging in Tremor

Currently, there are no routine applications for DWI in the clinical evaluation of tremor. However, changes in tensor-derived parameters such as MD and FA have been investigated in comparison to healthy control groups in a research context. These are summative measures of diffusion, and as such, white matter features such

as myelination, the packing density of axons, or axonal diameter have been shown to influence both FA and MD (Beaulieu 2009). Similar arguments apply to AD and RD as constituents of MD.

18.3.1 Parkinsonian Syndromes

In Parkinson's disease (PD), Yoshikawa et al. (2004) evaluated FA in structures of the extrapyramidal system in 12 patients with PD and 8 patients with progressive supranuclear palsy. They report a significant reduction of FA in both PSP and PD in the substantia nigra, and in ROIs placed along the nigrostriatal pathway. PSP patients generally exhibited changes of greater magnitude than those with PD. Still, changes in PD were detectable early in the course of disease, suggesting that diffusion imaging is sensitive to the underlying neurodegenerative process.

Vaillancourt et al. (2009) analysed FA within the substantia nigra in a group of 14 patients with a diagnosis of early-stage Parkinson's disease. The authors report decreased FA in the substantia nigra in PD patients, establishing the complete separation of PD patients from control subjects in their study group. A subsequent study in 10 PD patients confirmed a trend for lower FA of substantia nigra in PD patients, but failed to achieve the same separation from controls based on FA measurements (Menke et al. 2009). The authors reported alterations in the connectivity of the substantia nigra, such that the integrity of its connections to the putamen and the thalamus is reduced in PD. The authors argue that this alteration of the diffusion signal is caused by degeneration of the substantia nigra pars compacta, leading to a degeneration of its projections.

In an early study of tremor-dominant PD patients (Tessa et al. 2008), histograms of whole brain FA and MD measurements were compared to normal controls and a subgroup of akinetic-rigid PD patients. The authors did not detect a significant change of diffusion parameters in tremor-dominant PD, but they report a trend for higher FA in the highest quartile of brain voxels. The interpretation of this finding is not straightforward, and the authors argue for a possible partial volume effect due to grey matter loss. A later study with a larger patient collective using TBSS (Luo et al. 2017) reported increased MD and AD in white matter tracts including the cerebello-thalamo-cortical pathway in tremor-dominant PD patients only, in contrast to akinetic-rigid study participants. The mean AD value in clusters with a significant difference was correlated with resting tremor score in the tremor-dominant PD patients, underlining a possible biological link to the observed white matter diffusion abnormality. Another TBSS study found increased MD in tremor-dominant PD in white matter underlying the right primary somatosensory and the right inferior parietal lobule when comparing to either controls or akinetic rigid PD (Vervoort et al. 2016). The laterality of these findings is not easy to interpret, and the authors did not explore a possible link to tremor scores.

18.3.2 Essential Tremor

The neuropathology of essential tremor, the most common movement disorder, is currently under intense discussion (Louis and Faust 2020), with some evidence pointing at an underlying neurodegenerative process (for details, please refer to Chap. 7 of this book). Although the mechanisms remain to be elucidated, the involvement of the cerebellum is discussed in a majority of ET cases. If, indeed, degeneration takes place, it should be possible to locate changes in the microstructure of the brain consecutive to axonal loss or damage.

One study in 67 ET patients and 39 controls specifically looked at grey matter diffusion parameters. The authors detected increased MD in the cerebellar grey matter of ET patients when compared to controls (Novellino et al. 2016). This finding can be interpreted to support existing evidence for Purkinje cell pathology in ET (Louis et al. 2014; Choe et al. 2016), but may also indicate changes affecting the myelin fraction of the cerebellar cortex.

Shin et al. (2008) report on a diffusion tensor imaging study in a group of ten patients with ET. The authors use voxel-wise analysis to test for significant differences of FA with respect to an age-matched group of healthy controls. In this study, FA decreases were found in the cerebellum, the midbrain and in the white matter of the cerebral hemispheres, suggesting a widespread alteration of white matter integrity. The authors speculate that fibres of the cerebello-thalamo-corticocerebellar loop may be affected, suggesting the involvement of a tremor oscillator within this motor loop. Central oscillations are a mechanism putatively involved in the generation of ET (Deuschl et al. 2001), and these results argue for a role of axonal dysfunction in the evolution of a central oscillator.

Another study (Martinelli et al. 2007) in ten ET patients used a region-of-interest approach, testing for differences in the apparent diffusion coefficient (a measure related to MD) in a set of brain regions between ET patients and healthy controls. These regions comprised cortical, subcortical and cerebellar structures. Here, the authors did not report any significant differences between the two groups.

However, a later study (Nicoletti et al. 2010) in a larger group with familial essential tremor (25 patients) reported significant changes of FA and MD in the superior cerebellar peduncles, and change of FA in the dentate nucleus, differentiating these patients from both normal controls and patients suffering from PD. Perhaps the larger number of patients studied, and different ROI analysis methodologies, explain this apparent discrepancy.

Klein et al. (2011a) employed both a traditional ROI analysis and TBSS (Smith et al. 2006) to study a group of 14 ET patients. ROI analysis was performed in the cerebellar peduncles, carrying all input and output of the cerebellum in a highly collinear fibre system. This study reported increased MD bilaterally in the inferior cerebellar peduncles, and reduced FA in the right-sided ICP of ET patients, suggesting alteration of the white matter pathways feeding spinal input into the cerebellum. On TBSS, the authors detected a widespread increase of MD in the bihemispheric cerebral white matter of ET patients, with special emphasis on the left hemisphere of the brain (Fig. 18.2). Moreover, a regression analysis demonstrated

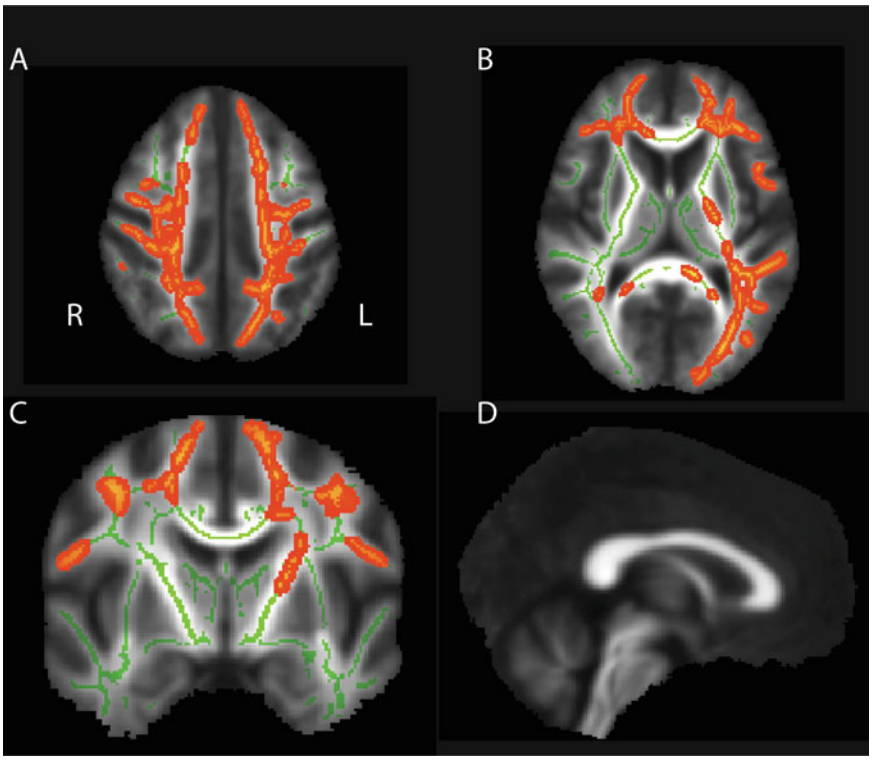

Fig. 18.2 In a group of patients with essential tremor, TBSS analysis demonstrated reduced MD bihemispherically (transaxial (**a**, **b**) and coronal view (**c**)). The corpus callosum was spared (**d**). (Reprinted with kind permission by Wiley (Klein et al. 2011a, b))

that MD in the brain regions affected was strongly correlated with Fahn tremor scores ($p = 0.02$, $R^2 = 0.81$), indicating a functional relationship between white matter abnormalities and tremor severity. A variant of the LINGO1 gene was identified as a risk factor in ET (Stefansson et al. 2009). LINGO1 is involved with myelination of the central nervous system, suggesting a link between myelination and tremor generation in the brain. With these findings, the authors suggest that distributed myelin disintegrity plays a role in tremor generation, supporting the idea of a tremor-generating network in the human brain (Deuschl et al. 2001).

18.4 Diffusion Tractography in Tremor

18.4.1 Essential Tremor

Further evidence implicating a wide-spread structural network in ET comes from a study enrolling 25 patients and controls respectively, which reported reduced bihemispheric connectivity in the cerebello-thalamo-corticocerebellar pathway

(Caligiuri et al. 2017). The reduced connectivity on network metrics observed in this study can be indirectly related to the tensor-derived data discussed above. ET is a progressive disorder, and it is likely that the connectivity differences observed are driven by pathological changes to the microstructure of the existing fibre pathways, rather than by alterations of the brain's connectional architecture.

In conclusion, there is mounting evidence that the underlying pathology of ET can be detected with diffusion imaging. However, the exact location of changes reported across research groups varies considerably.

18.4.2 Lesion Evaluation

Diffusion tractography can inform us about the distribution of neuronal connections in the brain. Disruption of these neural pathways can play a role in the generation of tremor, such as deafferentation caused by ischemic stroke or cerebral haemorrhage. Tractography can depict pathways affected by a lesion, allowing the observer to draw conclusions on possible remote effects of the disconnection caused. In this context, it is important to keep in mind that tractography can be hampered by many factors such as perilesional oedema, shifts of brain tissue caused by a macroscopic lesion, or infiltrating disease. Thus, failure to track a particular tract is not firm evidence that the track in question is indeed completely transected. However, with supporting clinical evidence, reduced traceability can be indicative of tract disruption.

Seidel et al. (2009) report on a case of dopamine-responsive Holmes tremor caused by localised haemorrhage into the pons and brainstem. Dopamine transporter imaging showed extensive damage to the presynaptic dopaminergic terminals in the striatum ipsilateral to the haemorrhage. On diffusion tractography, the authors found that connectivity was reduced between the tegmentum, where these dopaminergic projections arise, and the striatum ipsilateral to the haemorrhage. Moreover, they report diminished connectivity entering and exiting the middle and superior cerebellar peduncle. In conclusion, the haemorrhage affected the red nucleus directly, and affected nigrostriatal projections and the cortico-rubro-cerebellar loop via disruption of fibre pathways traversing the region of the haemorrhage. These findings point to remote deafferentation as a plausible mechanism for the clinical syndrome found in this patient.

18.4.3 Deep Brain Stimulation

Deep brain stimulation (DBS) is employed in the management of medically intractable tremor (Benabid et al. 1996). While success rates of surgery are high, there is an ongoing debate on the ideal target point for tremor-suppressive DBS (Speelman et al. 2002). Most commonly, VIM DBS is employed in the management

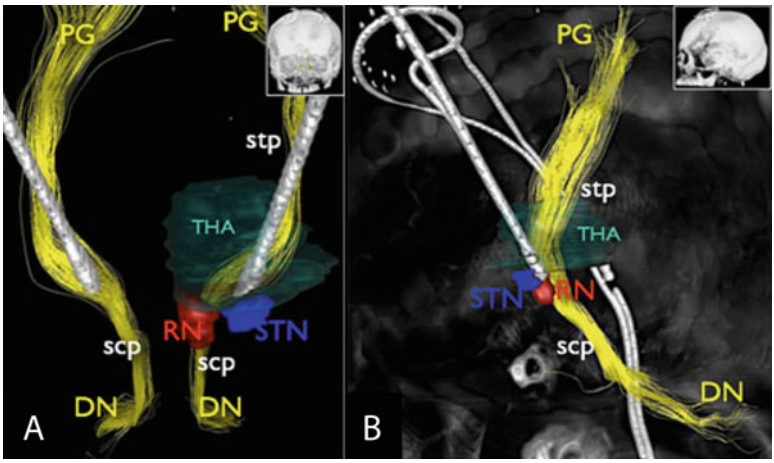

Fig. 18.3 3D rendering of the implanted electrodes in a patient with DBS for head tremor, demonstrating the relationship between deep brain nuclei, the dentatorubrothalamic tract and the implanted, tremor-suppressive DBS electrodes. (**a**) shows a frontal, (**b**) a lateral view. DN dentate nucleus, PG precentral gyrus, scp superior cerebellar peduncle, stp superior thalamic radiation, THA thalamus. (Reprinted with kind permission by Springer (Coenen et al. 2011))

of ET and tremor-dominant PD patients. The subthalamic nucleus (STN) is a frequent target in PD that is not tremor-dominant, since it has effects on both tremor and akinetic symptoms (Limousin et al. 1995). As such, it is the most common target for DBS altogether. More recently, MR-guided focused ultrasound (MRgFUS) has been developed as a lesional option that does not require craniotomy (Elias et al. 2013). It works on the same principle as earlier thalamotomy via craniotomy, and shares its disadvantages, such as irreversibility and inability to titrate treatment as the condition progresses. An associated risk is unintentional lesioning of the STN, causing contralateral chorea (Jameel et al. 2021). However, MRgFUS has a favourable safety profile for certain patient groups as it does not require general anaesthesia or craniotomy. Details of surgical therapy options are available in Chap. 10 of this book.

Coenen et al. (2011) employed diffusion tractography to target the dentato-rubro-thalamic tract (DRT) in a patient with head tremor. They were able to identify the DRT on pre-operative DWI, and used the tract's location relative to a standard stereotactic coordinate in the thalamus to plan the location for subsequent electrode implantation. Clinically, this approach achieved a successful reduction of tremor. Figure 18.3 shows the location of the implanted electrode relative to deep brain nuclei and the DRT traced bilaterally. While this is a single-patient study, it is encouraging to see that the clinically effective electrode is collocated with the DRT, indicating a functional relationship.

A study in a group of 12 tremor patients undergoing DBS of the ventral intermediate nucleus of the thalamus (VIM) mapped out the brain network of

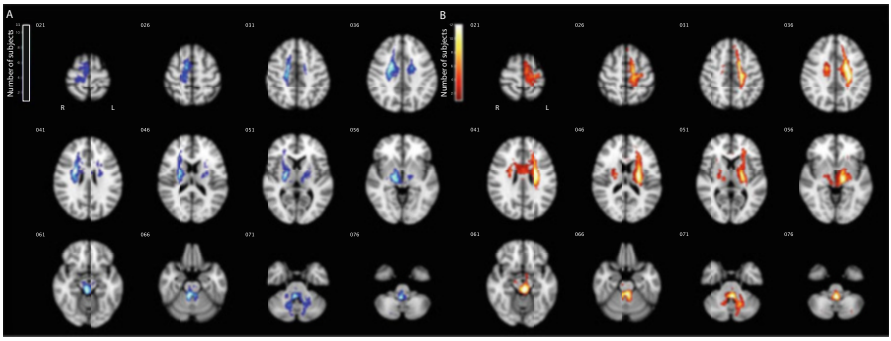

Fig. 18.4 Population probability map of connectivity estimated from individually effective VIM (ventral intermediate nucleus) stimulation sites in a group of tremor patients. Note the strong evidence of connectivity to primary sensorimotor, premotor, pallidal and cerebellar sites

successful, tremor-suppressive DBS after stereotactic surgery planning and intraoperative electrode testing (Fig. 18.4) (Klein et al. 2011b). This study described a network of remote targets comprising primary sensorimotor, premotor, pallidal, and cerebellar sites that is reproducible across patients, and in line with previous functional imaging studies into the effects of VIM DBS. In this study, the spatial location of the tremor-suppressive target was considerable and spanned several millimetres across subjects. This is because the individual, planned target site is always mapped electrophysiologically, and the electrode position is adjusted, during surgery. In contrast to spatial variability, the signature of the remote connections traced from these individually effective target sites is remarkably similar across the group of patients studied here. These findings point to a possible application of presurgical tractography to map out the thalamus and its vicinity with respect to the remote sites whose modulation was effective in the patient collective reported here.

A study in eight ET patients undergoing conventionally targeted MRgFUS for medically intractable tremor showed that overlap of the lesion in putative VIM with projections from the motor cortex predicts treatment efficacy, especially if fibres from the hand knob are selected for tractography (Tian et al. 2018). This corroborates the view that the connectional architecture of the neurosurgical target can predict clinical outcomes in tremor neuromodulation, whether it is lesional or not.

The connections of the subthalamic nucleus (STN) were also investigated with diffusion tractography (Aravamuthan et al. 2007). The authors assessed its connections to a predefined set of remote targets, informed by previous knowledge from tract tracing studies in animals. The STN has connections with motor, limbic and associative circuits. Ideally, DBS should avoid the latter two portions, whose stimulation is thought to contribute to potential neuropsychological side effects of the procedure. In this study, motor representations were found in the superior portion of the STN, as expected from both animal studies and clinical evaluation of DBS efficacy. Furthermore, the authors confirmed a somatotopic layout of the

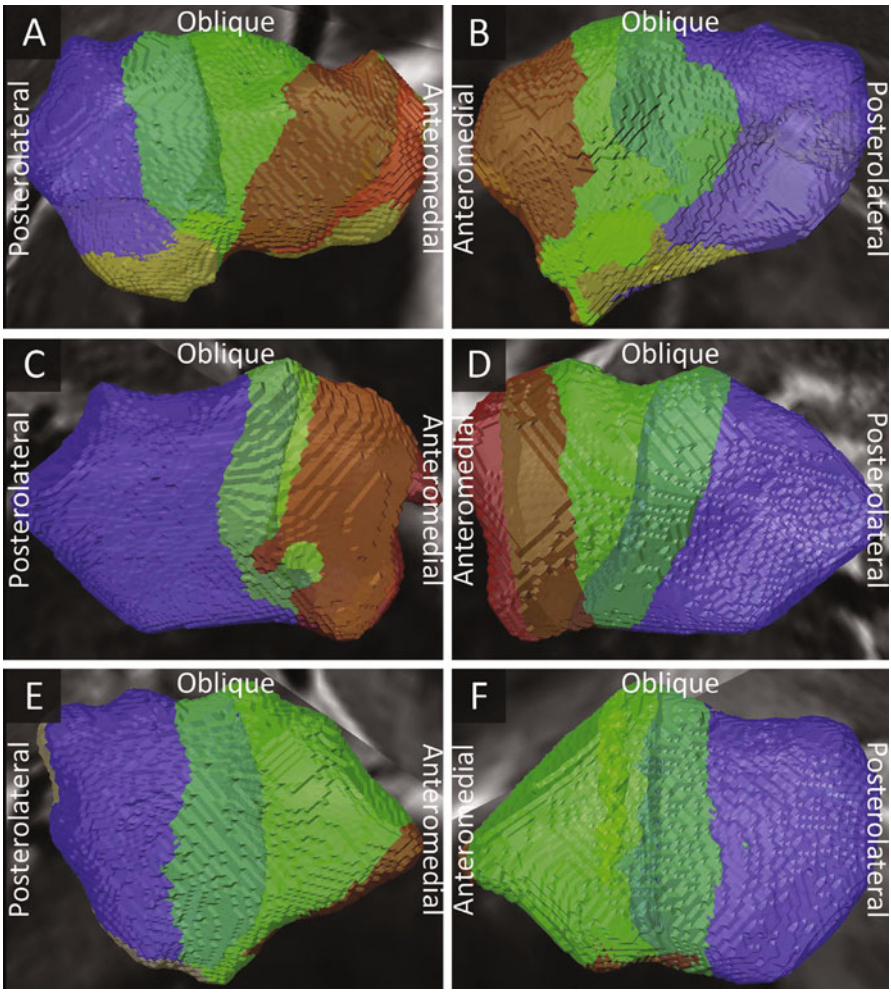

Fig. 18.5 Examples of the subdivisions of the left (**a**, **c**, **e**) and right (**b**, **d**, **f**) subthalamic nuclei of three subjects into a limbic (red), associative (green) and motor (blue) zone. Intermediate colours show overlap between the motor and associative zones (light blue) and between the associative and limbic zones (brown)

connections between the primary motor cortex and motor STN, similar to what was found in non-human primates previously. A related study using 7T MRI took this idea further to establish STN topography on an individual basis for 17 PD patients (Plantinga et al. 2018). The individualised topography of the STN robustly identifies the motor portion of the nucleus; however, there is considerable variability in the estimation of its borders (Fig. 18.5), and estimation of the limbic portion of the STN was achieved in 30 out of 34 hemispheres.

The topography confirmed in human STN could be exploited for DBS in the future, enabling neurosurgeons to specifically target motor regions in an individual patient to suppress both tremor and akinetic symptoms in PD patients.

In conclusion, diffusion tractography expands our knowledge about the tracts and remote connectional partner structures affected by DBS and MRgFUS in tremor disorders. This information may serve to guide interventional planning, and it may enable the presurgical evaluation of novel stimulation targets for DBS.

Diffusion imaging plays a unique role in the evaluation of tremor disorders: It is the only non-invasive modality that can reconstruct white matter pathways in the brain, and assess the microstructural integrity of the tissue at the same time. The integrity of these pathways, or of grey matter structures involved in motor functions, provides information on the specific pathophysiology of tremor disorders. Moreover, recent research suggests that diffusion tractography can aid in surgical targeting for DBS in invasive tremor therapy.

There is limited evidence on the utility of diffusion imaging in the differential diagnosis of tremor disorders, and further research is needed to assess the validity of diffusion-derived parameters for diagnosis or treatment planning in a clinical context.

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Bibliography

Aravamuthan BR, Muthusamy KA, Stein JF, Aziz TZ, Johansen-Berg H. Topography of cortical and subcortical connections of the human pedunculopontine and subthalamic nuclei. NeuroImage. 2007;37(3):694–705.

Beaulieu C. The biological basis of diffusion anisotropy. In: Johansen-Berg H, Behrens TEJ, editors. Diffusion MRI. Oxford: Academic; 2009. p. 105–26.

Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn Reson Med. 2003;50(5):1077–88.

Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg. 1996;84(2):203–14.

Caligiuri ME, Arabia G, Barbagallo G, Lupo A, Morelli M, Nisticò R, et al. Structural connectivity differences in essential tremor with and without resting tremor. J Neurol. 2017;264(9):1865–74.

Choe M, Cortes E, Vonsattel JP, Kuo SH, Faust PL, Louis ED. Purkinje cell loss in essential tremor: random sampling quantification and nearest neighbor analysis. Mov Disord. 2016;31(3):393–401.

Coenen VA, Allert N, Madler B. A role of diffusion tensor imaging fiber tracking in deep brain stimulation surgery: DBS of the dentato-rubro-thalamic tract (drt) for the treatment of therapy-refractory tremor. Acta Neurochir. 2011;153(8):1579–85. discussion 85.

Deuschl G, Raethjen J, Lindemann M, Krack P. The pathophysiology of tremor. Muscle Nerve. 2001;24(6):716–35.

Elias WJ, Huss D, Voss T, Loomba J, Khaled M, Zadicario E, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. N Engl J Med. 2013;369(7):640–8.

Jameel A, Gedroyc W, Nandi D, Jones B, Kirmi O, Molloy S, et al. Double lesion MRgFUS treatment of essential tremor targeting the thalamus and posterior sub-thalamic area: preliminary study with two year follow-up. Br J Neurosurg. 2021:1–10.

Johansen-Berg H, Rushworth MF. Using diffusion imaging to study human connectional anatomy. Annu Rev Neurosci. 2009;32:75–94.

Jones DK, Horsfield MA, Simmons A. Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. Magn Reson Med. 1999;42(3):515–25.

Klein JC, Lorenz B, Kang JS, Baudrexel S, Seifried C, van de Loo S, et al. Diffusion tensor imaging of white matter involvement in essential tremor. Hum Brain Mapp. 2011a;32(6):896–904.

Klein JC, Barbe MT, Seifried C, Baudrexel S, Runge M, Maarouf M, et al. The tremor network targeted by successful VIM deep brain stimulation in humans. Neurology. 2011b; under review.

Lange FJ, Ashburner J, Smith SM, Andersson JLR. A symmetric prior for the regularisation of elastic deformations: improved anatomical plausibility in nonlinear image registration. NeuroImage. 2020;219:116962.

Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci. 2003;4(6):469–80.

Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E, et al. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet. 1995;345(8942):91–5.

Louis ED, Faust PL. Essential tremor: the most common form of cerebellar degeneration? Cerebellum Ataxias. 2020;7:12.

Louis ED, Lee M, Babij R, Ma K, Cortes E, Vonsattel JP, et al. Reduced Purkinje cell dendritic arborization and loss of dendritic spines in essential tremor. Brain. 2014;137(Pt 12):3142–8.

Luo C, Song W, Chen Q, Yang J, Gong Q, Shang HF. White matter microstructure damage in tremor-dominant Parkinson's disease patients. Neuroradiology. 2017;59(7):691–8.

Martinelli P, Rizzo G, Manners D, Tonon C, Pizza F, Testa C, et al. Diffusion-weighted imaging study of patients with essential tremor. Mov Disord. 2007;22(8):1182–5.

Menke RA, Scholz J, Miller KL, Deoni S, Jbabdi S, Matthews PM, et al. MRI characteristics of the substantia nigra in Parkinson's disease: a combined quantitative T1 and DTI study. NeuroImage. 2009;47(2):435–41.

Nicoletti G, Manners D, Novellino F, Condino F, Malucelli E, Barbiroli B, et al. Diffusion tensor MRI changes in cerebellar structures of patients with familial essential tremor. Neurology. 2010;74(12):988–94.

Novellino F, Nicoletti G, Cherubini A, Caligiuri ME, Nistico R, Salsone M, et al. Cerebellar involvement in essential tremor with and without resting tremor: a Diffusion Tensor Imaging study. Parkinsonism Relat Disord. 2016;27:61–6.

Parker GJ, Alexander DC. Probabilistic Monte Carlo based mapping of cerebral connections utilising whole-brain crossing fibre information. Inf Process Med Imaging. 2003;18:684–95.

Plantinga BR, Temel Y, Duchin Y, Uludağ K, Patriat R, Roebroeck A, et al. Individualized parcellation of the subthalamic nucleus in patients with Parkinson's disease with 7T MRI. NeuroImage. 2018;168:403–11.

Seidel S, Kasprian G, Leutmezer F, Prayer D, Auff E. Disruption of nigrostriatal and cerebellothalamic pathways in dopamine responsive Holmes' tremor. J Neurol Neurosurg Psychiatry. 2009;80(8):921–3.

Shin DH, Han BS, Kim HS, Lee PH. Diffusion tensor imaging in patients with essential tremor. AJNR Am J Neuroradiol. 2008;29(1):151–3.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage. 2006;31(4):1487–505.

Speelman JD, Schuurman R, de Bie RM, Esselink RA, Bosch DA. Stereotactic neurosurgery for tremor. Mov Disord. 2002;17 Suppl 3:S84–8.

Stefansson H, Steinberg S, Petursson H, Gustafsson O, Gudjonsdottir IH, Jonsdottir GA, et al. Variant in the sequence of the LINGO1 gene confers risk of essential tremor. Nat Genet. 2009;41(3):277–9.

Tessa C, Giannelli M, Della Nave R, Lucetti C, Berti C, Ginestroni A, et al. A whole-brain analysis in de novo Parkinson disease. AJNR Am J Neuroradiol. 2008;29(4):674–80.

Tian Q, Wintermark M, Jeffrey Elias W, Ghanouni P, Halpern CH, Henderson JM, et al. Diffusion MRI tractography for improved transcranial MRI-guided focused ultrasound thalamotomy targeting for essential tremor. Neuroimage Clin. 2018;19:572–80.

Vaillancourt DE, Spraker MB, Prodoehl J, Abraham I, Corcos DM, Zhou XJ, et al. High-resolution diffusion tensor imaging in the substantia nigra of de novo Parkinson disease. Neurology. 2009;72(16):1378–84.

Vervoort G, Leunissen I, Firbank M, Heremans E, Nackaerts E, Vandenberghe W, et al. Structural brain alterations in motor subtypes of Parkinson's disease: evidence from probabilistic tractography and shape analysis. PLoS One. 2016;11(6):e0157743.

Yoshikawa K, Nakata Y, Yamada K, Nakagawa M. Early pathological changes in the parkinsonian brain demonstrated by diffusion tensor MRI. J Neurol Neurosurg Psychiatry. 2004;75(3):481–4.

Chapter 19
The Role of the Noradrenergic System in Tremor Pathogenesis

Rick C. Helmich, Anouk van der Heide, and Michiel F. Dirkx

Abstract The noradrenergic system, which is activated during psychological stress, has important modulatory effects on the brain as well as other organs. Activation of the locus coeruleus noradrenergic system prepares the motor system for readiness. It is well known that many different types of tremor are amplified during psychological stress. Furthermore, pharmacological interventions that attenuate the noradrenergic system, such as beta-blockers, can reduce different types of tremor. In this chapter we discuss the involvement of the noradrenergic system in the (patho-)physiology of physiological tremor, essential tremor, and Parkinson's disease tremor. We will outline that different types of tremor involve both central mechanisms (primarily the cerebello-thalamo-cortical circuit) and peripheral mechanisms (sensitivity of reflex loops). Furthermore, we will discuss how the noradrenergic system influences peripheral and central mechanisms involved in tremor: by excitatory projections to the thalamus, and by increasing the sensitivity of peripheral reflex loops.

Keywords Tremor · Noradrenaline · Psychological stress · Pathophysiology · Parkinson's disease · Essential tremor

19.1 Introduction

Tremor is defined as a rhythmic movement of one or more body parts (Bhatia et al. 2017; van de Wardt et al. 2020). It is one of the most common movement disorders worldwide, and can occur as an isolated symptom (e.g., in essential tremor [ET]) or combined with other symptoms (e.g., dystonic tremor syndromes and Parkinson's disease [PD] tremor). Furthermore, tremor is not always pathological (see this volume): a low-amplitude physiological tremor also occurs in the healthy motor

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system (Elble 2003), particularly during slow movements (Gross et al. 2002). The context in which tremor occurs varies between clinical syndromes: it can occur at rest, during postures, or during actions (kinetic tremor). It is a common observation that tremor increases during anxiety, stressful situations, or increased cognitive load. This is true both for physiological tremors, which were also called "nervous tremors" in the 1960s, and for pathological tremors. In PD, cognitive loading (e.g., asking patients to perform arithmetic) is almost a standard routine to "bring out the tremor" in the clinical examination room (Zach et al. 2015). Furthermore, it has long been known that drugs acting on the noradrenergic (NA) system can influence tremor, both by increasing it (e.g., sympathomimetics, which are used for treating asthma) and by reducing it (e.g., beta-blockers, which are a first-line treatment for essential tremor). Finally, there is some evidence from imaging and post-mortem studies that the integrity of the locus coeruleus (LC)–noradrenergic system is associated with essential tremor (ET) and PD tremor (Shill et al. 2011; Kinnerup et al. 2021). Taken together, this suggests that the noradrenergic system plays a role in the pathophysiology of tremor. In this chapter, we will review the potential mechanisms that mediate the interaction between the (nor)adrenergic system and circuits involved in tremor. We will focus on physiological tremor, essential tremor, and Parkinson's disease tremor.

19.2 The Functional Anatomy of Tremor (Fig. 19.1)

Tremor can implicate both central and peripheral mechanisms, or a combination of the two (Fig. 19.1). Physiological tremor is the oscillatory, involuntary movement of a body part that occurs normally in living organisms (Elble 2003). This type of tremor involves primarily peripheral mechanisms. These include mechanical oscillations, such as irregularities in motor-unit firing and the force of blood ejection during cardiac systole, and mechanical-reflex oscillations, such as entrainment of motor units through somatosensory receptors (e.g., muscle spindles) responding to these perturbations (Elble and Randall 1978). Usually, these responses are too weak to entrain motoneurons at the frequency of tremor, but this may be increased by stress, anxiety, or fatigue. The cardio-ballistic forcing accounts for essentially all of physiologic tremor at rest, but explains 10% or less of wrist postural tremor in most people (Elble and Randall 1978). The amplitude of physiological tremor is determined by the degree of synchronization of motor-unit discharges modulated by muscle spindle 1a afferents (Logigian et al. 1988). This process is exaggerated during anxiety and exercise and other conditions that enhance peripheral beta-adrenergic activity. The enhanced mechanical-reflex oscillation is called "enhanced physiologic tremor." Physiological tremor also involves central mechanisms: the amplitude of physiological tremor can be voluntarily modulated, suggesting a cortical influence (Carignan et al. 2009). Furthermore, electromyography (EMG) recordings suggest that about 10–35% of people with enhanced physiological tremor have a central oscillator (Elble 2003; Raethjen et al. 2000).

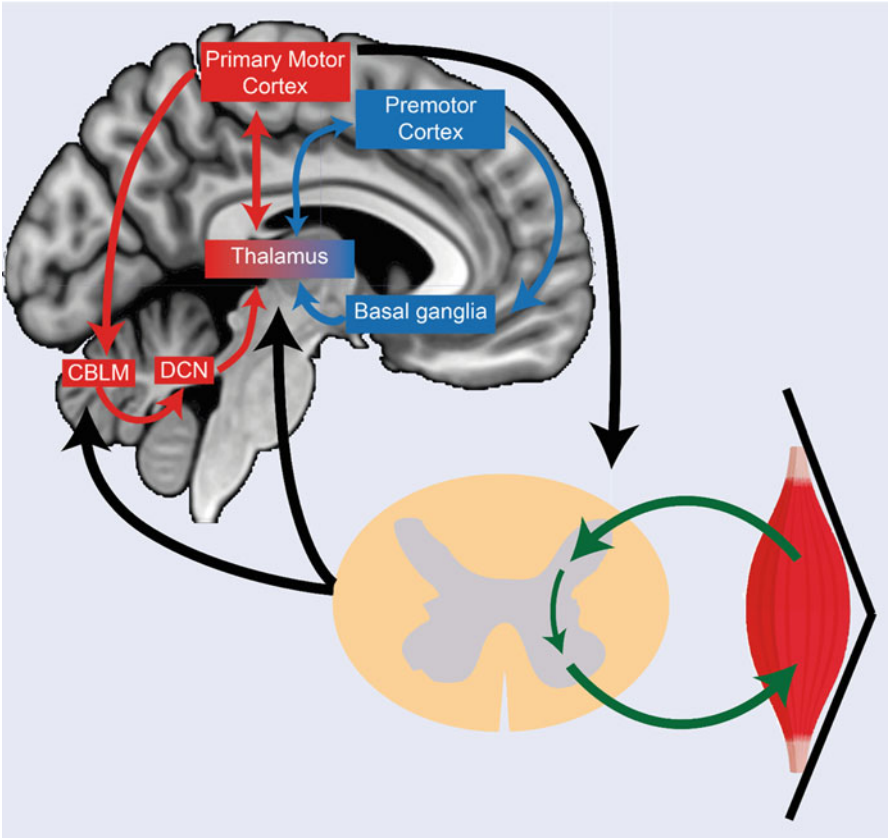

Fig. 19.1 Functional anatomy of tremor. Illustration of the central and peripheral mechanisms that underlie various types of tremor. Cerebral networks that are involved include a cerebello-dentato-thalamo-cortical (*red*) and basal ganglia loop (*blue*), which may interact at the level of (pre)motor cortex and/or thalamus. Tremor activity may either arise from a single oscillator (such as thalamus or cerebellum) or an oscillating network. In addition, a peripheral reflex loop (*green*) may also contribute to the production of tremor oscillations, for example via entrainment of motor units through somatosensory receptors (e.g., muscle spindles) responding to perturbations. *Black* arrows indicate pathways via which central and peripheral loops may interact

In contrast to physiological tremor, pathological tremors such as PD tremor, ET, orthostatic tremor, and dystonic tremor syndromes are thought to be caused primarily by central mechanisms, as explained in other chapters of this volume. These mechanisms could include a single oscillator, or an oscillating network. Some neurons in the brain, for example in the inferior olive, the dentate nucleus, and the thalamus, have neurophysiological properties that allow them to oscillate independently at a given frequency (Llinás 1988). Furthermore, specific cerebral circuits, such as the cerebello-thalamo-cortical circuit, the Guillain-Mollaret triangle (projection from dentate nucleus to red nucleus to inferior olivary nucleus to dentate

nucleus), and the pallido-subthalamic circuit, are prone to generate oscillations that may result in tremor (Helmich et al. 2013; Plenz and Kital 1999; Haubenberger and Hallett 2018). Across multiple tremor disorders, the cerebello-thalamo-cortical circuit is thought to play a key role in the production of tremor, although the primary oscillator may differ between disorders. For example, in PD, the tremor is thought to be triggered by abnormal activity in the basal ganglia, but amplified in the cerebello-thalamo-cortical circuit (Helmich 2018; Helmich et al. 2012; Lauro et al. 2021). This hypothesis has been termed the "dimmer-switch hypothesis," where the basal ganglia operate analogous to a switch, and the cerebello-thalamo-cortical circuit operates analogous to a dimmer. In contrast, in ET and dystonic tremor syndromes, the cerebello-thalamo-cortical circuit is thought to be driven into tremor by abnormal cerebellar activity, possibly caused by structural or molecular (e.g., GABA) deficiencies in Purkinje cells or climbing fibers that synapse onto Purkinje cells (Van den Berg and Helmich 2021; Nieuwhof et al. 2022; Buijink et al. 2015; Pan et al. 2020).

The thalamus, and more particularly the ventral intermediate nucleus (VIM), is a major hub within the cerebello-thalamo-cortical circuit. The VIM receives glutamatergic input from the cerebellar deep nuclei and the primary motor cortex, and it sends glutamatergic projections to the primary motor cortex. As such, the thalamus is well placed to arbitrate interactions between distributed neural assemblies in the motor network (Shine 2021). This excitatory effect of cerebellar outflow activity might drive the cerebral cortex in a "predictive" feedforward mode of signal processing (Morton and Bastian 2006). In a physiological situation, this might boost the anticipation of sensory consequences of motor actions (Blakemore and Sirigu 2003). In the context of tremor, one could speculate that these properties facilitate the propagation and amplification of oscillatory tremor-related activity. From microelectrode and local field potential recordings, tremor-specific activity is known to be present in the VIM (Lenz et al. 1988; Milosevic et al. 2018). Deep brain stimulation (DBS) targeting the VIM and its afferent fibers (the dentato-rubro-thalamic tract, DRRT) is successful in alleviating tremor with different underlying etiologies (Helmich et al. 2012; Cury et al. 2017).

While the primary mechanisms underlying pathological tremor syndromes are thought to be located within the brain, it is well accepted that peripheral mechanisms play an additional role (Helmich 2018; Anastasopoulos 2020; Volkmann et al. 1996). For instance, clinical observations suggest that PD tremor can be influenced by somatosensory afferents, such as minor adaptations of limb posture. This has been substantiated by a study where the authors found that PD tremor could be reset by median nerve stimulation (Britton et al. 1993). On the other hand, other studies have shown that mechanical perturbations of the tremulous limb were not able to reset the tremor in most patients (in contrast to ET) (Lee and Stein 1981), or only under particular conditions (Rack and Ross 1986). Furthermore, deafferentation of the tremulous limb (with Novocaine injections) left parkinsonian tremor unaltered in amplitude and frequency (Walshe 1924). This suggests that somatosensory afferents may have a role in stabilizing or maintain the tremor rhythm within the cerebello-thalamo-cortical circuit (Volkmann et al. 1996). Similar findings have been obtained

for ET, where median nerve stimulation could reset the tremor rhythm (Britton et al. 1993) and reduce its amplitude (Lin et al. 2018). The fact that peripheral mechanisms contribute to centrally generated tremors is perhaps not so surprising, because ultimately somatosensory afferents evoked by tremor are relayed to the same thalamic cells where rhythmic bursting at tremor frequency is observed, and where a functional lesion can reduce tremor (Lenz et al. 1988, 1994). Also, tremor-related signals from the primary motor cortex activate motor neurons in the spinal cord, which form peripheral reflex loops with somatosensory neurons arising from muscle spindles. Taken together, this suggests that noradrenergic activity may modulate tremor at different anatomical levels, both peripherally (e.g., by sensitizing mechanical-reflex loops by acting on muscle spindles (Hagbarth and Young 1979)) and centrally (e.g., by influencing the excitability of nodes within the cerebello-thalamo-cortical loop (Dirkx et al. 2020)), or both.

19.3 The Influence of Noradrenaline on the Motor System (Fig. 19.2)

It is clear that stress has a major influence on the human motor system (Metz 2007). The stress system is located both in the central and peripheral nervous system, and is activated in response to an incoming stressor, with the primary goal to restore homeostasis by eliciting a complex behavioral and physical adaptive response. Upon increasing levels of threat, animals activate qualitatively different defensive modes, including freezing and active fight-or-flight reactions (Roelofs 2017). During stress exposure, rapid activation of the sympathetic-adrenal-medullary system (SAM) results in the release of the neurotransmitters adrenaline (epinephrine) and noradrenaline (norepinephrine) (Fig. 19.2). The sympathetic branch of the autonomic nervous system and associated reactions (involving pupil dilation, heart rate increase, increased muscle tone, and rapid onset of fight-or-flight and freezing reactions) is largely driven by (nor)adrenaline. Activation of the hypothalamus-pituitary-adrenal (HPA) axis in turn results in the release of corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids, of which cortisol is the most important in humans (Roelofs 2017; Hermans et al. 2014). Many of these substances can influence different elements of the motor system (Metz 2007). Here we will focus specifically on noradrenaline, and how it interacts with those structures that are also implicated in the generation of tremor (see paragraph above).

Noradrenaline is produced by the adrenal glands and by postganglionic neurons of the sympathetic nervous system. As outlined above, its general role is to mobilize the brain and body for action. Noradrenaline release increases arousal and alertness, promotes vigilance, focuses attention, and may also increase restlessness and anxiety (De Kloet et al. 2005). Furthermore, noradrenaline release increases heart rate and blood pressure via β1 receptors, triggers the release of glucose

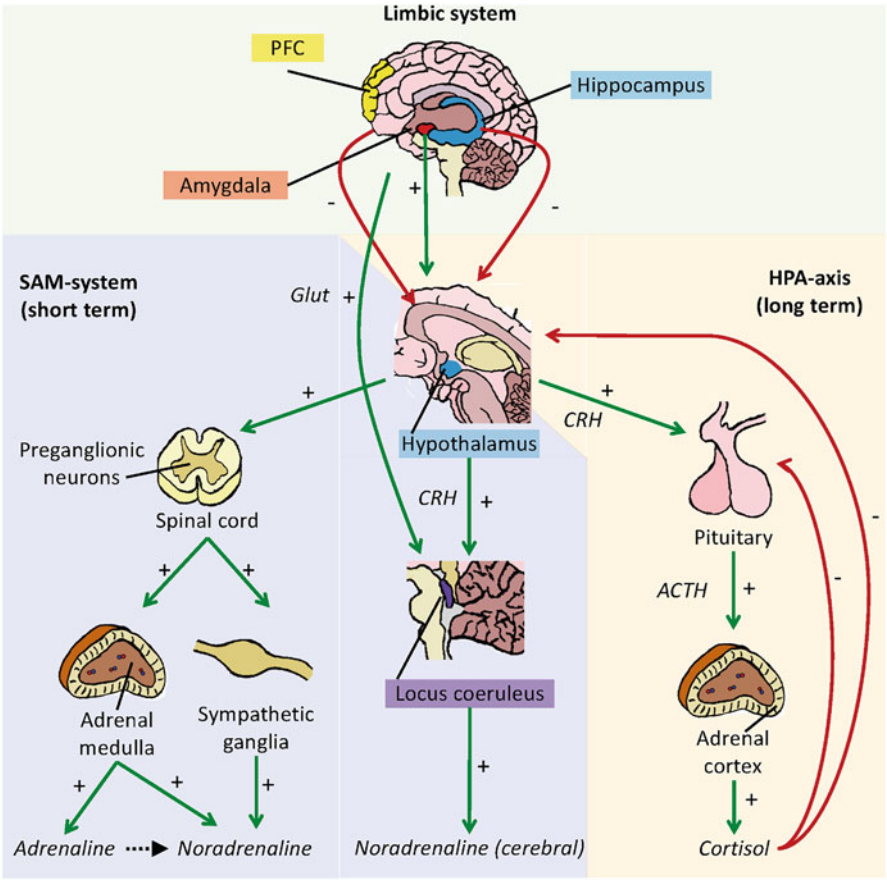

Fig. 19.2 The stress axis. When presented with a stressful stimulus, the hypothalamus stimulates the adrenal medulla via sympathetic preganglionic neurons in the spinal cord, which is called the sympathetic-adrenal-medullary (SAM) system, activated by the amygdala. The adrenal medulla and sympathetic ganglia then release the catecholamines noradrenaline and adrenaline into the bloodstream. In addition, the slower hypothalamic-pituitary-adrenal (HPA) axis is activated by the amygdala, whereas the hippocampus and prefrontal cortex (PFC) are largely inhibitory to HPA axis secretion. The hypothalamus synthesizes and secretes corticotropin-releasing hormone (CRH). In the anterior pituitary gland, CRH stimulates the synthesis and release of adrenocorticotropic hormone (ACTH) into the blood stream. In turn, ACTH signals the synthesis of glucocorticoids (cortisol) in the adrenal cortex. Negative-feedback loops to protect against prolonged activity of the stress system. In parallel to the peripheral HPA axis, CRH activates locus coeruleus (LC) neurons to produce and release noradrenaline throughout the brain. Glut glutamate

from energy stores primarily by binding to β2 receptors, and increases blood flow to skeletal muscle while reducing the overall blood flow to the gastrointestinal system by acting on α1 receptors. Noradrenaline also stimulates β3 receptors in the bladder and α1 receptors in the urethra to retain urine in the bladder. Adrenaline

is produced both by the adrenal glands and by a small number of neurons in the medulla oblongata. It does not cross the blood–brain barrier, and other than noradrenaline, its actions are mainly on visceral organs. Adrenaline has significant effects on the cardiovascular system, by increasing peripheral resistance via α1 receptor-dependent vasoconstriction and by increasing cardiac output by binding to β1 receptors. Noradrenaline can be metabolized to adrenaline.

In the brain, noradrenaline is produced by the locus coeruleus (LC) in the pons. In parallel to the peripheral stress response described in the previous paragraph, CRH release from the hypothalamus also activates LC neurons, resulting in the production and release of noradrenaline from axon terminals throughout the brain (Ross and Van Bockstaele 2021). The LC sends noradrenergic projections to various brain regions (Sara 2009), including all nodes of the cerebello-thalamo-cortical circuit (Samuels and Szabadi 2008). Within the cerebello-thalamo-cortical circuit, especially the thalamus is densely innervated (Sommerauer et al. 2017, 2018). In the macaque, careful anatomical studies using immunohistochemistry have shown that the most densely innervated thalamic nuclei are the midline nuclei, intralaminar nuclei (paracentral and parafascicular), and the medial sector of the mediodorsal nucleus (MDm). The ventral motor nuclei (including the VIM) and most somatosensory relay nuclei receive moderate noradrenergic innervation, while the pulvinar complex receives a heterogeneous innervation and the lateral geniculate nucleus (GL) has the lowest NA innervation (Pérez-Santos et al. 2021). In healthy people, activation of the LC noradrenergic system during cognitive tasks optimizes behavioral performance (Aston-Jones and Cohen 2005) and it increases signal-to-noise amplification in sensory systems, an effect that may be mediated in part by its actions onto the thalamus (Pape and McCormick 1989). More specifically, adrenergic agonists caused a selective dampening of neuronal responsiveness to large hyperpolarizing inputs, with little or no effect on phasic or tonic depolarizations. It was hypothesized that this may be responsible for the marked increase in efficacy of transfer or information through the thalamus during period of increased arousal and attentiveness (Pape and McCormick 1989). This may also suggest that noradrenaline makes the thalamus more susceptible to tremorogenic inputs that may originate elsewhere, but this has never been tested. There are also noradrenergic projections to the motor cortex (Sommerauer et al. 2018), and in mice, to the cerebellum (Lippiello et al. 2015).

In the peripheral nervous system, there is evidence for direct sympathetic innervation of the intrafusal fibers of muscle spindles (Radovanovic et al. 2015). This was demonstrated using antibodies against neuropeptide Y (NPY), which is an amidated 36-amino acid peptide that is stored and released with noradrenaline in many sympathetic nerves. NPY and NPY receptors were found on the intrafusal fibers, on the blood vessels supplying muscle spindles, and on free nerve endings in the peri-axial space. An important implication of the sympathetic innervation of muscle spindles is that an increase in sympathetic outflow depresses the feedback control of muscle length. Accordingly, a facilitation of the short-latency stretch reflex in the soleus muscle was observed during increased sympathetic outflow evoked by, among other things, mental arithmetic (Hjortskov et al. 1985). This suggests that

noradrenergic activity during stress conditions may influence peripheral stretch-reflex sensitivity via muscle spindles, which may amplify tremor even though it is generated centrally.

19.4 The Effect of Psychological Stress on Tremor

Psychological stress commonly leads to an increase in tremor severity. This effect holds for pathological tremors as well as for physiological tremor that can be observed in healthy individuals.

Several studies in PD patients confirmed that during cognitive tasks such as mental arithmetic, tremor amplitude directly increased, accompanied by activation of the arousal system (Fig. 19.3) (Dirkx et al. 2020; Lee et al. 2016; Marsden and Owen 1967). In addition to these immediate effects of stressful circumstances on symptoms like tremor, chronic stress plays an important role in PD as well. The prevalence of stress-related symptoms like depression and anxiety (Reijnders et al. 2008), and levels of cortisol, a marker of stress, are elevated (Soares 2019). This suggests that the balance in the stress system is disrupted in PD, making patients extra vulnerable to effects of stress. Furthermore, despite the positive effect of dopaminergic medication for the majority of PD symptoms, the effect on PD resting tremor is less consistent (Zach et al. 2020). One study showed that in 39% of included patients, the tremor was not responding to levodopa. Interestingly, cognitive stress further reduces the effect of levodopa in PD (Zach et al. 2017). Since dopaminergic medication does not always have a satisfying effect on PD tremor and side effects and habituation to these medications limit their application in general, patients could benefit from non-pharmacological ways to reduce stress and thereby tremor intensity. The same holds for essential tremor, for which first-line pharmacological symptomatic treatment with propranolol and primidone reduces tremor amplitudes by 55% on average (Deuschl et al. 2011).

Although the above suggests that tremor patients might benefit substantially from evidence-based stress-reducing strategies (e.g., mindfulness-based interventions, progressive muscle relaxation, deep breathing, or biofeedback), to date there have been only few studies looking into the effect of these techniques on tremor. A recent survey among 5000 PD patients gave some insights in what strategies PD patients use to reduce their stress levels and the effect they perceive on PD symptoms (van der Heide et al. 2021a). Patients perceived worsening in PD motor as well as non-motor symptoms during psychological stress, with the strongest effect on tremor (Fig. 19.4a). Physical exercise was most commonly used as a way to reduce stress in 83% of the patients, but also relaxation exercise (e.g., Yoga, Pilates, or Tai Chi) was employed by 43% and mindfulness by 39% of participants, of which 86% recommended this to other PD patients. Interestingly, patients experienced beneficial effects after mindfulness on all symptoms, but most prominently for depressive and anxiety symptoms and tremor (Fig. 19.4b). Other strategies that were often applied to reduce stress in this sample were focusing on

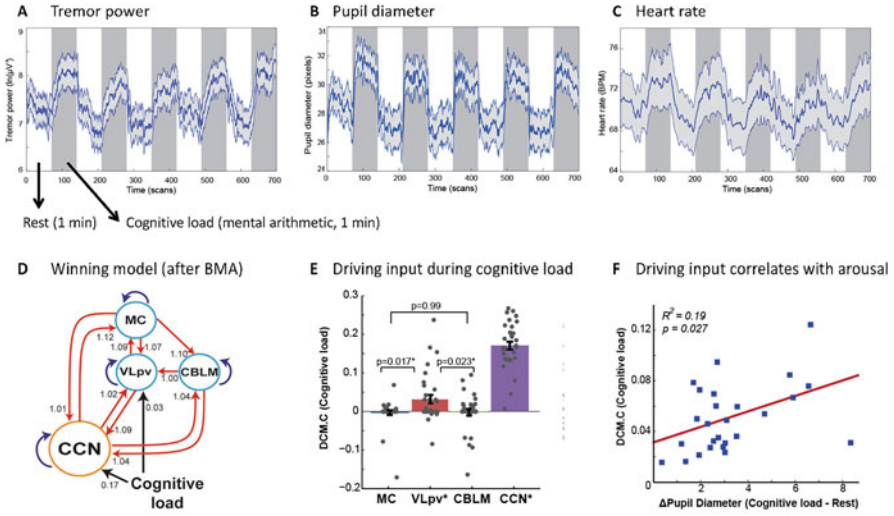

Fig. 19.3 Effect of cognitive load on Parkinson's disease (PD) tremor. (This figure is reproduced from (Dirkx et al. 2020)). In this study, 33 PD patients were measured in the functional magnetic resonance imaging (fMRI) scanner, while concurrent electromyography (EMG; panel **a**), pupil diameter (panel **b**), and heart rate (panel **c**) were recorded. Patients performed a mental arithmetic task (*gray* bars) alternated by rest (*white* bars). Cognitive load increased tremor, pupil diameter, and heart rate. Panel D shows how cognitive load influenced tremor-related cerebral activity in the motor cortex (MC), thalamus (posterior ventrolateral nucleus, VLpv), and cerebellum (CBLM), as well as a cognitive control network (CCN). That is, cognitive load specifically increased activity in the VLpv (panel **e**) and the CCN in a bottom-up manner, and it also strengthened the connectivity (*red* arrows, panel **d**) between the CCN and the tremor circuit (MC, VLpv, and CBLM). Panel F shows that the modulatory influence of cognitive load on the VLpv was associated with inter-individual variations in pupil dilation evoked by cognitive load—which is a measure of noradrenergic activity. These findings suggest that cognitive load amplifies tremor through bottom-up noradrenergic projections onto the thalamus (VLpv)

religion, listening or making music, and reading. The significant beneficial effects that patients experienced from self-management strategies such as mindfulness and physical exercise encourages future trials into the clinical effects and underlying mechanisms of these therapies.

19.5 The Role of the Noradrenergic System in Parkinson's Disease Tremor

The classical PD tremor occurs at rest at a frequency of 4–6 Hz and mainly involves the distal limbs. It is often visible as a pill-rolling movement. However, the majority of patients also have a postural tremor (Zach et al. 2015). In many cases, this is the resting tremor that re-emerges after stable posturing (Dirkx et al. 2018). This has led

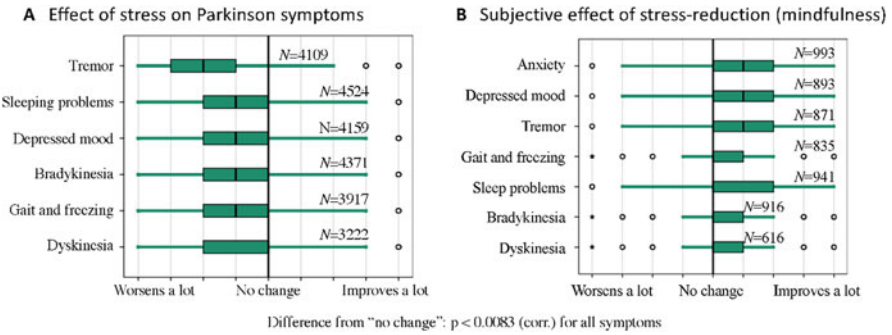

Fig. 19.4 Effect of psychological distress and mindfulness on Parkinson's disease (PD) tremor. (This figure is reproduced from (van der Heide et al. 2021a), based on a survey in 5000 PD patients). Responses are visualized in a boxplot, in which the box corresponds to 75% of responses and the tails are the remaining 25% (except outliers). Panel (**a**) shows the change that patients perceived on Parkinson's symptoms during stress, on a 9-point scale where 1 corresponds to severe symptom worsening, 5 stood for no change, and 9 for a lot of improvement (represented by the vertical lines). On the group level, all symptoms were perceived to worsen significantly during stress (i.e., different from "no change"); the strongest effect was on tremor. Panel (**b**) shows the change in PD symptoms that PD mindfulness users perceived since they started practicing mindfulness, again on a 9-point scale in which 1 stood for worsened symptom severity, 5 stood for no change, and 9 for a lot of improvement. They experienced significant improvement due to mindfulness for all reported symptoms when comparing the effect against a score of 5 ("no change"), with the strongest effect on psychological symptoms and tremor

to the idea that the classical parkinsonian tremor is actually a "tremor of stability," which emerges when the motor system has reached a *status quo* (Helmich et al. 2012; Hallett 2014). A minority of PD patients have a postural tremor that has a significantly higher frequency (>1.5 Hz difference) than resting tremor and starts immediately after posturing (Dirkx et al. 2018). This type of "pure postural tremor" is thought to have a different pathophysiology than resting tremor (and re-emergent tremor), but empirical evidence for this idea is lacking (Hallett and Deuschl 2010).

Besides the classical motor symptoms, many PD patients experience stress-related neuropsychiatric symptoms such as depression and anxiety (Carey et al. 2021; van der Heide et al. 2021b). It is well known that PD tremor increases with mental stress, anxiety, and cognitive load (Zach et al. 2015; Dirkx et al. 2020). The noradrenergic system has been hypothesized to have a role in amplifying PD tremor during stress and cognitive load (Helmich 2018; Dirkx et al. 2020; Isaias et al. 2011). For example, tremor-dominant PD patients show less degeneration of the locus coeruleus (LC) than non-tremor patients (Paulus and Jellinger 1991), and less degeneration of noradrenergic terminals in the LC and thalamus (Kinnerup et al. 2021). This suggests that the LC-noradrenergic system is relatively preserved in PD patients with tremor, and that noradrenergic activity during stress may increase tremor amplitude. On the other hand, perhaps counterintuitively, anxiety and depression in PD are associated with *reduced* noradrenergic (and dopaminergic) innervation of the limbic circuit (Carey et al. 2021; Remy et al. 2005).

Further evidence for the link between noradrenaline and tremor comes from pharmacological studies. For instance, it has been shown that intravenous injection of adrenaline increases PD tremor (Barcroft et al. 1952). Interestingly, further studies found that adrenalin administration only increased PD tremor when injected intravenously (i.e., systemically, enabling activation of the LC-noradrenergic system through the vagus nerve) (Hermans et al. 2014; Tank and Lee Wong 2015), but not when injected into an artery (which only distributes adrenalin directly to the muscle) (Constas 1962). This suggests that central rather than peripheral mechanisms mediate the increase in tremor. Marsden and colleagues found that propranolol, a non-selective beta-blocker that passes the blood–brain barrier, prevented the increase in tremor caused by injection of adrenaline. However, propranolol did not prevent the increase in PD tremor evoked by mental stress (arithmetic) (Owen and Marsden 1965; Marsden and Owen 1967). This suggests that mental stress may increase tremor through other mechanisms than circulating (peripheral) adrenaline, and that central mechanisms (termed "endogenous adrenaline") play an additional role. A possible candidate is of course the LC-noradrenergic system, which can also be activated "top-down" by stressful conditions rather than "bottom-up" by circulating adrenaline (Fig. 19.2). It is unlikely that psychological stress modulates tremor through spinal mechanisms (Passmore and Bruno 2012; Hasbroucq et al. 2000).

Other studies looked into the effect of propranolol on PD tremor, independent of stress, with varying findings. In a placebo-controlled trial in 18 PD patients on levodopa, propranolol (30 mg four times daily for up to 2 weeks) did not improve tremor (Marsden et al. 1974), while others have reported beneficial effects of propranolol in doses of more than 60 mg daily (Kissel et al. 1974). Another placebo-controlled study in eight PD patients showed that nadolol (at a dose of up to 240 mg per day), which is a non-selective beta-blocker with limited ability to cross the blood–brain barrier, led to a 34% reduction in tremor amplitude, measured with accelerometry (Foster et al. 1984). This suggests that peripheral noradrenergic mechanisms may play a role in PD tremor, and that inhibition of these mechanisms can reduce tremor. Alternatively, peripheral-acting beta-blockers may exert this effect by reducing anxiety (e.g., via bradycardia), which could indirectly lead to reduced activity of the central LC-noradrenergic system. Taken together, the available evidence suggests that noradrenergic activity may increase PD tremor both via central and via peripheral mechanisms.

A recent functional magnetic resonance imaging (fMRI) study by Dirkx and colleagues focused on the cerebral mechanism that mediates the increase in PD tremor during cognitive load, which was evoked by mental arithmetic (Dirkx et al. 2020). It was found that cognitive load was associated with increased tremor, larger pupil diameter, faster heart rate, and increased cerebral activity in a cognitive control network consisting of fronto-parietal cortex, insula, thalamus, and anterior cingulate cortex (Fig. 19.3). Although noradrenergic activity was not measured directly, increases in pupil diameter are a clear marker of activity of the LC noradrenergic system (Aston-Jones and Cohen 2005; Gilzenrat et al. 2010; Hermans et al. 2011). Tremor-related activity was observed in the cerebello-thalamo-cortical

network across both conditions. Most importantly, network analyses showed two different ways by which cognitive load modulated the cerebello-thalamo-cortical tremor circuit: directly by stimulating tremor-related processing at the level of the thalamus (posterior ventrolateral nucleus, VLpv); and indirectly by strengthening connectivity between a cognitive control network and the cerebello-thalamo-cortical circuit. The effect of cognitive load onto the VLpv correlated with load-related changes in pupil diameter, which suggests that this effect involves ascending arousal systems, likely the noradrenergic system (Fig. 19.3). The increased connectivity between stress-sensitive networks and the cerebello-thalamo-cortical motor network during cognitive load fits with findings that noradrenaline release leads to a pro-integration state (Shine et al. 2018; Shine 2019). In the physiological state, this state of integration may enhance cognitive performance by maximizing information process capacity, whereas segregation of networks promotes execution of more specific tasks, such as learning a complex movement via sensorimotor networks (Shine 2019). In Parkinson's disease there is increased cerebral network integration when compared to healthy subjects, although it is unsure whether this reflects pathological (Kim et al. 2017) or compensatory activity (Shine et al. 2019). Although speculative, it is possible that a stress-induced loss of segregation between cerebral networks may contribute to the emergence of a dominant oscillation that translates into tremor. Similar findings have been observed in ET, where interactions between visual and motor networks lead to an increase in tremor amplitude (Archer et al. 2017; Roy et al. 2018).

19.6 The Role of the Noradrenergic System in Essential Tremor

Essential tremor is one of the most common movement disorders worldwide. ET is characterized by an action tremor of both arms, during at least 3 years, with or without tremor in other locations (e.g., head, voice, or lower limbs), and in the absence of other neurological signs, such as dystonia, ataxia, or parkinsonism (Bhatia et al. 2017; van de Wardt et al. 2020). The pathophysiology of ET involves increased activity in the cerebello-thalamo-cortical circuit (Schnitzler et al. 2009; Broersma et al. 2016), where the cerebellum likely plays a major role in driving tremor oscillations (Van den Berg and Helmich 2021; Buijink et al. 2015). An older study by Marshall and colleagues reported that injection of intravenous adrenaline in 18 patients with tremor, of whom 6 had ET, increased tremor amplitude in all but 1 patient (Marshall and Schnieden 1966). The other patients had parkinsonian tremor, cerebellar tremor, enhanced physiological tremor, and tremor due to a brainstem lesion (likely Holmes tremor). In contrast, injection of noradrenaline and atropine did not influence tremor in any of the patients. These findings suggest that noradrenaline may primarily influence tremor within the brain, while adrenaline may influence tremor via peripheral mechanisms or

by activating the cerebral LC-noradrenergic system via the adrenergic receptors on the vagus nerve (Tank and Lee Wong 2015; Miyashita and Williams 2006). Nuclear imaging studies investigating the state of the noradrenergic system in ET are unfortunately lacking (Pasquini and Ceravolo 2021). Most post-mortem studies in ET have found structural abnormalities in the cerebellum (Louis and Faust 2020). One post-mortem study also reported LC abnormalities: parvalbumin, a marker of GABA-ergic neurons, was reduced in the LC region in ET patients compared to controls (Shill et al. 2011). However, this finding has not been replicated in further research.

More convincing evidence for the role of the noradrenergic system in ET comes from pharmacological studies with beta-blockers. Currently, there are three first-line drugs for treating ET: propranolol, a beta-blocker, and primidone and topiramate, which are two anti-epileptics. According to a recent review of the available evidence, propranolol is the only beta-blocker that is deemed "efficacious" for the treatment of ET (Ferreira et al. 2019). It is not exactly clear how propranolol works in reducing ET, and whether it acts centrally or peripherally (Deuschl et al. 2011). Young et al. suggested that suppression of ET by propranolol is mediated by central rather than peripheral mechanisms (Young et al. 1975). This was suggested in a study where healthy controls and ET patients received intra-arterial infusion of isoproterenol (isoprenaline), a beta-adrenergic stimulating agent, which increased tremor in ET patients and introduced tremor in controls. Intra-arterial or intravenous propranolol blocked the drug-induced tremor, but it did not affect ET (Young et al. 1975). This suggests that the pathophysiology of ET does not involve peripheral tremorogenic receptors, while these receptors do play a role in enhanced physiological, catecholamine-induced "nervous tremors." The effect of prolonged intake of propranolol was hypothesized to be mediated "perhaps within the central nervous system (CNS)." On the other hand, it was found in a placebo-controlled study that sotalol, a non-selective beta-blocker, was effective in reducing ET, even though this drug achieves only low central nervous system (CNS) concentrations after oral intake (Leigh et al. 1981, 1983). In that same study, atenolol, a selective beta 1 receptor antagonist, had less effect on ET. Hence, the authors concluded that beta 2 antagonism is needed for ET suppression, but that these effects are not (only) mediated through the CNS, but (also) through peripheral mechanisms. Taken together, similar to PD, evidence suggests that beta-blockers may attenuate ET via peripheral and central mechanisms.

19.7 The Role of Serotonin in Tremor

Besides noradrenaline and dopamine, serotonin is another neurotransmitter that has been associated with tremor and with stress-related neuropsychiatric disorders such as depression. It is well known that tremor is one of the key symptoms of the serotonin syndrome (Boyer and Shannon 2005). Furthermore, tremor has been reported as a side effect of selective serotonin reuptake inhibitors (SSRIs), such as

fluoxetine (Serrano-Dueñas 2002). On the other hand, another study found that the SSRI paroxetine *reduced* isometric tremor (Henderson et al. 2022). This suggests that the relationship between tremor and serotonin is not a simple linear one. In contrast, mirtazapine did not have an effect on ET (Pahwa and Lyons 2003).

Several studies have pointed toward a role of serotonergic dysfunction in the pathophysiology of PD tremor. Specifically, an (11)C-WAY 100635 PET study showed a reduction of 5-HT(1A) receptor binding in the raphe nuclei of PD patients, which was correlated with resting tremor severity (Doder et al. 2003). A large [123]I-beta-FP-CIT SPECT study in 345 drug naïve early PD patients reported reduced transporter availability in the brainstem raphe nuclei (where it binds to the serotonin transporter) compared to controls, which correlated with rest tremor amplitude and constancy (Qamhawi et al. 2015). This study did not report a relationship with action or postural tremor. Finally, another [123]I-beta-CIT SPECT study found lower thalamic transporter binding in tremor-dominant versus non-tremor PD patients (Caretti et al. 2008). This was interpreted as altered 5-HT binding (given the density of serotonergic versus dopaminergic transporters in the thalamus), but this ligand also binds to the dopamine transporter. Given the presence of dopaminergic projections to the thalamus (Sánchez-González et al. 2005), the reduced thalamic binding may thus involve both dopaminergic (Dirkx et al. 2017) and/or serotonergic cell loss. Finally, in a subsequent study, the raphe/putamen binding ratio of [123]I-beta-FP-CIT correlated with the clinical dopamine response of PD tremor. This suggests that the serotonergic system may play a relatively larger role in patients with a relatively dopamine-resistant PD tremor (Pasquini et al. 2018). Taken together, there are indications that the serotonergic system is involved in tremor, both in physiological tremor and in PD tremor. It remains to be seen to what extent the serotonergic system contributes to the increase in tremor during psychological stress.

19.8 Conclusion

We have reviewed evidence regarding the role of the noradrenergic system in tremor. It is clear that stress-related activation of the LC-noradrenergic system increases tremor severity across many different types of tremor: this effect is seen both in (enhanced) physiological tremor and in clinical tremor syndromes such as PD tremor and ET. Stress hormones such as noradrenaline and adrenaline have important effects on the motor system, both centrally and peripherally, and beta-blockers are effective in reducing different types of tremor. In PD and ET, the available evidence suggests that noradrenergic mechanisms have a role in modulating the expression of tremor, but there is little evidence that noradrenergic dysfunction is involved in the pathophysiological mechanisms that give rise to tremor in the first place. New treatments aimed at attenuating the amplifying effects of stress-related noradrenergic activity on tremor may help to reduce its burden in daily life.

References

Anastasopoulos D. Tremor in Parkinson's disease may arise from interactions of central rhythms with spinal reflex loop oscillations. J Parkinsons Dis. 2020;10:383–92. https://doi.org/10.3233/JPD-191715.

Archer DB, Coombes SA, Chu WT, Chung JW, Burciu RG, Okun MS, et al. A widespread visually-sensitive functional network relates to symptoms in essential tremor. Brain. 2017;141:472–85. https://doi.org/10.1093/brain/awx338.

Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci. 2005;28:403–50. https://doi.org/10.1146/annurev.neuro.28.061604.135709.

Barcroft H, Peterson E, Schwab RS. Action of adrenaline and noradrenaline on the tremor in Parkinson's disease. Neurology. 1952;2:154–60.

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2017;33:75–87. https://doi.org/10.1002/mds.27121.

Blakemore S-J, Sirigu A. Action prediction in the cerebellum and in the parietal lobe. Exp Brain Res. 2003;153:239–45. https://doi.org/10.1007/s00221-003-1597-z.

Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005;352:1112–20. https://doi.org/10.1056/NEJMra041867.

Britton TC, Thompson PD, Day BL, Rothwell JC, Findley LJ, Marsden CD. Modulation of postural tremors at the wrist by supramaximal electrical median nerve shocks in essential tremor, Parkinson's disease and normal subjects mimicking tremor. J Neurol Neurosurg Psychiatr. 1993;56:1085–9.

Broersma M, van der Stouwe AMM, Buijink AWG, de Jong BM, Groot PFC, Speelman JD, et al. Bilateral cerebellar activation in unilaterally challenged essential tremor. Neuroimage Clin. 2016;11:1–9. https://doi.org/10.1016/j.nicl.2015.12.011.

Buijink AWG, van der Stouwe AMM, Broersma M, Sharifi S, Groot PFC, Speelman JD, et al. Motor network disruption in essential tremor: a functional and effective connectivity study. Brain. 2015;138:2934–47. https://doi.org/10.1093/brain/awv225.

Caretti V, Stoffers D, Winogrodzka A, Isaias I-U, Costantino G, Pezzoli G, et al. Loss of thalamic serotonin transporters in early drug-naïve Parkinson's disease patients is associated with tremor: an [123I]β-CIT SPECT study. J Neural Transm. 2008;115:721–9. https://doi.org/10.1007/s00702-007-0015-2.

Carey G, Görmezoğlu M, de Jong JJA, Hofman PAM, Backes WH, Dujardin K, et al. Neuroimaging of anxiety in Parkinson's disease: a systematic review. Mov Disord. 2021;36:327–39. https://doi.org/10.1002/mds.28404.

Carignan B, Daneault J-F, Duval C. The amplitude of physiological tremor can be voluntarily modulated. Exp Brain Res. 2009;194:309–16. https://doi.org/10.1007/s00221-008-1694-0.

Constas C. The effects of adrenaline, noradrenaline, and isoprenaline on parkinsonian tremor. J Neurol Neurosurg Psychiatry. 1962;25:116–21.

Cury RG, Fraix V, Castrioto A, Pérez Fernández MA, Krack P, Chabardes S, et al. Thalamic deep brain stimulation for tremor in Parkinson disease, essential tremor, and dystonia. Neurology. 2017. https://doi.org/10.1212/WNL.0000000000004295.

De Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005;6:463–75. https://doi.org/10.1038/nrn1683.

Deuschl G, Raethjen J, hellriegel H, Elble RJ. Treatment of patients with essential tremor. The Lancet Neurol. 2011;10:148–61. https://doi.org/10.1016/S1474-4422(10)70322-7.

Dirkx MF, den Ouden HEM, Aarts E, Timmer MHM, Bloem BR, Toni I, et al. Dopamine controls Parkinson's tremor by inhibiting the cerebellar thalamus. Brain. 2017;140:721–34. https://doi.org/10.1093/brain/aww331.

Dirkx MF, Zach H, Bloem BR, Hallett M, Helmich RC. The nature of postural tremor in Parkinson disease. Neurology. 2018;90:e1095–103. https://doi.org/10.1212/WNL.0000000000005215.

Dirkx MF, Zach H, van Nuland AJ, Bloem BR, Toni I, Helmich RC. Cognitive load amplifies Parkinson's tremor through excitatory network influences onto the thalamus. Brain. 2020;143:1498–511. https://doi.org/10.1093/brain/awaa083.

Doder M, Rabiner EA, Turjanski N, Lees AJ, Brooks DJ, 11C-WAY 100635 PET study. Tremor in Parkinson's disease and serotonergic dysfunction: an 11C-WAY 100635 PET study. Neurology. 2003;60:601–5.

Elble RJ. Characteristics of physiologic tremor in young and elderly adults. Clin Neurophysiol. 2003;114:624–35. https://doi.org/10.1016/S1388-2457(03)00006-3.

Elble RJ, Randall JE. Mechanistic components of normal hand tremor. Electroencephalogr Clin Neurophysiol. 1978;44:72–82. https://doi.org/10.1016/0013-4694(78)90106-2.

Ferreira JJ, Mestre TA, Lyons KE, Benito-León J, Tan E-K, Abbruzzese G, et al. MDS evidence-based review of treatments for essential tremor. Mov Disord. 2019;34:950–8. https://doi.org/10.1002/mds.27700.

Foster NL, Newman RP, LeWitt PA, Gillespie MM, Larsen TA, Chase TN. Peripheral beta-adrenergic blockade treatment of parkinsonian tremor. Ann Neurol. 1984;16:505–8. https://doi.org/10.1002/ana.410160412.

Gilzenrat MS, Nieuwenhuis S, Jepma M, Cohen JD. Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. Cogn Affect Behav Neurosci. 2010;10:252–69. https://doi.org/10.3758/CABN.10.2.252.

Gross J, Timmermann L, Kujala J, Dirks M, Schmitz F, Salmelin R, et al. The neural basis of intermittent motor control in humans. Proc Natl Acad Sci U S A. 2002;99:2299–302. https://doi.org/10.1073/pnas.032682099.

Hagbarth KE, Young RR. Participation of the stretch reflex in human physiological tremor. Brain. 1979;102:509–26. https://doi.org/10.1093/brain/102.3.509.

Hallett M. Tremor: pathophysiology. Parkinsonism Relat Disord. 2014. https://doi.org/10.1016/S1353-8020(13)70029-4.

Hallett M, Deuschl G. Are we making progress in the understanding of tremor in Parkinson's disease? Ann Neurol. 2010;68:780–1. https://doi.org/10.1002/ana.22253.

Hasbroucq T, Akamatsu M, Burle B, Bonnet M, Possamaï CA. Changes in spinal excitability during choice reaction time: the H reflex as a probe of information transmission. Psychophysiology. 2000;37:385–93.

Haubenberger D, Hallett M. Essential tremor. N Engl J Med. 2018;378:1802–10. https://doi.org/10.1056/NEJMcp1707928.

Helmich RC. The cerebral basis of parkinsonian tremor: a network perspective. Mov Disord. 2018;33:219–31. https://doi.org/10.1002/mds.27224.

Helmich RC, Hallett M, Deuschl G, Toni I, Bloem BR. Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? Brain. 2012;135:3206–26. https://doi.org/10.1093/brain/aws023.

Helmich RC, Toni I, Deuschl G, Bloem BR. The pathophysiology of essential tremor and Parkinson's tremor. Curr Neurol Neurosci Rep. 2013;13:378. https://doi.org/10.1007/s11910-013-0378-8.

Henderson TT, Thorstensen JR, Morrison S, Tucker MG, Kavanagh JJ. Physiological tremor is suppressed and force steadiness is enhanced with increased availability of serotonin regardless of muscle fatigue. J Neurophysiol. 2022;127:27–37. https://doi.org/10.1152/jn.00403.2021.

Hermans EJ, van Marle HJF, Ossewaarde L, Henckens MJAG, Qin S, van Kesteren MTR, et al. Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. Science. 2011;334:1151–3. https://doi.org/10.1126/science.1209603.

Hermans EJ, Henckens MJAG, Joëls M, Fernández G. Dynamic adaptation of large-scale brain networks in response to acute stressors. Trends Neurosci. 2014;37:304–14. https://doi.org/10.1016/j.tins.2014.03.006.

Hjortskov N, Skotte J, Hye-Knudsen C, Fallentin N. Sympathetic outflow enhances the stretch reflex response in the relaxed soleus muscle in humans. J Appl Physiol. 1985;98(2005):1366–70. https://doi.org/10.1152/japplphysiol.00955.2004.

Isaias IU, Marzegan A, Pezzoli G, Marotta G, Canesi M, Biella GEM, et al. A role for locus coeruleus in Parkinson tremor. Front Hum Neurosci. 2011;5:179. https://doi.org/10.3389/fnhum.2011.00179.

Kim J, Criaud M, Cho SS, Díez-Cirarda M, Mihaescu A, Coakeley S, et al. Abnormal intrinsic brain functional network dynamics in Parkinson's disease. Brain. 2017;140:2955–67. https://doi.org/10.1093/brain/awx233.

Kinnerup MB, Sommerauer M, Damholdt MF, Schaldemose JL, Ismail R, Terkelsen AJ, et al. Preserved noradrenergic function in Parkinson's disease patients with rest tremor. Neurobiol Dis. 2021;152:105295. https://doi.org/10.1016/j.nbd.2021.105295.

Kissel P, Tridon P, André JM. Letter: Levodopa-propranolol therapy in parkinsonian tremor. Lancet. 1974;1:403–4.

Lauro PM, Lee S, Akbar U, Asaad WF. Subthalamic-cortical network reorganization during Parkinson's tremor. J Neurosci. 2021;41:9844–58. https://doi.org/10.1523/JNEUROSCI.0854-21.2021.

Lee RG, Stein RB. Resetting of tremor by mechanical perturbations: a comparison of essential tremor and parkinsonian tremor. Ann Neurol. 1981;10:523–31. https://doi.org/10.1002/ana.410100606.

Lee HJ, Lee WW, Kim SK, Park H, Jeon HS, Kim HB, et al. Tremor frequency characteristics in Parkinson's disease under resting-state and stress-state conditions. J Neurol Sci. 2016;362:272–277. http://doi.org/10.1016/j.jns.2016.01.058

Leigh PN, Marsden CD, Twomey A, Jefferson D. beta-Adrenoceptor antagonists and essential tremor. Lancet. 1981;1:1106. https://doi.org/10.1016/s0140-6736(81)92276-5.

Leigh PN, Jefferson D, Twomey A, Marsden CD. Beta-adrenoreceptor mechanisms in essential tremor; a double-blind placebo controlled trial of metoprolol, sotalol and atenolol. J Neurol Neurosurg Psychiatry. 1983;46:710–5. https://doi.org/10.1136/jnnp.46.8.710.

Lenz FA, Tasker RR, Kwan HC, Schnider S, Kwong R, Murayama Y, et al. Single unit analysis of the human ventral thalamic nuclear group: correlation of thalamic "tremor cells" with the 3-6 Hz component of parkinsonian tremor. J Neurosci. 1988;8:754–64.

Lenz FA, Kwan HC, Martin RL, Tasker RR, Dostrovsky JO, Lenz YE. Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. Brain. 1994;117(Pt 3):531–43.

Lin PT, Ross EK, Chidester P, Rosenbluth KH, Hamner SR, Wong SH, et al. Noninvasive neuromodulation in essential tremor demonstrates relief in a sham-controlled pilot trial. Mov Disord. 2018;33:1182–3. https://doi.org/10.1002/mds.27350.

Lippiello P, Hoxha E, Volpicelli F, Lo Duca G, Tempia F, Miniaci MC. Noradrenergic modulation of the parallel fiber-Purkinje cell synapse in mouse cerebellum. Neuropharmacology. 2015;89:33–42. https://doi.org/10.1016/j.neuropharm.2014.08.016.

Llinás RR. The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. Science. 1988;242:1654–64.

Logigian EL, Wierzbicka MM, Bruyninckx F, Wiegner AW, Shahahi BT, Young RR. Motor unit synchronization in physiologic, enhanced physiologic, and voluntary tremor in man. Ann Neurol. 1988;23:242–50. https://doi.org/10.1002/ana.410230306.

Louis ED, Faust PL. Essential tremor pathology: neurodegeneration and reorganization of neuronal connections. Nat Rev Neurol. 2020:1–15. https://doi.org/10.1038/s41582-019-0302-1.

Marsden CD, Owen D. Mechanisms underlying emotional variation in parkinsonian tremor. Neurology. 1967;17:711.

Marsden CD, Parkes JD, Rees JE. Letter: propranolol in Parkinson's disease. Lancet. 1974;2:410.

Marshall J, Schnieden H. Effect of adrenaline, noradrenaline, atropine, and nicotine on some types of human tremor. J Neurol Neurosurg Psychiatry. 1966;29:214–8.

Metz GA. Stress as a modulator of motor system function and pathology. Rev Neurosci. 2007;18:209–22.

Milosevic L, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD. Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. Brain. 2018;15:1052–14. https://doi.org/10.1093/brain/awy139.

Miyashita T, Williams CL. Epinephrine administration increases neural impulses propagated along the vagus nerve: role of peripheral beta-adrenergic receptors. Neurobiol Learn Mem. 2006;85:116–24. https://doi.org/10.1016/j.nlm.2005.08.013.

Morton SM, Bastian AJ. Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. J Neurosci. 2006;26:9107–16. https://doi.org/10.1523/JNEUROSCI.2622-06.2006.

Nieuwhof F, Toni I, Dirkx MF, Gallea C, Vidailhet M, Buijink AWG, et al. Cerebello-thalamic activity drives an abnormal motor network into dystonic tremor. Neuroimage Clin. 2022;33:102919. https://doi.org/10.1016/j.nicl.2021.102919.

Owen DA, Marsden CD. Effect of adrenergic beta-blockade on parkinsonian tremor. Lancet. 1965;2:1259–62. https://doi.org/10.1016/s0140-6736(65)92279-8.

Pahwa R, Lyons KE. Mirtazapine in essential tremor: a double-blind, placebo-controlled pilot study. Mov Disord. 2003;18:584–7. https://doi.org/10.1002/mds.10371.

Pan M-K, Li Y-S, Wong S-B, Ni C-L, Wang Y-M, Liu W-C, et al. Cerebellar oscillations driven by synaptic pruning deficits of cerebellar climbing fibers contribute to tremor pathophysiology. Sci Transl Med. 2020;12 https://doi.org/10.1126/scitranslmed.aay1769.

Pape HC, McCormick DA. Noradrenaline and serotonin selectively modulate thalamic burst firing by enhancing a hyperpolarization-activated cation current. Nature. 1989;340:715–8. https://doi.org/10.1038/340715a0.

Pasquini J, Ceravolo R. The molecular neuroimaging of tremor. Curr Neurol Neurosci Rep. 2021:1–12. https://doi.org/10.1007/s11910-021-01157-4.

Pasquini J, Ceravolo R, Qamhawi Z, Lee J-Y, Deuschl G, Brooks DJ, et al. Progression of tremor in early stages of Parkinson's disease: a clinical and neuroimaging study. Brain. 2018;15:692–11. https://doi.org/10.1093/brain/awx376.

Passmore SR, Bruno PA. Anatomically remote muscle contraction facilitates patellar tendon reflex reinforcement while mental activity does not: a within-participants experimental trial. Chiropr Man Therap. 2012;20:29. https://doi.org/10.1186/2045-709x-20-29.

Paulus W, Jellinger K. The neuropathologic basis of different clinical subgroups of Parkinson's disease. J Neuropathol Exp Neurol. 1991;50:743–55.

Pérez-Santos I, Palomero-Gallagher N, Zilles K, Cavada C. Distribution of the noradrenaline innervation and adrenoceptors in the macaque monkey thalamus. Cereb Cortex. 2021;31:4115–39. https://doi.org/10.1093/cercor/bhab073.

Plenz D, Kital ST. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. Nature. 1999;400:677–82. https://doi.org/10.1038/23281.

Qamhawi Z, Towey D, Shah B, Pagano G, Seibyl J, Marek K, et al. Clinical correlates of raphe serotonergic dysfunction in early Parkinson's disease. Brain. 2015;138:2964–73. https://doi.org/10.1093/brain/awv215.

Rack PM, Ross HF. The role of reflexes in the resting tremor of Parkinson's disease. Brain. 1986;109(Pt 1):115–41.

Radovanovic D, Peikert K, Lindström M, Domellöf FP. Sympathetic innervation of human muscle spindles. J Anat. 2015;226:542–8. https://doi.org/10.1111/joa.12309.

Raethjen J, Pawlas F, Lindemann M, Wenzelburger R, Deuschl G. Determinants of physiologic tremor in a large normal population. Clin Neurophysiol. 2000;111:1825–37.

Reijnders JSAM, Ehrt U, Weber WEJ, Aarsland D, Leentjens AFG. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord. 2008;23:183–9; quiz 313. https://doi.org/10.1002/mds.21803.

Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain. 2005;128:1314–22. https://doi.org/10.1093/brain/awh445.

Roelofs K. Freeze for action: neurobiological mechanisms in animal and human freezing. Philos Trans R Soc Lond Ser B Biol Sci. 2017;372:20160206–10. https://doi.org/10.1098/rstb.2016.0206.

Ross JA, Van Bockstaele EJ. The locus coeruleus-norepinephrine system in stress and arousal: unraveling historical, current, and future perspectives. Front Psych. Frontiersin.org. n.d.. 2021. https://doi.org/10.3389/fpsyt.2020.601519.

Roy A, Coombes SA, Chung JW, Archer DB, Okun MS, Hess CW, et al. Cortical dynamics within and between parietal and motor cortex in essential tremor. Mov Disord. 2018;34:95–104. https://doi.org/10.1002/mds.27522.

Samuels ER, Szabadi E. Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part II: physiological and pharmacological manipulations and pathological alterations of locus coeruleus activity in humans. Curr Neuropharmacol. 2008;6:254–85. https://doi.org/10.2174/157015908785777193.

Sánchez-González MA, García-Cabezas MA, Rico B, Cavada C. The primate thalamus is a key target for brain dopamine. J Neurosci. 2005;25:6076–83. https://doi.org/10.1523/JNEUROSCI.0968-05.2005.

Sara SJ. The locus coeruleus and noradrenergic modulation of cognition. 2009;10:211–23. https://doi.org/10.1038/nrn2573.

Schnitzler A, Münks C, Butz M, Timmermann L, Gross J. Synchronized brain network associated with essential tremor as revealed by magnetoencephalography. Mov Disord. 2009;24:1629–35. https://doi.org/10.1002/mds.22633.

Serrano-Dueñas M. Fluoxetine-induced tremor: clinical features in 21 patients. Parkinsonism Relat Disord. 2002;8:325–7. https://doi.org/10.1016/s1353-8020(01)00043-8.

Shill HA, Adler CH, Beach TG, Lue L-F, Caviness JN, Sabbagh MN, et al. Brain biochemistry in autopsied patients with essential tremor. Mov Disord. 2011;27:113–7. https://doi.org/10.1002/mds.24004.

Shine JM. Neuromodulatory influences on integration and segregation in the brain. Trends Cogn Sci (Regul Ed). 2019;23:572–83. https://doi.org/10.1016/j.tics.2019.04.002.

Shine JM. The thalamus integrates the macrosystems of the brain to facilitate complex, adaptive brain network dynamics. Prog Neurobiol. 2021;199:101951. https://doi.org/10.1016/j.pneurobio.2020.101951.

Shine JM, van den Brink RL, Hernaus D, Nieuwenhuis S, Poldrack RA. Catecholaminergic manipulation alters dynamic network topology across cognitive states. Netw Neurosci. 2018;2:381–96. https://doi.org/10.1162/netn_a_00042.

Shine JM, Bell PT, Matar E, Poldrack RA, Lewis SJG, Halliday GM, et al. Dopamine depletion alters macroscopic network dynamics in Parkinson's disease. Brain. 2019;142:1024–34. https://doi.org/10.1093/brain/awz034.

Soares NM. Cortisol levels, motor, cognitive and behavioral symptoms in Parkinson's disease: a systematic review. J Neural Transm. 2019;126:219–32. https://doi.org/10.1007/s00702-018-1947-4.

Sommerauer M, Fedorova TD, Hansen AK, Knudsen K, Otto M, Jeppesen J, et al. Evaluation of the noradrenergic system in Parkinson's disease: an 11C-MeNER PET and neuromelanin MRI study. Brain. 2017;141:496–504. https://doi.org/10.1093/brain/awx348.

Sommerauer M, Hansen AK, Parbo P, Fedorova TD, Knudsen K, Frederiksen Y, et al. Decreased noradrenaline transporter density in the motor cortex of Parkinson's disease patients. Mov Disord. 2018;101:195. https://doi.org/10.1002/mds.27411.

Tank AW, Lee Wong D. Peripheral and central effects of circulating catecholamines. Compr Physiol. 2015;5:1–15. https://doi.org/10.1002/cphy.c140007.

van de Wardt J, van der Stouwe AMM, Dirkx M, Elting JWJ, Post B, Tijssen MA, et al. Systematic clinical approach for diagnosing upper limb tremor. J Neurol Neurosurg Psychiatry. 2020;91:822–30. https://doi.org/10.1136/jnnp-2019-322676.

Van den Berg KRE, Helmich RC. The role of the cerebellum in tremor - evidence from neuroimaging. Tremor Other Hyperkinet Mov (N Y). 2021;11:49. https://doi.org/10.5334/tohm.660.

van der Heide A, Speckens AEM, Meinders MJ, Rosenthal LS, Bloem BR, Helmich RC. Stress and mindfulness in Parkinson's disease - a survey in 5000 patients. NPJ Parkinsons Dis. 2021a;7:7. https://doi.org/10.1038/s41531-020-00152-9.

van der Heide A, Meinders MJ, Speckens AEM, Peerbolte TF, Bloem BR, Helmich RC. Stress and mindfulness in Parkinson's disease: clinical effects and potential underlying mechanisms. Mov Disord. 2021b;36:64–70. https://doi.org/10.1002/mds.28345.

Volkmann J, Joliot M, Mogilner A, Ioannides AA, Lado F, Fazzini E, et al. Central motor loop oscillations in parkinsonian resting tremor revealed by magnetoencephalography. Neurology. 1996;46:1359–70.

Walshe FMR. Observations on the nature of the muscular rigidity of paralysis agitans, and on its relationship to tremor. Brain. 1924;47(2):159–177. http://doi.org/10.1093/brain/47.2.159.

Young RR, Growdon JH, Shahani BT. Beta-adrenergic mechanisms in action tremor. N Engl J Med. 1975;293:950–3. https://doi.org/10.1056/NEJM197511062931902.

Zach H, Dirkx M, Bloem BR, Helmich RC. The clinical evaluation of Parkinson's tremor. J Parkinsons Dis. 2015;5:471–4. https://doi.org/10.3233/JPD-150650.

Zach H, Dirkx MF, Pasman JW, Bloem BR, Helmich RC. Cognitive stress reduces the effect of levodopa on Parkinson's resting tremor. CNS Neurosci Ther. 2017;23:209–15. https://doi.org/10.1111/cns.12670.

Zach H, Dirkx MF, Roth D, Pasman JW, Bloem BR, Helmich RC. Dopamine-responsive and dopamine-resistant resting tremor in Parkinson disease. Neurology. 2020;95:e1461–70. https://doi.org/10.1212/WNL.0000000000010316.

Chapter 20
Metabolic Networks in Parkinson's Disease

Prashin Unadkat, Martin Niethammer, and David Eidelberg

Abstract Our understanding of Parkinson's disease (PD) has progressed from a focal disorder primarily of the basal ganglia to a more widespread "network" disorder alongside our evolving understanding of the basal ganglia's complex interconnections. Interestingly, metabolic brain imaging with [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) positron emission tomography (PET) has allowed us to explore and expand upon these network ideas in novel ways. The application of network-oriented image analysis to [^{18}F]-FDG PET provides valuable information concerning functional connectivity and is thus particularly well suited to the study of complex brain disorders like PD and related parkinsonian syndromes. In this chapter, we will review clinical and research applications of PD-related metabolic networks for the differential diagnosis and assessment of disease progression and therapeutic benefit.

Keywords Parkinson's disease · Metabolic networks · Motor · Cortico–striato–pallidal–thalamocortical circuits · Patterns · Atypical parkinsonian syndromes

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20.1 Introduction

The idea that Parkinson's disease (PD) is a "network" disorder has emerged alongside our evolving understanding of the basal ganglia's complex interconnections. The notion of a direct and indirect pathway has remained an important concept even as we have increasingly come to acknowledge the oversimplifications of the construct. Metabolic brain imaging with [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) positron emission tomography (PET) has allowed us to explore and expand upon these network ideas in novel ways. The application of network-oriented image analysis to [^{18}F]-FDG PET provides valuable information concerning functional connectivity and is thus particularly well suited to the study of complex brain disorders like PD and related parkinsonian syndromes. We will discuss the historical evolution of network analysis and the subsequent utility in diagnosis, monitoring progression and assessing treatment response. With the availability of newer structural, functional, and perfusion magnetic resonance imaging (MRI) techniques, we discuss the applications of these and newer analysis techniques.

20.2 Metabolic Networks in Parkinson's Disease

20.2.1 The Derivation of Metabolic Networks

Parkinson's disease (PD) is characterized by a progressive degeneration of dopaminergic neurons in the substania niagra pars compacta (and locus ceruleus) and leads to denervation of its projections to the striatum and ventral tegmental area (via the nigrostriatal and mesolimbic and mesocortical pathways) as well as widespread deposition of Lewy bodies (alpha synuclein) in the central nervous system. This is thought to be the principal driver of the motor and cognitive symptoms seen in PD (Braak and Del Tredici 2009; Halliday and McCann 2010). This progressive dopaminergic denervation leads to overactivity within the putamen and its subsequent projections within the globus pallidus and thalamus (Crossman 1990). Glucose metabolism measured using [^{18}F]-FDG provides a good measure of regional synaptic activity (Eidelberg et al. 1997) with new evidence suggesting that this increased glucose activity at the synapse is driven primarily by astrocytes and not neurons (Zimmer et al. 2017). These findings raise the possibility of a role of altered astrocyte activity in PD-related networks.

[^{18}F]-FDG PET imaging in PD has shown hypermetabolic states in the globus pallidus, pons, and cerebellum, while the dorsolateral prefrontal cortex, associated motor areas, parietal, and occipital association areas show an inverse hypometabolic state (Eckert et al. 2005; Eckert et al. 2007a; Booij et al. 2012). Parallel efforts employing [^{15}O]-labeled water ([^{15}O]-H_2O) have been used to identify disease-related abnormalities in regional cerebral blood flow (CFB). Network patterns derived from [^{15}O]-H_2O PET have correlated well with results from [^{18}F]- FDG

PET showing a high degree of coupling between CBF and FDG uptake in deriving PD-related patterns (Ma and Eidelberg 2007), potentially paving the way for using less invasive modalities such as arterial spin labeling MRI (Ma et al. 2010).

Early PET studies confined assessments to local metabolism and did not take into account metabolic impact on distantly connected regions. These metabolic changes can be evaluated at the regional (voxel) level using standard mass-univariate approaches. However, these techniques had limited utility for diagnostic purposes and creating a biomarker to monitor disease progression. It is now better appreciated that localized pathology can alter functional connectivity globally in a disease specific manner (Eidelberg 2009). This understanding has opened the door for assessing brain functional organization at the network level using multivariate analytical procedures. A strength of the network approach is that it takes into account large-scale functional changes within a defined neural system as opposed to examining the regional changes in isolation. Spatial covariance analysis based on principal component analysis (PCA) is one such method that has gained particular interest and detects network level functional abnormalities in PD (Eckert et al. 2007a; Eidelberg et al. 1994). The scaled subprofile model (SSM) is applied to a combination of healthy and diseased patient data from which a pattern distinguishing the two groups is derived and quantified. Individuals affected by that particular disorder may have different magnitudes of pattern expression depending on a number of factors such as the severity or duration of disease with pattern expression usually increasing as the disease progresses, making this approach particularly useful for the objective evaluation of neurodegenerative disorders with variable rates of progression (Feigin et al. 2007a; Tang et al. 2010a).

20.2.2 The PD-Related Motor Pattern

The Parkinson's disease-related pattern (PDRP) is the most validated network pattern in PD and has been consistently identified in multiple populations (Eckert et al. 2007a; Teune et al. 2013; Wu et al. 2013; Tripathi et al. 2016; Tomse et al. 2017) with excellent within subject reproducibility (Ma et al. 2007). The network is characterized by increased metabolic activity with pallidothalamic and pontine areas with relative reductions in premotor, supplementary motor cortex, and parietal association areas (Fig. 20.1a). The relatively localized loss of nigral dopaminergic neurons leads to specific functional changes involving anatomically interconnected elements of cortico–striato–pallidal–thalamocortical (CSPTC) circuits and related pathways. For example, functional overactivity of the subthalamic nucleus (STN) and the internal segment of the globus pallidus results in reduced output from the ventrolateral thalamus to the motor cortices (Alexander and Crutcher 1990; Parent and Hazrati 1995). Expression of this network has also been correlated strongly with presynaptic dopaminergic activity (Holtbernd et al. 2015; Ko et al. 2017a). Additionally, PDRP expression and alterations in the basal ganglia have been

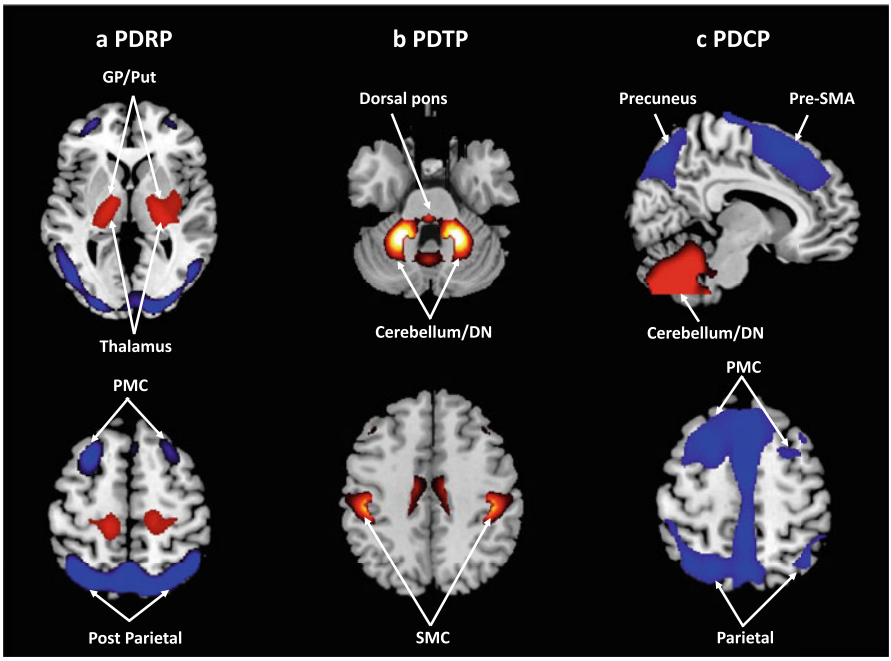

Fig. 20.1 Abnormal metabolic networks in Parkinson's disease. (**a**) Parkinson's disease motor-related pattern (PDRP) identified by network analysis of [^{18}F]-fluorodeoxyglucose (FDG) PET scans from 33 PD patients and 33 age-matched normal volunteer subjects (Ma et al. 2007). This spatial covariance pattern is characterized by increases (red) in the metabolic activity of the putamen/globus pallidus (Put/GP), thalamus, pons, cerebellum, and sensorimotor cortex, associated with relative decreases (blue) in the lateral premotor cortex (PMC) and in parieto-occipital association regions. (Adapted from Eidelberg (2009), Copyright 2009, with permission from Elsevier). (**b**) PD tremor-related metabolic pattern (PDTP) identified using a within-subject network analysis of FDG PET scans from nine tremor-dominant PD patients scanned at baseline and during ventrointermediate (Vim) thalamic deep brain stimulation (DBS) (Mure et al. 2011). This pattern is characterized by covarying increases in the metabolic activity of the sensorimotor cortex (SMC), cerebellum, pons, and putamen. (Reprinted from Mure et al. (2011) Copyright 2010, with permission from Elsevier). (**c**) PD cognition-related metabolic pattern (PDCP) identified in a separate network analysis of FDG PET scans from 15 non-demented PD patients (Huang et al. 2007b). This spatial covariance pattern is characterized by decreases in the metabolic activity (blue) of the rostral supplementary motor area (pre-SMA), precuneus, and the posterior parietal and prefrontal regions, associated with relative increases (red) in the dentate nucleus (DN) and cerebellar cortex. (Reprinted from Eidelberg (2009), Copyright 2009, with permission from Elsevier)

demonstrated with strong correlations between spontaneous subthalamic nucleus activity recorded via microelectrode recordings (Lin et al. 2008).

Clinically, expression scores for PDRP correlate with Unified Parkinson's Disease Rating Scale (UPDRS) motor ratings for bradykinesia and rigidity (Niethammer and Eidelberg 2012; Eidelberg et al. 1995; Lozza et al. 2004) but not tremor, which has been found to correlate with its own distinct metabolic pattern. The

expression of PDRP is typically suppressed by dopaminergic medications and surgical interventions targeting the STN (lesioning, deep brain stimulation (DBS), subthalamic AAV2-GAD gene therapy) (Asanuma et al. 2006; Pourfar et al. 2009; Trošt et al. 2006; Feigin et al. 2001; Feigin et al. 2007b). One recent study showed this positive effect of DBS on PDRP at 3 months with a rollback in PDRP expression that correlated with UPDRS at one year further demonstrating its utility monitoring treatment response (Ge et al. 2020). Additionally, these PD-related topographies develop independently of chronic levodopa treatment (Schindlbeck et al. 2020).

Regional cerebral metabolic activity has been found to correlate with corresponding regional blood flow measurements, in the untreated baseline state (Ma and Eidelberg 2007). However, the effects of levodopa treatment cause a dissociation of this relationship with suppression of cerebral metabolic rate and paradoxical increase in cerebral blood flow. Interestingly, this effect is not seen with DBS, suggesting that this maybe a feature of levodopa treatment and potentially a mechanism for levodopa induced dyskinesia (Hirano et al. 2008). Thus, PDRP activity can be measured with methods that measure cerebral perfusion, including radionuclide imaging with [^{15}O]-H_2O PET (Ma and Eidelberg 2007; Ma et al. 2007) or 99mTc-ethylcysteine dimer (ECD) single photon emission computed tomography (SPECT) (Eckert et al. 2007b; Feigin et al. 2002). Similarly, PDRP expression can be quantified noninvasively with perfusion-weighted MRI methods such as arterial spin labeling (ASL) (Ma et al. 2010). Unlike PET or SPECT, ASL uses an endogenous material, namely magnetically labeled arterial blood water, to measure cerebral blood flow. This approach potentially allows for repeated network measurements in a single subject without concerns over radiation exposure. Indeed, PDRP expression in individual subjects has been found to be tightly coupled regardless of whether measured using [^{18}F]-FDG PET, [^{15}O]-H_2O PET, or perfusion MRI (Ma and Eidelberg 2007; Teune et al. 2014).

The use of functional MRI (fMRI) to reproduce results seen using [^{18}F]-FDG PET has the potential to broaden its use in clinical settings. Early studies looking at functional connectivity matrices demonstrated the utility in differentiating PD patients from healthy controls (Wu et al. 2009; Helmich et al. 2011; Szewczyk-Krolikowski et al. 2014). Using SSM-PCA analysis on resting-state fMRI (rs-fMRI), averaged square root of the power maps of low frequency blood oxygen level-dependent signals was applied on data from PD and healthy controls. The topographic pattern was similar to the PET-derived PDRP, differentiating PD, and healthy controls with good accuracy (Wu et al. 2015). In another study, using a novel independent component analysis (ICA) pipeline, a PDRP pattern (termed fPDRP) was derived with significant correlation in network expression scores between those derived from [^{18}F]-FDG PET. Additionally, fPDRP scores also correlated strongly with UPDRS scores for rigidity and akinesia but not tremor with validation of results on an independent dataset (Vo et al. 2017). Further validation and reproducibility of this method were demonstrated using this method (Rommal et al. 2021).

20.2.3 The PD-Related Tremor Pattern

The pathophysiology of tremor in PD that remains uncertain is distinct from that of the other cardinal motor features (Mure et al. 2011). Tremor does not appear to correlate strongly with the degree of dopaminergic loss and does not uniformly respond to dopaminergic replacement. Similarly, as opposed to rigidity and bradykinesia, this manifestation of PD is not captured by the PDRP metabolic network. Indeed, PDRP expression has been observed to be similar in patients with the same degree of akinetic rigidity, irrespective of the presence or intensity of tremor (Antonini et al. 1998; Isaias et al. 2010). A discrete PD tremor-related metabolic covariance pattern (PDTP) was identified when using [^{18}F]-FDG PET acquired on tremor-predominant PD patients, who had undergone ventrointermediate (Vim) thalamic DBS for these symptoms (Mure et al. 2011). Metabolic images obtained on- and off-stimulation were analyzed using a within-subject guided PCA method termed Ordinal Trends Canonical Variates Analysis (OrT/CVA) (Habeck et al. 2005). This approach revealed a stable PDTP topography (Fig. 20.1b) that was characterized by covarying increases in the activity of the cerebellum and primary cortex as well as, to a lesser degree, the caudate and putamen. In contrast to the PDRP, prospectively computed PDTP scores (Fig. 20.2) were found to correlate well with tremor but not with bradykinesia and rigidity ratings with excellent test-retest reliability and with a significant elevation in the pattern in the tremor dominant patients. Further highlighting the difference between the two patterns, the authors

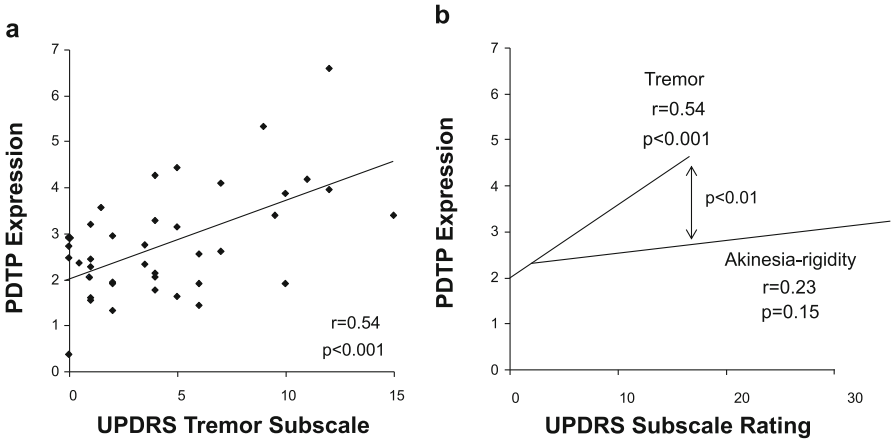

Fig. 20.2 Validation of PD tremor-related metabolic pattern (PDTP) expression as a network correlate of parkinsonian tremor. (**a**) PDTP expression values (Mure et al. 2011) computed in a testing group of 41 PD patients correlated ($r = 0.54$, $p < 0.001$) with UPDRS subscale ratings for tremor. (**b**) However, multiple regression analysis (Mure et al. 2011) revealed that the correlation between PDTP values and tremor ratings was of significantly greater magnitude ($p < 0.01$) than the corresponding correlation with akinesia-rigidity ratings. (**a**, **b**: Reprinted from Mure et al. (2011), Copyright 2010, with permission from Elsevier)

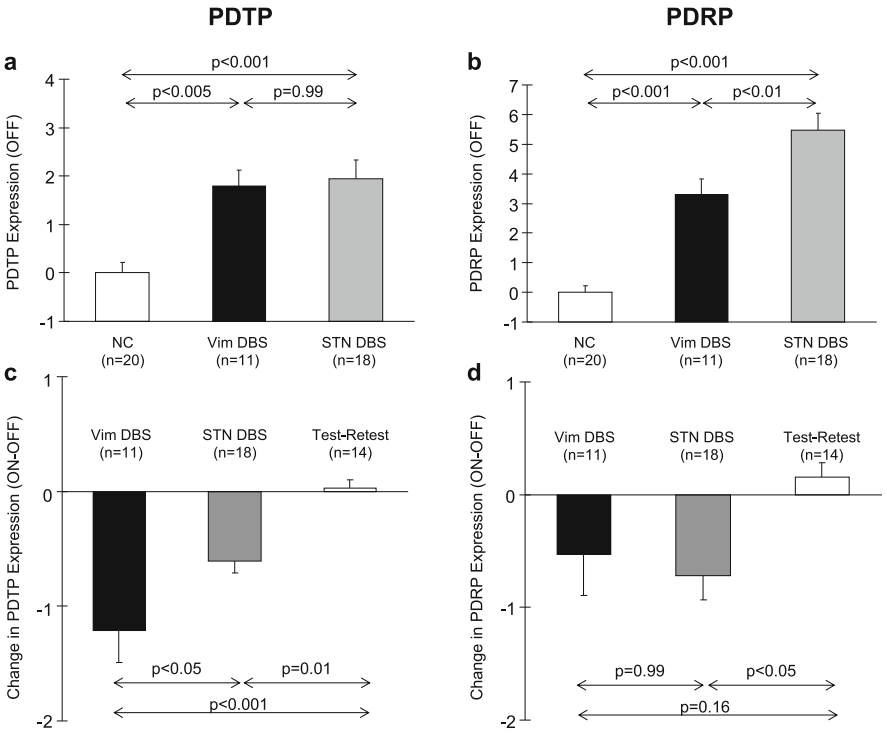

Fig. 20.3 Changes in metabolic network activity with deep brain stimulation for PD tremor. (**a**) Bar graphs (Mure et al. 2011) showing mean baseline PDTP expression (±SE) in the Vim DBS patients (black), the STN DBS patients (gray), and the healthy control subjects (white). There was a significant difference in PDTP expression across the three groups ($p < 0.001$; one-way ANOVA), with comparable elevations in baseline pattern expression in both the Vim DBS ($p < 0.005$) and STN DBS groups ($p < 0.001$) relative to controls. (**b**) Baseline PDRP expression also differed across the three groups ($p < 0.001$), with higher expression in both treatment groups relative to controls ($p < 0.001$). Nonetheless, PDRP expression was higher in the STN than in the Vim DBS group ($p < 0.01$). (**c**) Treatment-mediated changes (Mure et al. 2011) in mean PDTP expression (±SE) in the Vim DBS patients (black), the STN DBS patients (gray), and the test–retest PD control subjects (white). Changes in PDTP expression were different across the three groups ($p < 0.001$; one-way ANOVA), with stimulation-mediated declines in network activity in both DBS groups (Vim: $p < 0.001$; STN: $p = 0.01$, relative to the test–retest control group). PDTP modulation was greater with Vim than STN stimulation ($p < 0.05$). (**d**) There was also a significant group difference in treatment-mediated PDRP modulation ($p = 0.02$). Treatment-mediated reductions in PDRP expression reached significance ($p < 0.05$) with STN stimulation, but not with Vim stimulation ($p = 0.16$). (**a–d**: Reprinted from Mure et al. (2011), Copyright 2010, with permission from Elsevier)

observed (Fig. 20.3) that Vim thalamic stimulation (which is generally not effective for rigidity or akinesia) reduced baseline elevations in PDTP—but not PDRP—expression, whereas STN stimulation (effective for all cardinal features) reduced both PDTP and PDRP network expression. Both PDRP and PDTP were found to

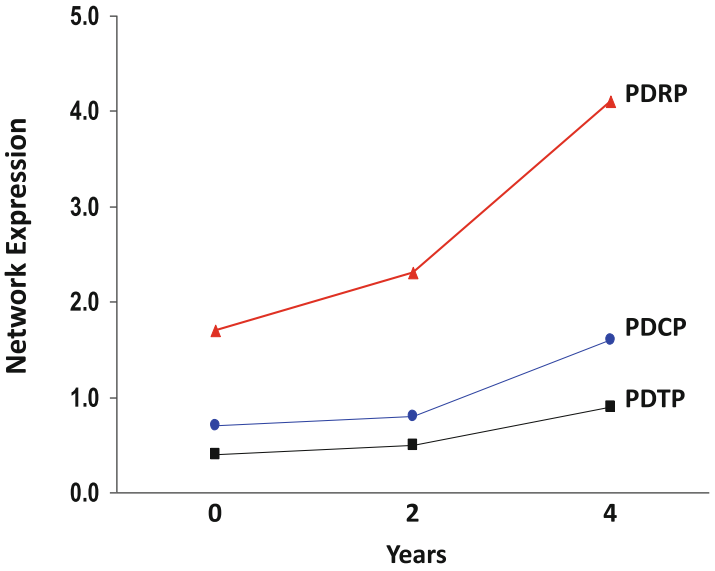

Fig. 20.4 Changes in the whole-brain expression of metabolic networks with disease progression. Time courses of the whole-brain expression of the PD-related motor (PDRP), cognitive (PDCP), and tremor (PDTP) patterns. All three networks exhibited significantly increased activity over time (PDRP: $p < 0.0001$; PDCP: $p < 0.0001$; PDTP: $p = 0.01$), but at different rates of progression ($p < 0.01$). PDRP expression increased at the fastest rate while PDTP the slowest. Subject scores for each network were z-transformed so that the normal mean is 0 and standard deviation is 1. (Reprinted from Mure et al. (2011), Copyright 2010, with permission from Elsevier; also reprinted from Tang and Eidelberg (2010), Copyright 2010)

progress over time (Fig. 20.4), although the tremor pattern did so at a much slower rate than the PDRP. In aggregate, these findings point to major differences between tremor- and akinesia/rigidity-related brain networks, in terms of clinical correlates, treatment effects, and natural history.

Localized tremor-related circuitry has also been studied by quantifying the effects of differing intensities of stimulation on brain metabolism. Several studies have demonstrated differences in metabolic activity when comparing effective versus subtherapeutic levels of stimulation (Deiber et al. 1993; Parker et al. 1992), helping to differentiate between the physiological effect of tremor suppression and the nonspecific effect of electrical stimulation. Deiber et al. demonstrated with $[^{15}O]$-H_2O PET that effective stimulation was associated with metabolic decreases in the contralateral cerebellum, whereas ineffective stimulation was associated with decreases in ipsilateral supplementary motor cortices (SMC) (Riedel et al. 2008). Using correlation statistical parametric mapping (SPM) analysis, another study investigated how differing degrees of Vim stimulation modulated cerebello–thalamo–cortical activity, using $[^{15}O]$-H_2O PET to study eight tremor-predominant PD patients with Vim DBS with stimulation turned off, partially effective stimulation, and optimal stimulation. Tremor reduction was associated

with decreases in the SMC ipsilateral to stimulation and in the contralateral cerebellum with concurrent increases in the ventral thalamus localized to the DBS target. Furthermore, changes in SMC activity were preferentially modeled by tremor amplitude, whereas changes in cerebellar activity were better modeled by tremor frequency. Thus, both changes in regional glucose metabolism and cerebral blood flow point to enhanced cerebello–thalamo–cortical activity with tremor and the suppression of this pathway by thalamic stimulation.

20.2.4 The PD-Related Cognitive Pattern

In addition to motor symptoms, [^{18}F]-FDG PET has been used to study the cognitive changes associated with PD. The prevalence of frank dementia in PD can range from 17% to 43% (Riedel et al. 2008), but the presence of mild cognitive deficits is higher still and can be present from a relatively early stage (Caviness et al. 2007). Early identification of such cognitive changes, even when mild, is of significant importance severely affecting quality of life, function, and can have significant economic consequences over and above motor symptoms (Chandler et al. 2021; Aarsland et al. 2021). A distinct and highly reproducible metabolic pattern associated with cognitive dysfunction in non-demented PD patients has been identified. This PD-related cognitive pattern (PDCP) (Fig. 20.1c) is statistically unrelated to the PDRP and is characterized by hypometabolism in medial frontal and parietal association cortices with relative increases in the cerebellar vermis and dentate nuclei (Huang et al. 2007a; Mattis et al. 2016; Mattis et al. 2011; Niethammer et al. 2013). It can differentiate PD subjects with mild cognitive impairment from those without (Huang et al. 2008; Meles et al. 2015), and has been found to correlate with neuropsychological test performance (Huang et al. 2007a), particularly with tests of executive function (Trošt et al. 2016). Additionally, like PDRP and PDTP, it has an excellent test-retest reliability (Huang et al. 2007a). The slow rate of PDCP progression is particularly evident when assessed in individual subjects undergoing serial longitudinal PET imaging (Tang et al. 2010a; Huang et al. 2013) (Fig. 20.4). Abnormal PDCP expression typically happens later in the disease course, reflecting the usual latency between onset of motor and cognitive symptoms. Likewise, the trajectory of PDCP progression over time is nonlinear and independent of the PDRP (Huang et al. 2007b). While PDRP correlates well with striatal and putamen dopamine transporter binding (Huang et al. 2007b), PDCP was found to correlate well with bilateral dopaminergic input to the caudate (Niethammer et al. 2013). Another difference from the motor network is that cognitive network activity is not significantly altered by treatment of motor symptoms with levodopa, stereotaxic interventions, or gene therapy (Asanuma et al. 2006; Feigin et al. 2007b; Hirano et al. 2008). That said, some evidence points to PDCP modulation by levodopa treatment at the individual subject level, in proportion to the degree that the pattern is expressed in the baseline (unmedicated) condition (Mattis et al. 2011). These observations are particularly meaningful in assessing interventions targeting the

cognitive aspects of PD (captured by changes in PDCP expression), as compared with the more treatment-responsive motor symptoms (captured by changes in PDRP expression).

20.3 Atypical Parkinsonian Syndromes

Differentiating typical from atypical parkinsonian syndromes (APS) on clinical grounds can often be challenging, particularly early in the course of disease. Many parkinsonian syndromes first present with common features of rigidity and bradykinesia, with hallmark characteristics of each specific disorder (e.g., dysautonomia in multiple system atrophy (MSA)) developing only years later. The occasional initial response to dopaminergic therapy in atypical syndromes further clouds the early clinical impression. This is evidenced by postmortem pathological confirmation of atypical syndromes in up to 10% of the patients who were diagnosed with PD in life (Hughes et al. 2002). Clinical diagnosis typically is progressively more accurate only years after symptom onset and is only 26% accurate in early patients or those not clearly responsive to dopamine (Adler et al. 2014). Standard dopaminergic neuroimaging approaches (such as [^{18}F]-FDG PET and DAT SPECT imaging) can help rule out essential tremor and drug-induced parkinsonism in a patient with clinical parkinsonism but cannot reliably differentiate between PD and APS. As the prognosis and treatment implications differ considerably between parkinsonian syndromes, having the ability to identify the correct diagnosis early on is helpful to the clinician, the researcher, and the patient.

Two of the most common atypical syndromes include MSA and progressive supranuclear palsy (PSP). Specific and highly stable metabolic networks have similarly been characterized for both MSA and PSP in two independent patient groups compared with control subjects (Eckert et al. 2008). Multiple studies have demonstrated high specificity and positive predictive value (Fig. 20.5c, d) in diagnosing and differentiating PD, MSA, and PSP (Tripathi et al. 2016; Tang et al. 2010b; Tripathi et al. 2012), demonstrating the network patterns' potential value as an excellent diagnostic tool. The MSA-related pattern (MSARP) demonstrates bilateral metabolic reductions in the putamen and cerebellum (Fig. 20.5a), while the PSP-related pattern (PSPRP) demonstrates more diffuse abnormalities compared with both PD and MSA and is characterized by metabolic reductions in the upper brainstem, medial prefrontal cortex, medial thalamus, caudate, anterior cingulate, ventrolateral prefrontal cortex, and frontal eye fields (Fig. 20.5b). One clear differentiator between the PDRP and the metabolic patterns for both atypical syndromes is the presence of basal ganglia hypometabolism in atypical syndromes (as opposed to hypermetabolism in idiopathic PD, resulting from pre- and postsynaptic degeneration that occurs in both MSA and PSP (Tang et al. 2010b; Poston et al. 2012).

Similar approaches aimed at identifying other atypical syndromes such as corticobasal degeneration (CBD) have identified a unique pattern termed CBDRP,

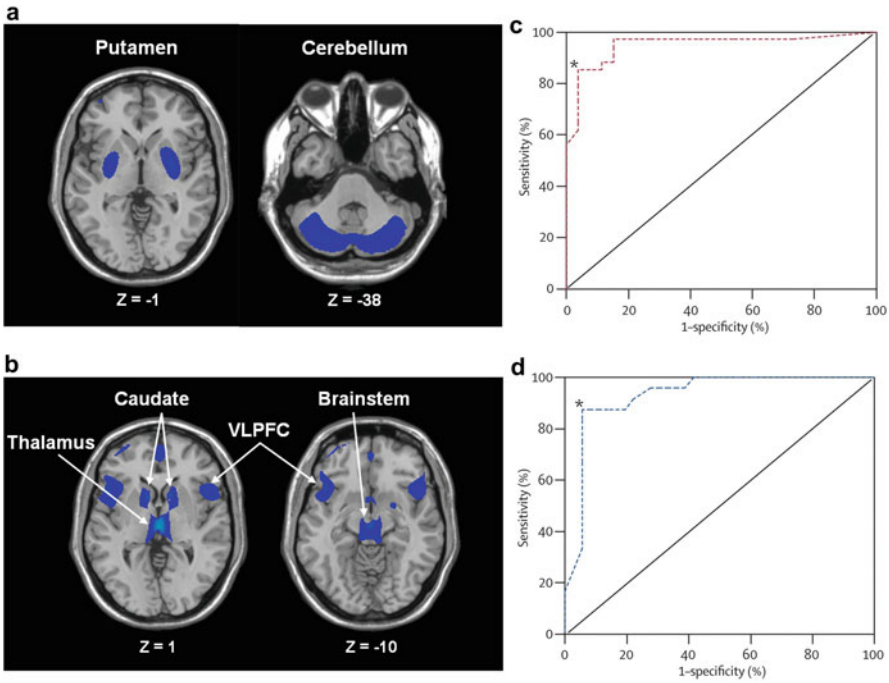

Fig. 20.5 Spatial covariance patterns associated with multiple system atrophy and progressive supranuclear palsy. (**a**) Metabolic pattern (Eckert et al. 2008) associated with multiple system atrophy (MSARP) characterized by covarying metabolic decreases in the putamen and cerebellum. (**b**) Metabolic pattern (Eckert et al. 2008) associated with progressive supranuclear palsy (PSPRP) characterized by covarying metabolic decreases in the medial prefrontal cortex (PFC), frontal eye fields, ventrolateral prefrontal cortex (VLPFC), caudate nuclei, medial thalamus, and in the upper brainstem. (The covariance patterns were overlaid on T1-weighted MR-template images. The displays represent regions that contributed significantly to the network and that were demonstrated to be reliable by bootstrap resampling. Voxels with negative region weights (metabolic decreases) are color-coded blue.) (**a**, **b**: Reprinted from Eckert et al. (2008), Copyright© 2008 with permission of John Wiley & Sons, Inc.) (**c**, **d**) Receiver operating characteristic (ROC) curves for categorization based on the MSARP and the PSPRP are displayed (Tang et al. 2010b). The areas under each curve are, respectively, 0.95 (95% CI 0.89–1.00) and 0.93 (95% CI 0.86–0.99). (Reprinted from Tang et al. (2010b), Copyright 2010, with permission from Elsevier)

with elevated pattern expression in the disease compared to healthy controls and which allows successful discrimination from MSA. This pattern expression could not discriminate between PSP (presumably due to significant overlap between the two metabolic topographies); however, this could be overcome after calculating hemispheric asymmetry scores (Niethammer et al. 2014).

20.4 Metabolic Networks in Prodromal States and Rapid Eye Movement Disorder

In recent years, substantial interest has developed in the discovery of predictive biomarkers for use in individuals at high risk for PD, such as those with rapid eye movement sleep behavior disorder (RBD). These patients have been found to exhibit cell loss in the same brain regions as in PD (Boeve et al. 2007) and is now considered one of the biggest non-genetic risk factors in the development of PD (Berg et al. 2015). Prior imaging studies have reported deficits in presynaptic nigrostriatal dopaminergic function in RBD patients demonstrating a progressive decrease in tracer uptake in the putamen when going from healthy controls to RBD and then PD with RBD, while tracer uptake overlapped in PD patients with and without RBD (Bauckneht et al. 2018). Another study using [^{18}F]-FDG PET and ethylcysteinate dimer SPECT found PDRP expression increased in patients with RBD in both the groups, with about half the patients converting to PD or LBD (Holtbernd and Eidelberg 2014). While RBD patients that go on to convert to PD have high PDRP expression, abnormally low expression levels seem to favor conversion to MSA (Holtbernd et al. 2014). A separate RBD-related pattern has also been described with some topographical overlap with PDRP (Wu et al. 2014; Meles et al. 2018).

While RBD represents a prodromal state of PD, evidence suggests PDRP expression may be helpful in diagnosis in other prodromal states as well. In studies looking at patients with hemiparkinsonism, PDRP expression was similarly elevated in both hemispheres, with parallel and linear increases on follow up scans (Tang et al. 2010a; Ko et al. 2014).

20.5 Network Changes with Treatment

The use of an imaging biomarker to accurately diagnose and more objectively assess treatment response is of significant interest. Correct clinical diagnosis, especially in early stage disease trials, is particularly challenging. One longitudinal study that compared patients with scans without evidence of dopamine deficit (SWEDD) versus those with DAT deficit found that 44% of those with SWEDD had their diagnosis changed from PD at follow up compared to 3.6% in the DAT group (Marek et al. 2014). In the REAL-PET study, designed to study the rates of dopamine loss in the striatum between patients receiving ropinirole versus levodopa, about 11% patients were excluded after randomization to treatment due to normal [^{18}F]-FDOPA PET studies at onset (Whone et al. 2003). In another study evaluating the differences in treatment response in patients diagnosed with PD patients, only 40% of the patients with SWEDD had any response to an array of treatments with no worsening of tremor on withdrawal of dopamine, while those with abnormal DAT scans had an 84% response (Schwingenschuh et al. 2010).

Another utility for imaging criteria is in assessing response to treatment beyond clinical evaluations. Both PDRP and PDCP expression is decreased with appropriate treatment, this effect is currently relatively modest and may be considered insufficient for clinical trials (Asanuma et al. 2006; Pourfar et al. 2009; Jourdain et al. 2016). However, metabolic imaging can give unique insight to functional reorganization that occurs with therapy, such as in the AAV2-GAD gene therapy trial where using an OrT/CVA method a unique treatment dependent GAD-related pattern (GADRP) was identified, demonstrating new polysynaptic functional pathways linking STN to motor cortices. Of note, metabolic imaging was also used in the AAV2-GAD gene therapy trial to screen patients for the appropriate diagnosis, and 16% patients were screened out solely due to imaging criteria, highlighting the utility of implementation of imaging cutoffs. Additionally, imaging biomarkers may be helpful in differentiating placebo effect which is a major confounder in PD therapy trials (Galpern et al. 2012). Ko et al. in the AAV2-GAD gene therapy trial were also able to identify a specific metabolic brain network associated with placebo response that linked the posterior cerebellar vermis to the limbic cortex via the ventral anterior thalamus, amygdala and caudate (Ko et al. 2014). More interestingly, the effects of the network were reversed with unblinding.

20.6 Future Research Applications

While considerable work has been done to demonstrate the utility of a network analysis approach in the diagnosis and monitoring of PD, this is primarily used in the research domain with larger clinical implementation still lacking.

Currently, considerable interest exists in accurate diagnosis in the prodromal stages as well as early PD where clinical symptoms can often be misleading. Conditions such as RBD are important risk factors in developing PD and been found to exhibit dopaminergic cell loss as seen in PD (Boeve et al. 2007; Uchiyama et al. 1995) with presynaptic dopaminergic function at intermediate levels between healthy controls and PD (Stiasny-Kolster et al. 2005).

Differentiating PD from APS is another area of significant interest as their clinical course and subsequent treatments can be very different. Abnormal metabolic networks have been characterized (Meles et al. 2018) for atypical forms of parkinsonism including MSA and PSP, and in preliminary form in CBD described previously in this chapter. Indeed, these patterns have been used in concert with the PDRP for accurate differential diagnosis of individual cases, even at early clinical stages of disease (Tang et al. 2010b; Spetsieris et al. 2009). Nonetheless, rates of network progression in MSA and PSP are not currently available and larger validation studies are still required. Longitudinal studies conducted in atypical populations will provide critical data concerning network progression in these patient groups.

Newer mathematical tools such as graph theory can help parse known functional networks such as PDRP into finer details (Schindlbeck and Eidelberg 2018). For

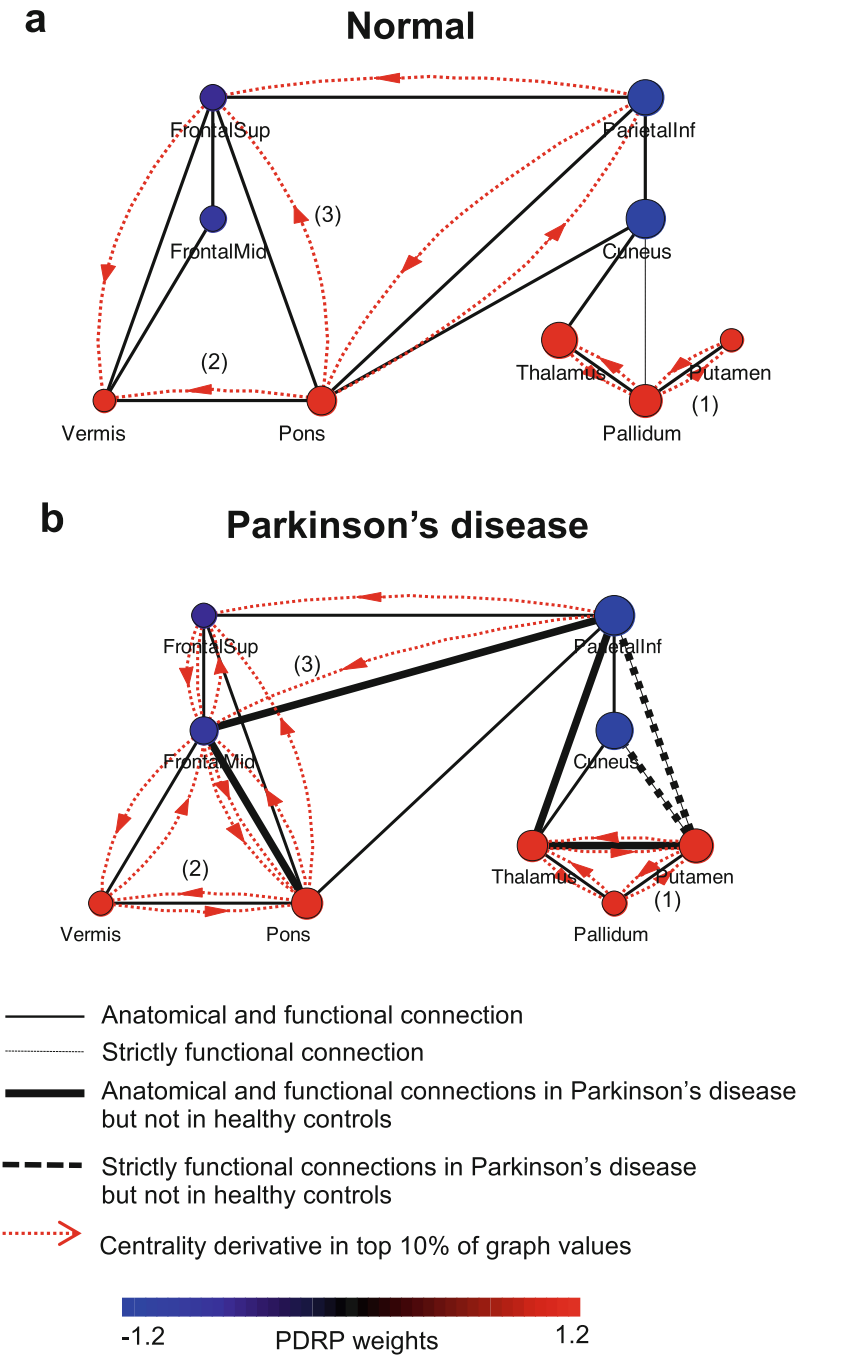

Fig. 20.6 Abnormal network-level clustering in Parkinson's disease (PD). Graph theory can identify regions within the network space in which clustering (defined by the number of triangles or closed

example, using graph analysis, the PDRP pattern was divided into a metabolically active core including the putamen, globus pallidus, and thalamus with weaker connections linking less active cortical areas, with a separate module connecting that was defined by interconnected active nodes in the cerebellum, pons, frontal cortex, and limbic areas (Fig. 20.6) (Ko et al. 2017b). Characterization of subnetworks can also explain specific clinical features within the basal ganglia subnetwork that are associated with bradykinesia and rigidity, while the brainstem and cerebellum subnetworks are associated with tremor. Furthermore, these techniques give insights into the disease process by characterizing the exaggerated small worldness, a property that describes the increased clustering and reduced average path length between key nodes in the network, which leads to high metabolic costs and inefficient, noisy information transfer between network regions (Ko et al. 2017b). Besides giving insights into the disease process, graph analysis can also help understand mechanisms of treatment. For example, levodopa treatment improves global efficiency of information transfer by normalizing the average path length within the PDRP space; however, it only partially corrects the properties of small worldness.

Additionally, graph analysis can also be utilized to understand the phenotypic differences between PD patients with LRKK2 and GBA1 genes (characterized by a much slower and more aggressive course, respectively) with strikingly different patterns of increased network connectivity between the two genotypes (Schindlbeck et al. 2019).

In addition to static connectivity analysis, dynamic functional connectivity analysis has recently been explored and demonstrated hyperconnected and hypoconnected states in PD patients that reveal response to some treatments in only one particular state (Wu et al. 2021).

Fig. 20.6 (continued) triples formed when a node's nearest neighbors are connected) is increased in one group of patients relative to another. The radius of each node is proportional to its influence on the network—i.e., its centrality. For each network node, corresponding PDRP region weights were color-coded such that metabolically active regions (PDRP weights ≥ 1.0) are depicted in red while relatively underactive regions (PDRP weights ≤ -1.0) are depicted in blue. (**a**) In a group of healthy controls, three discrete sets of interconnected nodes (open triples) were seen in (1) the putamen, globus pallidus, and the thalamus; (2) the pons, cerebellar vermis, and frontal cortex; and (3) superior and middle frontal gyri, and inferior parietal lobule. (**b**) In the PD group (age-matched to the healthy controls), additional interactions (i.e., edges) were detected, sealing off each of the triples as a discrete triangle (bold black lines). These edges denote specific node-to-node functional interactions present in patients with PD, but not in healthy controls. Notably, the closed triples (triangles) in areas (1) and (2) were located within the core zones identified in the structural analysis of the PD network. These triples were formed by abnormal functional connections linking the nearest neighbors of core nodes through bidirectional, mutually facilitating interactions (red arrows). (Reprinted from Schindlbeck and Eidelberg (2018), Copyright 2018, with permission from Elsevier; adapted from Ko et al. (2017b), Copyright 2017, with permission from Oxford University Press)

20.7 Conclusions

In this chapter, we have described the historical evolution of network analysis and its impact on understanding the various domains of PD patients. Exciting new work with MRI and more sophisticated mathematical tools such as graph analysis and dynamic functional connectivity may further elaborate our understanding of the disease and the effect of treatment; however, significant more work is needed.

References

Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K, et al. Parkinson disease-associated cognitive impairment. Nat Rev Dis Primers. 2021;7(1):1–21.

Adler CH, Beach TG, Hentz JG, Shill HA, Caviness JN, Driver-Dunckley E, et al. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. Neurology. 2014;83(5):406–12.

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 1990;13(7):266–71.

Antonini A, Moeller JR, Nakamura T, Spetsieris P, Dhawan V, Eidelberg D. The metabolic anatomy of tremor in Parkinson's disease. Neurology. 1998;51(3):803–10.

Asanuma K, Tang C, Ma Y, Dhawan V, Mattis P, Edwards C, et al. Network modulation in the treatment of Parkinson's disease. Brain. 2006;129(Pt 10):2667–78.

Bauckneht M, Chincarini A, De Carli F, Terzaghi M, Morbelli S, Nobili F, et al. Presynaptic dopaminergic neuroimaging in REM sleep behavior disorder: a systematic review and meta-analysis. Sleep Med Rev. 2018;41:266–74.

Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2015;30(12):1600–11.

Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain. 2007;130(Pt 11):2770–88.

Booij J, Teune LK, Verberne HJ. The role of molecular imaging in the differential diagnosis of parkinsonism. Q J Nucl Med Mol Imaging. 2012;56(1):17–26.

Braak H, Del Tredici K. Neuroanatomy and pathology of sporadic Parkinson's disease. Adv Anat Embryol Cell Biol. 2009;201:1–119.

Caviness JN, Driver-Dunckley E, Connor DJ, Sabbagh MN, Hentz JG, Noble B, et al. Defining mild cognitive impairment in Parkinson's disease. Mov Disord. 2007;22(9):1272–7.

Chandler J, Nair R, Biglan K, Ferries EA, Munsie L, Changamire T, et al. Characteristics of Parkinson's disease in patients with and without cognitive impairment. J Parkinsons Dis. 2021;(Preprint):1–12.

Crossman A. A hypothesis on the pathophysiological mechanisms that underlie levodopa-or dopamine agonist-induced dyskinesia in Parkinson's disease: implications for future strategies in treatment. Mov Disord. 1990;5(2):100–8.

Deiber MP, Pollak P, Passingham R, Landais P, Gervason C, Cinotti L, et al. Thalamic stimulation and suppression of parkinsonian tremor. Evidence of a cerebellar deactivation using positron emission tomography. Brain. 1993;116(Pt 1):267–79.

Eckert T, Barnes A, Dhawan V, Frucht S, Gordon MF, Feigin AS, et al. FDG PET in the differential diagnosis of parkinsonian disorders. NeuroImage. 2005;26(3):912–21.

Eckert T, Tang C, Eidelberg D. Assessment of the progression of Parkinson's disease: a metabolic network approach. Lancet Neurol. 2007a;6(10):926–32.

Eckert T, Van Laere K, Tang C, Lewis DE, Edwards C, Santens P, et al. Quantification of Parkinson's disease-related network expression with ECD SPECT. Eur J Nucl Med Mol Imaging. 2007b;34(4):496–501.

Eckert T, Tang C, Ma Y, Brown N, Lin T, Frucht S, et al. Abnormal metabolic networks in atypical parkinsonism. Mov Disord. 2008;23(5):727–33.

Eidelberg D. Metabolic brain networks in neurodegenerative disorders: a functional imaging approach. Trends Neurosci. 2009;32(10):548–57.

Eidelberg D, Moeller J, Dhawan V, Spetsieris P, Takikawa S, Ishikawa T, et al. The metabolic topography of parkinsonism. J Cereb Blood Flow Metab. 1994;14(5):783–801.

Eidelberg D, Moeller JR, Ishikawa T, Dhawan V, Spetsieris P, Chaly T, et al. Assessment of disease severity in parkinsonism with fluorine-18-fluorodeoxyglucose and PET. J Nucl Med. 1995;36(3):378–83.

Eidelberg D, Moeller JR, Kazumata K, Antonini A, Sterio D, Dhawan V, et al. Metabolic correlates of pallidal neuronal activity in Parkinson's disease. Brain J Neurol. 1997;120(8):1315–24.

Feigin A, Fukuda M, Dhawan V, Przedborski S, Jackson-Lewis V, Mentis MJ, et al. Metabolic correlates of levodopa response in Parkinson's disease. Neurology. 2001;57(11):2083–8.

Feigin A, Antonini A, Fukuda M, De Notaris R, Benti R, Pezzoli G, et al. Tc-99m ethylene cysteinate dimer SPECT in the differential diagnosis of parkinsonism. Mov Disord. 2002;17(6):1265–70.

Feigin A, Tang C, Ma Y, Mattis P, Zgaljardic D, Guttman M, et al. Thalamic metabolism and symptom onset in preclinical Huntington's disease. Brain. 2007a;130(Pt 11):2858–67.

Feigin A, Kaplitt MG, Tang C, Lin T, Mattis P, Dhawan V, et al. Modulation of metabolic brain networks after subthalamic gene therapy for Parkinson's disease. Proc Natl Acad Sci. 2007b;104(49):19559–64.

Galpern WR, Corrigan-Curay J, Lang AE, Kahn J, Tagle D, Barker RA, et al. Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations. Lancet Neurol. 2012;11(7):643–50.

Ge J, Wang M, Lin W, Wu P, Guan Y, Zhang H, et al. Metabolic network as an objective biomarker in monitoring deep brain stimulation for Parkinson's disease: a longitudinal study. EJNMMI Res. 2020;10(1):1–10.

Habeck C, Krakauer JW, Ghez C, Sackeim HA, Eidelberg D, Stern Y. A new approach to spatial covariance modeling of functional brain imaging data: ordinal trend analysis. Neural Comput. 2005;17:1602–45.

Halliday GM, McCann H. The progression of pathology in Parkinson's disease. Ann N Y Acad Sci. 2010;1184:188–95.

Helmich RC, Janssen MJ, Oyen WJ, Bloem BR, Toni I. Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. Ann Neurol. 2011;69(2):269–81.

Hirano S, Asanuma K, Ma Y, Tang C, Feigin A, Dhawan V, et al. Dissociation of metabolic and neurovascular responses to levodopa in the treatment of Parkinson's disease. J Neurosci. 2008;28(16):4201–9.

Holtbernd F, Eidelberg D. The utility of neuroimaging in the differential diagnosis of parkinsonian syndromes. Semin Neurol. 2014;34(2):202–9.

Holtbernd F, Gagnon JF, Postuma RB, Ma Y, Tang CC, Feigin A, et al. Abnormal metabolic network activity in REM sleep behavior disorder. Neurology. 2014;82(7):620–7.

Holtbernd F, Ma Y, Peng S, Schwartz F, Timmermann L, Kracht L, et al. Dopaminergic correlates of metabolic network activity in Parkinson's disease. Hum Brain Mapp. 2015;36(9):3575–85.

Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D. Metabolic brain networks associated with cognitive function in Parkinson's disease. NeuroImage. 2007a;34(2):714–23.

Huang C, Tang C, Feigin A, Lesser M, Ma Y, Pourfar M, et al. Changes in network activity with the progression of Parkinson's disease. Brain. 2007b;130(Pt 7):1834–46.

Huang C, Mattis P, Perrine K, Brown N, Dhawan V, Eidelberg D. Metabolic abnormalities associated with mild cognitive impairment in Parkinson disease. Neurology. 2008;70(16 Pt 2):1470–7.

Huang C, Ravdin LD, Nirenberg MJ, Piboolnurak P, Severt L, Maniscalco JS, et al. Neuroimaging markers of motor and nonmotor features of Parkinson's disease: an 18f fluorodeoxyglucose positron emission computed tomography study. Dement Geriatr Cogn Disord. 2013;35(3–4):183–96.

Hughes A, Daniel S, Ben-Shlomo Y, Lees A. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain. 2002;125(Pt 4):861–70.

Isaias IU, Marotta G, Hirano S, Canesi M, Benti R, Righini A, et al. Imaging essential tremor. Mov Disord. 2010;25(6):679–86.

Jourdain VA, Tang CC, Holtbernd F, Dresel C, Choi YY, Ma Y, et al. Flow-metabolism dissociation in the pathogenesis of levodopa-induced dyskinesia. JCI Insight. 2016;1(15):e86615.

Ko JH, Feigin A, Mattis PJ, Tang CC, Ma Y, Dhawan V, et al. Network modulation following sham surgery in Parkinson's disease. J Clin Invest. 2014;124(8):3656–66.

Ko JH, Lee CS, Eidelberg D. Metabolic network expression in parkinsonism: clinical and dopaminergic correlations. J Cereb Blood Flow Metab. 2017a;37(2):683–93.

Ko JH, Spetsieris PG, Eidelberg D. Network structure and function in Parkinson's disease. Cereb Cortex. 2017b;28(12):4121–35.

Lin TP, Carbon M, Tang C, Mogilner AY, Sterio D, Beric A, et al. Metabolic correlates of subthalamic nucleus activity in Parkinson's disease. Brain. 2008;131(Pt 5):1373–80.

Lozza C, Baron JC, Eidelberg D, Mentis MJ, Carbon M, Marie RM. Executive processes in Parkinson's disease: FDG-PET and network analysis. Hum Brain Mapp. 2004;22(3):236–45.

Ma Y, Eidelberg D. Functional imaging of cerebral blood flow and glucose metabolism in Parkinson's disease and Huntington's disease. Mol Imaging Biol. 2007;9(4):223–33.

Ma Y, Tang C, Spetsieris P, Dhawan V, Eidelberg D. Abnormal metabolic network activity in Parkinson's disease: test-retest reproducibility. J Cereb Blood Flow Metab. 2007;27(3):597–605.

Ma Y, Huang C, Dyke JP, Pan H, Alsop D, Feigin A, et al. Parkinson's disease spatial covariance pattern: noninvasive quantification with perfusion MRI. J Cereb Blood Flow Metab. 2010;30(3):505–9.

Marek K, Seibyl J, Eberly S, Oakes D, Shoulson I, Lang AE, et al. Longitudinal follow-up of SWEDD subjects in the PRECEPT study. Neurology. 2014;82(20):1791–7.

Mattis PJ, Tang CC, Ma Y, Dhawan V, Eidelberg D. Network correlates of the cognitive response to levodopa in Parkinson disease. Neurology. 2011;77(9):858–65.

Mattis PJ, Niethammer M, Sako W, Tang CC, Nazem A, Gordon ML, et al. Distinct brain networks underlie cognitive dysfunction in Parkinson and Alzheimer diseases. Neurology. 2016;87(18):1925–33.

Meles SK, Tang CC, Teune LK, Dierckx RA, Dhawan V, Mattis PJ, et al. Abnormal metabolic pattern associated with cognitive impairment in Parkinson's disease: a validation study. J Cereb Blood Flow Metab. 2015;35(9):1478–84.

Meles SK, Renken RJ, Janzen AHO, Vadasz D, Pagani M, Arnaldi D, et al. The metabolic pattern of idiopathic REM sleep behavior disorder reflects early-stage Parkinson's disease. J Nucl Med. 2018;59(9):1437–44.

Mure H, Hirano S, Tang CC, Isaias IU, Antonini A, Ma Y, et al. Parkinson's disease tremor-related metabolic network: characterization, progression, and treatment effects. NeuroImage. 2011;54(2):1244–53.

Niethammer M, Eidelberg D. Metabolic brain networks in translational neurology: concepts and applications. Ann Neurol. 2012;72(5):635–47.

Niethammer M, Tang CC, Ma Y, Mattis PJ, Ko JH, Dhawan V, et al. Parkinson's disease cognitive network correlates with caudate dopamine. NeuroImage. 2013;78:204–9.

Niethammer M, Tang CC, Feigin A, Allen PJ, Heinen L, Hellwig S, et al. A disease-specific metabolic brain network associated with corticobasal degeneration. Brain. 2014;137(Pt 11):3036–46.

Parent A, Hazrati L-N. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidium in basal ganglia circuitry. Brain Res Rev. 1995;20(1):128–54.

Parker F, Tzourio N, Blond S, Petit H, Mazoyer B. Evidence for a common network of brain structures involved in parkinsonian tremor and voluntary repetitive movement. Brain Res. 1992;584(1–2):11–7.

Poston KL, Tang CC, Eckert T, Dhawan V, Frucht S, Vonsattel JP, et al. Network correlates of disease severity in multiple system atrophy. Neurology. 2012;78(16):1237–44.

Pourfar M, Tang C, Lin T, Dhawan V, Kaplitt MG, Eidelberg D. Assessing the microlesion effect of subthalamic deep brain stimulation surgery with FDG PET. J Neurosurg. 2009;110(6):1278–82.

Riedel O, Klotsche J, Spottke A, Deuschl G, Förstl H, Henn F, et al. Cognitive impairment in 873 patients with idiopathic Parkinson's disease. Results from the German study on epidemiology of Parkinson's disease with dementia (GEPAD). J Neurol. 2008;255(2):255–64.

Rommal A, Vo A, Schindlbeck KA, Greuel A, Ruppert MC, Eggers C, et al. Parkinson's disease-related pattern (PDRP) identified using resting-state functional MRI: validation study. Neuroimage: Rep. 2021;1(3):100026.

Schindlbeck KA, Eidelberg D. Network imaging biomarkers: insights and clinical applications in Parkinson's disease. Lancet Neurol. 2018;17(7):629–40.

Schindlbeck KA, Vo A, Nguyen N, Tang CC, Niethammer M, Dhawan V, et al. LRRK2 and GBA variants exert distinct influences on Parkinson's disease-specific metabolic networks. Cereb Cortex. 2019;30(5):2867–78.

Schindlbeck KA, Lucas-Jimenez O, Tang CC, Morbelli S, Arnaldi D, Pardini M, et al. Metabolic network abnormalities in drug-naive Parkinson's disease. Mov Disord. 2020;35(4):587–94.

Schwingenschuh P, Ruge D, Edwards MJ, Terranova C, Katschnig P, Carrillo F, et al. Distinguishing SWEDDs patients with asymmetric resting tremor from Parkinson's disease: a clinical and electrophysiological study. Mov Disord. 2010;25(5):560–9.

Spetsieris PG, Ma Y, Dhawan V, Eidelberg D. Differential diagnosis of parkinsonian syndromes using PCA-based functional imaging features. NeuroImage. 2009;45(4):1241–52.

Stiasny-Kolster K, Doerr Y, Möller J, Höffken H, Behr T, Oertel W, et al. Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for α-synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT. Brain. 2005;128(1):126–37.

Szewczyk-Krolikowski K, Menke RA, Rolinski M, Duff E, Salimi-Khorshidi G, Filippini N, et al. Functional connectivity in the basal ganglia network differentiates PD patients from controls. Neurology. 2014;83(3):208–14.

Tang CC, Eidelberg D. Abnormal metabolic brain networks in Parkinson's disease from blackboard to bedside. Prog Brain Res. 2010;184:161–76.

Tang CC, Poston KL, Dhawan V, Eidelberg D. Abnormalities in metabolic network activity precede the onset of motor symptoms in Parkinson's disease. J Neurosci. 2010a;30(3):1049–56.

Tang CC, Poston KL, Eckert T, Feigin A, Frucht S, Gudesblatt M, et al. Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis. Lancet Neurol. 2010b;9(2):149–58.

Teune LK, Renken RJ, Mudali D, De Jong BM, Dierckx RA, Roerdink JB, et al. Validation of parkinsonian disease-related metabolic brain patterns. Mov Disord. 2013;28(4):547–51.

Teune LK, Renken RJ, de Jong BM, Willemsen AT, van Osch MJ, Roerdink JB, et al. Parkinson's disease-related perfusion and glucose metabolic brain patterns identified with PCASL-MRI and FDG-PET imaging. Neuroimage Clin. 2014;5:240–4.

Tomse P, Jensterle L, Grmek M, Zaletel K, Pirtosek Z, Dhawan V, et al. Abnormal metabolic brain network associated with Parkinson's disease: replication on a new European sample. Neuroradiology. 2017;59(5):507–15.

Tripathi M, Tang C, Peng S, Dhawan V, Sharma R, Jaimini A, et al. Metabolic image-based algorithm for accurate differential diagnosis of parkinsonism: prospective validation in Indian patient population. J Nucl Med. 2012;53(Suppl 1):1974.

Tripathi M, Tang CC, Feigin A, De Lucia I, Nazem A, Dhawan V, et al. Automated differential diagnosis of early parkinsonism using metabolic brain networks: a validation study. J Nucl Med. 2016;57(1):60–6.

Trošt M, Su S, Su P, Yen R-F, Tseng H-M, Barnes A, et al. Network modulation by the subthalamic nucleus in the treatment of Parkinson's disease. NeuroImage. 2006;31(1):301–7.

Trošt M, Brezovar S, Tang C, Eidelberg D, Križnar Z, Kramberger G, et al. Metabolic brain changes related to specific cognitive impairment in non-demented Parkinson's disease patients: 1306. Mov Disord. 2016;31.

Uchiyama M, Isse K, Tanaka K, Yokota N, Hamamoto M, Aida S, et al. Incidental Lewy body disease in a patient with REM sleep behavior disorder. Neurology. 1995;45(4):709–12.

Vo A, Sako W, Fujita K, Peng S, Mattis PJ, Skidmore FM, et al. Parkinson's disease-related network topographies characterized with resting state functional MRI. Hum Brain Mapp. 2017;38(2):617–30.

Whone AL, Watts RL, Stoessl AJ, Davis M, Reske S, Nahmias C, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. Ann Neurol. 2003;54(1):93–101.

Wu T, Long X, Zang Y, Wang L, Hallett M, Li K, et al. Regional homogeneity changes in patients with Parkinson's disease. Hum Brain Mapp. 2009;30(5):1502–10.

Wu P, Wang J, Peng S, Ma Y, Zhang H, Guan Y, et al. Metabolic brain network in the Chinese patients with Parkinson's disease based on 18F-FDG PET imaging. Parkinsonism Relat Disord. 2013;19(6):622–7.

Wu P, Yu H, Peng S, Dauvilliers Y, Wang J, Ge J, et al. Consistent abnormalities in metabolic network activity in idiopathic rapid eye movement sleep behaviour disorder. Brain. 2014;137(12):3122–8.

Wu T, Ma Y, Zheng Z, Peng S, Wu X, Eidelberg D, et al. Parkinson's disease-related spatial covariance pattern identified with resting-state functional MRI. J Cereb Blood Flow Metab. 2015;35(11):1764–70.

Wu C, Matias C, Foltynie T, Limousin P, Zrinzo L, Akram H. Dynamic network connectivity reveals markers of response to deep brain stimulation in Parkinson's disease. Front Hum Neurosci. 2021:450.

Zimmer ER, Parent MJ, Souza DG, Leuzy A, Lecrux C, Kim H-I, et al. [18F]FDG PET signal is driven by astroglial glutamate transport. Nat Neurosci. 2017;20(3):393–5.

Chapter 21
Deep Brain Stimulation for Tremor

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Abstract Tremor is one of the most frequent complaints in the movement disorder clinic. Not only it can be encountered in multiple different syndromes, but it can also present with variable characteristics of complexity, frequency, topography, and state-dependency within the spectrum of single disease. Pharmacological therapy of severe tremor is often unsatisfactory irrespective of the underlying diagnosis and phenomenology, and surgical treatment represents a highly effective alternative. Since the publication of the first edition of this book, an exponential progress of imaging techniques and device engineering has generated incredible advancements in the field of invasive neuromodulation, contributing to increase our knowledge of the physiopathology and improve surgical targeting and programming. Multiple references to these exciting developments are disseminated throughout this chapter, which start with a brief history of deep brain stimulation for tremor, followed by a description of the anatomy of surgical targets, and general principles of stimulation programming. The subsequent paragraphs are dedicated to the use of deep brain stimulation in the clinic, according to specific tremor diagnosis. Common indications such as Parkinson's disease, essential tremor, and tremor associated with dystonia are discussed, as well as more phenomenologically complex, uncommon tremor syndromes. An account of side effects and their pathogenic mechanisms occupies the end of this section. Finally, a discussion of promising future directions in the field is included at the end of the chapter.

Keywords Tremor · Deep Brain Stimulation · Surgery · Thalamus

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21.1 Introduction

For a large part of the last century, before introduction of pharmacological therapy, surgical treatment of tremor was essentially the only option for severely disabled patients, primarily those affected by Parkinson's disease (PD).

The first unrefined attempts at tremor relief included primary motor cortectomy, lesioning of unilateral corticospinal tracts at various levels, and severance of cervical nerve roots, often leading to hemiparesis or death (Novak et al. 2011). Pioneering transventricular surgery of basal ganglia structures was next, but soon abandoned due to high mortality rates (Speelman and Bosch 1998). Gradually, surgical techniques became more sophisticated, thanks to the introduction of stereotaxy in 1947 allowing for an exponential increase of their application in the 1950s and 1960s.

Stereotactic procedures performed in this era used controlled heating, cooling, or mechanical techniques applied through deep cerebral probes. Multiple targets were explored including the internal globus pallidus (GPi) and the adjacent ansa lenticularis (pallidofugal fibers directed to the thalamus), the ventro-lateral thalamus (Hassler et al. 1960), and the adjacent posterior subthalamic area (PSA) (Wertheimer et al. 1960; Mundinger 1969).

From 1969 until the mid-1970s, much of the interest in surgical treatment of parkinsonian tremor declined due to the introduction of levodopa, but thalamotomy ultimately regained popularity due to the limitations of long-term antiparkinsonian treatment, including the often unsatisfactory benefit on tremor (Lyons et al. 2003; Olanow et al. 2001; Pahwa and Lyons 2003; Deuschl et al. 2002). Posteroventral pallidotomy was also introduced in 1985 as an alternative to thalamotomy, with comparable results (Laitinen 1995).

In the meantime, deep brain stimulation (DBS) was being developed and employed for neurological and psychiatric diseases since 1950. There were some preliminary reports of its application in tremor disorders, encouraged by the observation of tremor reduction with the high frequency testing performed during ablation procedures to ensure correct lesion location.

In the late 1980s, DBS of the ventrolateral thalamus became an established treatment for medication-refractory tremor (Benabid et al. 1996; Tasker 1998; Schuurman et al. 2000; Pahwa et al. 2001). It soon replaced thalamotomy due to its nonablative and adjustable nature, allowing for better results and lower rate of adverse events such as cognitive deterioration, dysarthria, gait or balance disturbance, and limb ataxia, especially common with bilateral procedures (Hassler et al. 1960).

Of relevance, in several thalamotomy cases, surgery needed to be repeated to achieve a satisfactory response, thus increasing morbidity (Stellar and Cooper 1968; Hirai et al. 1983; Benabid et al. 1996; Pollak et al. 2002; Tasker 1998; Lund-Johansen et al. 1996; Schuurman et al. 2000). This became unnecessary with DBS. Ventral intermediate nucleus (VIM) DBS was demonstrated to be not only greatly

effective on parkinsonian tremor (Lyons et al. 2001; Pahwa et al. 2006; Rehncrona et al. 2001; Albanese et al. 1999; Hariz et al. 2008) but also safe in patients with prior contralateral thalamotomies or pallidotomies (Nishio et al. 2009).

DBS of the GPi and subthalamic (STN) nuclei was later introduced to improve benefit on rigidity and bradykinesia, not susceptible to treatment with VIM DBS (Tarsy et al. 2003; Krack et al. 1998), and gradually became the preferred surgical approach for PD.

Today, DBS is considered a mainstay treatment for drug-resistant tremor, which represents one of the most common indications for the procedure (Kremer et al. 2021). The most frequent etiologies are still PD and essential tremor (ET) (Deuschl et al. 1998), but there are also a number of less common indications (Ramirez-Zamora and Okun 2016) which will be discussed in the following paragraphs.

21.2 Anatomical Targets for Deep Brain Stimulation in Tremor Disorders

The choice of anatomical targets for DBS surgeries in tremor syndromes is based on underlying diagnosis and patient phenotype. As discussed in the introduction, different targets have been proposed and successfully used to treat tremor in the relatively brief history of DBS.

Recent advances in structural and functional imaging led to significant innovations on targeting modalities for DBS. The possibility to model individual volumes of tissue activated (VTAs) by DBS (McIntyre et al. 2004a, b; Butson et al. 2007) and to correlate their spatial distribution with clinical outcomes fostered numerous studies aimed at identifying the "sweet spot" for the control of specific symptoms, including tremor (Middlebrooks et al. 2018; Tsuboi et al. 2021; Elias et al. 2021; Kremer et al. 2021). This technological developments are now available in clinical settings and facilitate DBS programming based on individual patient-specific anatomical templates (Lange et al. 2021; Waldthaler et al. 2021). Furthermore, the availability of structural and functional connectivity maps (Horn et al. 2019; Riskin-Jones et al. 2021) allowed to identify dysfunctional brain networks involved in the generation of specific symptoms. Indeed, growing evidence suggests a common role of the cerebello-thalamo-cortical circuitry in the pathophysiology of tremor (Isaias et al. 2010; Mure et al. 2011; Helmich et al. 2011; Hallett 2014), possibly triggered in PD patients by noradrenergic fibers arising from the locus coeruleus (Isaias et al. 2011, 2012).

Based on these new developments, the following sections will discuss recommendations on optimal targeting and programming of DBS, along with clinical use and possible side effects.

21.2.1 The Motor Thalamus

Historically, the motor thalamus has been the first target used in functional neurosurgery for the treatment of tremor. Several nomenclatures have been proposed for its nuclei (Hassler 1959; Walker 1982; Hirai and Jones 1989; Jones 1990). According to Hassler (1959), the motor thalamus occupies a ventral lateral position and it comprises several nuclei: the lateral polaris (LPo) which receives input from the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNr), the ventralis oralis anterior (VOa), and ventral oralis posterior (VOp) which receive input from the GPi, the ventral intermediate nucleus (VIM) which receives input from the cerebellum through the dentato-rubro-thalamic tract (DRTT) and the lemniscal system (Krack et al. 2002). The ventral caudal nucleus (VC), which receives sensory input from the medial lemniscus, lies posterior to the VIM.

Microelectrode recordings during stereotactic surgery identified the presence of tremor cells within the VIM (Jones and Tasker 1990; Lenz et al. 1988, 1994). Subsequently, this area was found to be the most effective target for ablative surgical treatment (Hassler et al. 1960). Due to its structural connectivity to both the cerebellum and the motor cortex, the VIM is a fundamental relay station in the cerebello-thalamo-cortical circuitry, and there is evidence that effectiveness of DBS of this nucleus might be correlated with the strength of such connectivity (Riskin-Jones et al. 2021). The hyperactivity of this network has been demonstrated to correlate with tremor amplitude and genesis in a highly convergent fashion across different clinical entities (Hallett 2014; Helmich et al. 2011), which could explain the versatility of VIM as surgical target.

The standard stereotactic coordinates for thalamic DBS are located at the border between the VIM and the subthalamic white matter (Benabid et al. 1996; Krack et al. 2002). Directional leads might increase targeting accuracy and reduce energy requirements (Rebelo et al. 2018; Veerappan et al. 2021; Rammo et al. 2022; Krüger et al. 2021). More recent studies employing electrophysiology and structural connectivity imaging have suggested the existence of stimulation "sweet spots" anteriorly in the VOp nucleus, particularly for dystonic tremor (Tsuboi et al. 2021), or at the VIM/VOp border (Papavassiliou et al. 2004; Middlebrooks et al. 2018; Elias et al. 2021).

21.2.2 The Posterior Subthalamic Area/Caudal Zona Incerta

The posterior subthalamic area (PSA) is a heterogeneous region underlying the motor thalamus. It encompasses numerous interrelated structures: the caudal zona incerta (cZi), pallido-thalamic white matter (fields of Forel H1, H2), and the prelemniscal radiation which includes the DRTT and other cerebello-fugal fibers projecting to the motor thalamus. Its borders are defined anteromedially by the hypothalamus and periaqueductal gray matter, anterolaterally by the internal capsule, posteriorly

by the tegmental area and medial lemniscus, and medially by the red nucleus (Ramirez-Zamora et al. 2016).

The cZi is a sparse collection of nuclei connected to the cerebellum, motor cortex, basal ganglia and VL thalamus, and it has been postulated to be responsible for the generation of axial and proximal limb movements including locomotion. Interestingly, low frequency stimulation of this area has been observed to induce tremor in patients affected by a tremulous PD, further indicating a possible role in tremor pathogenesis (Plaha et al. 2008).

The PSA was introduced as a possible target for subthalamotomies in patients with tremor syndromes (Wertheimer et al. 1960; Mundinger 1969), but did not achieve the same popularity as VIM due to a greater potential for side effects, including weakness, apathy, and contralateral neglect in case of large lesions (Velasco et al. 1986). Therefore, the interest for applying DBS to this area was initially limited (Velasco et al. 2001).

However, with advances in surgical and stimulation techniques, a number of case series have challenged the concept of neurostimulation of the thalamus proper demonstrating better results with electrodes placed within the subthalamic area (Kitagawa et al. 2000; Murata et al. 2003; Plaha et al. 2004; Herzog et al. 2007; Blomstedt et al. 2010; Sandvik et al. 2011). A 2016 review of uncontrolled studies regarding PSA DBS for tremor in several tremor syndromes showed better results for PSA compared to VIM stimulation (79% vs 50% tremor reduction) (Ramirez-Zamora et al. 2016). More recently, this evidence has been complemented by two randomized controlled studies comparing VIM and PSA stimulation in different clinical entities: special surgical trajectories were employed to target both with a single DBS lead, and stimulation to one or the other applied in a cross-over experimental design. Both studies concluded for a superiority of PSA stimulation in tremor abatement, at lower stimulation intensities (Barbe et al. 2016; Kvernmo et al. 2022).

PSA DBS seems to be particularly advantageous for tremor involving the proximal limbs, with higher intentional component, and complex associated cerebellar or dystonic features (Ramirez-Zamora et al. 2016). There is also some indication that it could be more effective for head tremor (Kvernmo et al. 2022).

Lastly, PSA DBS has been shown to ameliorate bradykinesia and rigidity in patients with PD, and this should be considered in patient selection (Velasco et al. 2001; Kitagawa et al. 2005; Carrillo-Ruiz et al. 2008; Blomstedt et al. 2012). However, further studies are needed to clarify the long-term effects of stimulation in this target.

21.2.3 The Dentatorubrothalamic Tract

Thanks to the development and increasing availability of MRI tractography, allowing for the identification of specific white matter tracts in individual brains, it is now

possible to base surgical planning for DBS on the topography of the dentato-rubro-thalamic tract (DRTT).

The DRTT is the main output of the lateral cerebellum: it projects to the primary motor cortex via the VL thalamus, representing the "highway" of the cerebello-thalamo-cortical circuitry.

In 2011, Coenen and colleagues described a striking improvement in head tremor with bilateral DBS of the DRTT in a patient with myoclonus-dystonia (Coenen et al. 2011). After that first report, a number of retrospective studies have confirmed the relevance of DRTT as a surgical target across different tremor syndromes, showing better tremor control for contacts in close proximity to the DRTT (Groppa et al. 2014; Akram et al. 2018; Al-Fatly et al. 2019; Dembek et al. 2020; Petry-Schmelzer et al. 2020; Elias et al. 2021; Tsuboi et al. 2021; Kübler et al. 2021; Ikramuddin et al. 2022).

Based on this evidence, a unifying hypothesis has emerged, postulating that VIM, cZi, and PSA stimulation all exert their effect through structural connectivity with the DRTT (Middlebrooks et al. 2021; Nowacki et al. 2022). Indeed, direct targeting of the DRTT at the intersection with the VIM has been successfully used for DBS procedures in a handful of studies, proving superior to conventional planning in terms of efficacy, tolerability, and energy requirements (Sammartino et al. 2016; Fenoy and Schiess 2018; Morrison et al. 2021).

The DRTT can also be targeted at its passage through the PSA, which has showed more stable and better tremor control compared to PSA DBS, as well as lower incidence of stimulation-related side effects (Low et al. 2019).

Finally, there is preliminary indication that targeting of the DRTT coupled with the STN in advanced tremulous PD could be a feasible and effective therapeutic option for refractory tremor in this population (Coenen et al. 2016).

21.2.4 The Subthalamic Nucleus

The STN is a DBS target primarily used for the treatment of PD, which is often, but not invariably, associated with tremor. This nucleus is part of the input layer of the basal ganglia, receiving afferents from the striatum and the cortex, and projecting to the output structures (GPi, GPe, and SNr). The STN is surrounded by white matter tracts including the internal capsule anteriorly and laterally, the lemniscal radiations and cerebello-thalamic tracts medially and the Zi dorsally and posteriorly, along with the PSA.

Of specific interest for tremor pathophysiology, recent evidence of a disynaptic connection between the STN and the cerebellum has been gathered from animal (Bostan et al. 2010) and human studies (Wang et al. 2020), linking this nucleus to the cerebello-thalamo-cortical circuit. Furthermore, tremor-locked, rhythmic neural activity can be recorded from STN electrodes coherently with peripheral tremor

(Bergman et al. 1994; Rodriguez et al. 1998; Levy et al. 2000). This, along with the observation of a striking benefit of STN DBS on parkinsonian tremor (Kumar et al. 1998; Krack et al. 2003; Kim et al. 2010), seems to indicate an important pathophysiological role towards tremor genesis.

Regarding the optimal electrode placement within the STN, it is worth mentioning that this nucleus is internally organized in three functional territories, with different connectivity profiles. The limbic STN occupies the anterior pole of the nucleus, while the motor region is located in the dorsolateral caudal aspect, variably overlapping with a rostroventral associative portion (Hamani et al. 2017).

It is generally accepted that the "sweet spot" for STN stimulation in movement disorders corresponds to the dorsolateral border of the nucleus and the adjacent white matter, including the dorsal Zi. However, there is no agreement on the existence of a symptom-specific "sweet spot" for tremor (De Roquemaurel et al. 2021).

By means of particular trajectories, STN can be targeted along with the underlying PSA/cZi using a single DBS lead. This approach has been proposed for the treatment of ET and might provide superior tremor control (Blomstedt et al. 2011).

21.2.5 The Internal Globus Pallidus

The GPi is primarily used for the treatment of tremor in the context of PD or dystonia. It constitutes one of the output structures of the basal ganglia, and projects inhibitory efferents to the motor thalamus. Important surrounding structures are the GPe, located dorsally and laterally, the optic tract, ventrally, and the internal capsule, medially and posteriorly. As with the STN, the GPi is divided into functional territories including an anteroventral limbic portion, an associative anterior region, and a proper sensorimotor GPi, located posteroventrolaterally (Patriat et al. 2018).

A recent model of tremor physiopathology suggested a dopamine depletion in the GPi as the potential origin of transient pathologic striato-pallidal activity, ultimately triggering aberrant tremor-related oscillations in the cerebello-thalamo-cortical circuit (Helmich et al. 2011). Further studies, however, have not confirmed this hypothesis and pallidal dopaminergic denervation appears unrelated to rest tremor severity in early PD (Isaias et al. 2012; Lee et al. 2018). Still, rhythmic, tremor-coherent activity can be identified also in the GPi (Hutchison et al. 1997; Magnin et al. 2000) supporting the involvement of this brain area in tremor-generating network making the GPi a possible target for DBS.

The optimal location of the DBS electrode within the sensorimotor territory lies at the border between the ventroposterior GPi and the adjacent subpallidal white matter and it largely overlaps across clinical indications (Au et al. 2021; Reich et al. 2019; Elias et al. 2021).

21.3 Mechanism(s) of Action

The brain can basically be compared with an electronic device. Information is processed by integrating excitatory and inhibitory postsynaptic electrical potentials and encoded in the subsequent train of electrical action potentials.

DBS systems use impulses of electrical energy with variable pulse width, deliverable at adjustable frequencies, to modulate pathological neuronal activity. Although the basic physiological mechanism of DBS is unknown, most evidence suggests that its effects rely on the electrical excitation of fiber tracts (Holsheimer et al. 2000; Kiss et al. 2003; Anderson et al. 2004, 2006; Montgomery and Gale 2008) and presynaptic terminals in the vicinity of the DBS electrode, including those that project to and from neurons in the stimulated target (Beurrier et al. 2001; Kiss et al. 2002; Magariños-Ascone et al. 2002; Montgomery 2010). The mechanisms of this DBS-induced neuromodulation are unclear, but the therapeutic benefit is likely determined by a combination of local and distributed effects. Accordingly, stimulation within the thalamus, subthalamic or GPi nuclei might influence neuronal activity of local projection neurons (McIntyre et al. 2004a, b), while stimulation of the PSA/cZI would impact afferent cerebello-thalamic fibers (Anderson et al. 2006). However, this may be just an oversimplistic description, as electrical stimulation has both ortho- and antidromic effects, and has been shown to impact synaptic plasticity (Herrington et al. 2016).

For the purpose of discussing field shaping in everyday clinical practice, we will hold to the oversimplified notion that the purpose of DBS is to excite the intended brain target while minimizing stimulation or spread of current to other elements (see below, Adverse Events). Stimulation parameters that can be modulated in order to achieve this result include electrode location and polarity, voltage or current amplitude (which are interrelated by Ohm's law), pulse width, and frequency of stimulation.

Recent electrophysiology studies with dual microelectrodes used to microstimulate and record cellular responses at the same time in different surgical targets have shown DBS effects to be frequency-dependent according to the underlying microcircuit anatomy of the studied nucleus (Liu et al. 2012; Milosevic et al. 2017, 2018). In general, effective cell inhibition is obtained through high frequency stimulation, at different thresholds identifiable for each structure. Specifically for tremor-coherent cells in the motor thalamus, an optimal effect of synaptic suppression correlating with clinical response has been demonstrated for microstimulation trains at 200 Hz, which parallels the clinical observation that VIM DBS produces better results with higher frequencies than typically employed for other targets (Milosevic et al. 2018).

Variations in pulse width and polarity of stimulation can affect the volume of stimulated tissue and the population of excited fibers. Lower pulse width values are usually associated with a wider therapeutic window thanks to higher side effect thresholds (Moldovan et al. 2018; Bouthour et al. 2018).

The most commonly used polarity configuration is cathodic monopolar stimulation, in which electrical pulses are delivered through one of the DBS electrodes as the cathode and the anode are represented by the internal pulse generator (IPG). This kind of stimulation excites axons around the electrode with the lowest threshold and latency both for clinical benefit and side effects. Bipolar stimulation, in which two contacts on the DBS lead are used as anode and cathode, provides more focal stimulation volumes thereby widening the therapeutic window (Reich et al. 2015; Soh et al. 2019). Anodic stimulation, in which the polarities of the DBS electrode and IPG are reversed, also may improve the therapeutic window by preferentially impacting fibers with different orientation in case of adverse events limiting stimulation intensity (Kirsch et al. 2018; Anderson et al. 2019; Boogers et al. 2022). A similar effect has been demonstrated acutely for symmetric biphasic stimulation with alternating polarity (Boogers et al. 2022). This modality is still available only for research, and its benefit needs to be confirmed in large cohorts and in chronic settings. In addition, other parameters than traditional cathodic stimulation generally result in higher battery cost (Soh et al. 2019), and this has to be taken into consideration in device selection, especially given the availability of rechargeable IPGs.

Another useful strategy to increase therapeutic window and minimize spread of current to unwanted structures has become available with the recent introduction of segmented leads and multiple independent current control, allowing for more focal stimulation through horizontal current steering (Steigerwald et al. 2016). This technical innovation can significantly improve clinical outcomes and facilitate and speed up DBS programming (Lange et al. 2021; Waldthaler et al. 2021), especially when combined with interface softwares capable of model-based real-time VTA reconstruction (Rebelo et al. 2018; Veerappan et al. 2021; Rammo et al. 2022; Krüger et al. 2021).

Currently available IPGs differ on whether voltage or electrical current is controlled. Constant-current IPGs provide a specified amperage (electrical current), whereas constant-voltage IPGs provide a specified voltage, with electrical current varying according to impedance (Montgomery 2010). Consequently, in some patients with constant-voltage stimulation, likely because of increases in tissue impedance during the postoperative formation of the electrode–tissue interface, voltage needs to be increased over the first weeks following surgery to preserve tremor control (Benabid et al. 1987, b; Hariz et al. 1999; Tarsy et al. 2005).

However, besides proficient electrode programming, successful DBS therapy also relies on a series of interrelated issues, including accurate candidate selection, precise lead placement, expert medication adjustment, patient education, and support (Moro et al. 2006; Isaias and Tagliati 2008). Managing patient expectations is extremely important as DBS cannot cure the underlying neurological disorder, and disease-related symptoms may progress despite optimal programming.

21.4 DBS as a Symptomatic Treatment for Tremor

In this section, we will discuss DBS clinical use in different tremor syndromes by diagnosis, focusing on specific targets and effectiveness. Side effects will be treated in detail in a dedicated paragraph.

21.4.1 Tremor in Parkinson's Disease

Tremor is present in 75% of patients affected by PD, and can be functionally disabling (Chen et al. 2017). The GPi or the STN is the preferred surgical target due to their combined effect on bradykinesia and rigidity (Tarsy et al. 2003; Krack et al. 1998). Even when these clinical manifestations are not prominent compared to tremor, GPi or STN is usually favored as a worsening of hypokinetic symptoms can be expected along with disease progression (Tarsy et al. 2005).

As a general rule, DBS in PD is considered in patients with an established clinical diagnosis, with more than 5 years of disease duration, and manifesting long-term pharmacological treatment complications, such as motor fluctuations and dyskinesias. The occurrence of severe medication-refractory tremor is still the most important exception to this procedural rule, even in earlier disease stages. Interestingly, there are indications that early STN DBS in tremulous PD could have a role in slowing tremor progression (Hacker et al. 2018). There is intense debate about DBS in early-stage PD as a disease modifying therapy (Schübpach et al. 2013, 2014; Hacker et al. 2020, 2021).

There is a long-standing controversy about which surgical target between STN and GPi is more suitable to control tremor in PD. Despite the STN being generally favored, no randomized studies have revealed any advantage of one target over the other (Wong et al. 2019). Comparable rates of 70–80% tremor improvement have been reported for both targets, sustained for over 5–6 years (Moro et al. 2010; Benabid et al. 2009). Patients with significant on-medication tremor at baseline might be at higher risk of tremor control failure with GPi DBS and therefore better candidates for STN procedures (Azghadi et al. 2021). This population, however, has been identified through a single-center retrospective case series, and this finding needs therefore to be confirmed with more systematic investigation.

The decision between STN or GPi DBS should be based on the accompanying phenomenology in terms of bradykinesia and rigidity, presence and severity of dyskinesias, and pharmacological considerations. It is generally recognized that STN DBS has a greater impact on medication reduction (Moro et al. 2010), while GPi DBS provides better control of levodopa-induced dyskinesias (Munhoz et al. 2014).

VIM remains a possible primary target for elderly non-fluctuating patients with slowly progressive tremor-predominant PD or *benign tremulous parkinsonism*, especially if unilateral (Hariz et al. 2008; Savica et al. 2011). It is important to keep

in mind that when VIM DBS is used to control PD resting tremor, there is no (Krack et al. 1998) or very little effect in terms of medication reduction (Hubble et al. 1997; Tasker 1998). However, the procedure remains very effective, with reported rates of 70–80% tremor suppression at 1 year (Limousin et al. 1999; Cury et al. 2017), sustained over time (Cury et al. 2017; Hariz et al. 2008).

The PSA/cZI may be employed as an alternative to VIM, as it has been demonstrated to improve both tremor and parkinsonian negative signs (Velasco et al. 2001; Kitagawa et al. 2005; Carrillo-Ruiz et al. 2008; Blomstedt et al. 2012), and might even be superior for tremor control (Plaha et al. 2006; Kvernmo et al. 2022).

Another possibility is combined targeting of different structures, both with single and multiple lead implantations. This can be done either as a rescue treatment after failure of tremor control with the first target, or as a primary strategy to minimize the risk of such failure in particularly severe or complex tremors (e.g., in the rare cases in which an association with ET is present). Possible combinations are GPi and VIM (Azghadi et al. 2021), STN and VIM/DRTT (Coenen et al. 2016; Fayed et al. 2021), VIM and PSA (Kvernmo et al. 2022).

21.4.2 Essential Tremor

Essential tremor is the most common tremor disorder (Zesiewicz et al. 2011). At present, the VIM of the thalamus is the most commonly targeted site for DBS in medication-resistant, functionally disabled patients with ET. There have been several retrospective, unblinded, and uncontrolled studies reporting the great benefit of VIM DBS in ET (Pahwa et al. 2001, 2006; Koller et al. 1997, 2001; Limousin et al. 1999; Sydow et al. 2003; Putzke et al. 2003, 2004). Multiple long-term studies, with 1–7 years follow-up, demonstrated a significant improvement in up to 91% in hand tremor after thalamic DBS (Koller et al. 2001; Sydow et al. 2003; Rehncrona et al. 2003; Putzke et al. 2004; Pahwa et al. 2006). These studies have also shown significant benefit in axial tremor, involving face, tongue, voice, and head, ranging from 15% to 100%, with greater benefit achieved by bilateral procedures, usually sustained over time.

One randomized and double blind study on VIM DBS in 18 patients with ET demonstrated a tremor score improvement in 49% at 2 years and 47% at last follow-up (up to 7 years after surgery). Improvement in tremor when writing, drawing, and pouring amounted to 75% at 2 years and 55% at 6–7 years. The stimulation off condition at follow-up did not differ from baseline (Rehncrona et al. 2003).

Voice tremor has been demonstrated to improve about 30% on average with unilateral implants and 60% with bilateral DBS (Limousin et al. 1999; Obwegeser et al. 2000; Sydow et al. 2003). Carpenter et al. specifically studied the effect of VIM DBS on voice tremor in five ET patients with bilateral DBS and two with unilateral implants. Four patients showed a remarkable improvement, especially with bilateral DBS (Carpenter et al. 1998).

One study investigating thalamic DBS for isolated head tremor reported complete resolution 9 months after bilateral thalamic DBS in two patients (Berk and Honey 2002). Several other studies on patients receiving thalamic DBS for disabling hand tremor (Limousin et al. 1999; Koller et al. 1999; Obwegeser et al. 2000; Ondo et al. 2001; Sydow et al. 2003; Putzke et al. 2004, 2005) described therapeutic benefit on head involvement ranging from 15–51% for unilateral procedures to 39–100% for bilateral implants.

Unfortunately, VIM DBS therapeutic benefit exhibits a decrement over time (Lu et al. 2020). It is still debated whether this represents disease progression due to neuronal dysfunction/neuronal loss or development of tolerance to stimulation (Fasano and Helmich 2019). Sometimes, the development of habituation is linked to stimulation-induced delayed ataxia (Reich et al. 2016) (see below, Adverse Events), although the association between the two has not been well characterized yet.

Targeting the PSA/cZI might be protective against the development of such long-term complications, as it requires lower stimulation intensities. PSA/cZI DBS has been demonstrated to be equivalent or superior to the VIM for tremor suppression, especially for proximal limb and complex tremors (Ramirez-Zamora et al. 2016; Barbe et al. 2016; Kvernmo et al. 2022). Considering the success of studies directly targeting the DRTT at its intersection with the VIM or PSA/cZI, it seems reasonable to partly attribute PSA/cZI success to closer electrode proximity to the DRTT (Middlebrooks et al. 2021; Nowacki et al. 2022).

Particular trajectories targeting VIM and PSA/cZI at the same time can also be employed in order to maximize probability of tremor suppression (Barbe et al. 2016; Kvernmo et al. 2022).

Finally, there is some anecdotal evidence that STN DBS can provide tremor relief in ET (Blomstedt et al. 2011), although the thalamic and PSA/cZI targets are almost invariably preferred.

21.4.3 Dystonic Tremor

Dystonic tremor (DT), broadly defined as tremor occurring in a body part affected by dystonia or associated with it, can be observed in up to 87% of dystonic patients (Defazio et al. 2015), mostly affecting the head and upper limbs.

GPi DBS is a very effective treatment for generalized and focal dystonia with significant disability and unsatisfactory response to medications and botulinum toxin (Vidailhet et al. 2007; Azoulay-Zyss et al. 2011). Unfortunately, specific tremor outcomes of large DBS trials for dystonia have been underreported in the literature.

The optimal target for dystonia and particularly for DT is still debated (Blomstedt et al. 2009; Morishita et al. 2010) and GPi, VIM, STN and PSA/cZI DBS can all be considered. To this regard, thalamic DBS seems to be associated with faster improvement compared with pallidal DBS (Gruber et al. 2010). Anecdotal reports suggest early (minutes to days), target-dependent, improvement in myoclonus and tremor.

Hedera et al. (2013) reported their single center experience in ten patients with either GPi, VIM, or dual GPi and VIM DBS: GPi DBS improved DT of about 50% and markedly improved dystonia, while better results on tremor were achieved with VIM DBS, at the expense of lower control of dystonic posturing.

A recent systematic review of 89 cases indicated that VIM is the most commonly targeted structure in DT, with good tremor suppression (40–50%) even with unilateral implants, and variable but often not satisfactory results on dystonia (Tsuboi et al. 2020), despite some very favorable single case reports (Mason et al. 2022; Evidente et al. 2021). Regarding the best target within the ventrolateral thalamus, there is some evidence that focusing stimulation at the anterior border of the VIM proper, confining with the adjacent VO nucleus, could further improve tremor control and potentially ameliorate dystonia, possibly by intervening on pallido-thalamic afferents (Tsuboi et al. 2020).

Targeting the PSA/cZI might even be more effective in terms of tremor control, with encouraging results on concurrent dystonia (Tsuboi et al. 2020; Kvernmo et al. 2022), although more studies are needed to definitely establish long term effects of this target.

GPi DBS can be very effective on tremor, but it is usually preferred when dystonia is predominant, and optimal tremor control might require rescue implantation in the VIM (Hedera et al. 2013). Combined DBS of the VIM and GPi has also been postulated to be protective against the development of habituation in DT, although this has to be confirmed by systematic investigation (Peters and Tisch 2021).

Finally, STN DBS in DT has been reported in a handful of cases with promising results, but it is considered less effective than GPi for dystonic posturing (Tsuboi et al. 2020).

21.4.4 Tremor Secondary to Multiple Sclerosis

Tremor is a common and often very disabling complication of Multiple Sclerosis (MS). About half of patients with MS may suffer from disabling tremor (part of Charcot's triad) mostly due to cerebellar or brainstem lesions. These usually cause a large-amplitude, 2.5–7 Hz postural, kinetic, or intention tremor that most commonly affects the upper extremities, although lower limbs, head, neck, or trunk can be involved (Koch et al. 2007). Furthermore, ET, dystonic and iatrogenic tremors can manifest coincidentally with MS, and therefore treatment should be based on the specific phenomenology.

Some limitations of DBS in this setting need to be taken into consideration along with specific concerns. First of all, tremor is rarely the sole source of disability in MS, therefore the tremor affected body region should not present additional weakness, ataxia, or sensory loss that could cause persistent disability despite successful tremor suppression. Second, proximal tremor is common in MS, and unfortunately poorly responsive to traditional VIM targeting. Third, DBS procedures have a 10–20% risk of triggering an MS relapse (Montgomery Jr et al.

1999; Wishart et al. 2003), and thus surgical candidates should present stable symptoms without relapses for at least 6 months prior to implant. MS patients may have an inherently higher risk of seizures (Ramirez-Zamora and Okun 2016) as well as infections, due to iatrogenic immunosuppression. Lastly, the alteration of neural anatomy may render DBS targeting more difficult. Sensible patient selection and management of patients' expectations are therefore of utmost importance.

Several studies examined the effects of thalamic DBS on MS tremor. The majority of these are single-center studies with small sample sizes (Geny et al. 1996; Schulder et al. 1999, 2003; Berk et al. 2002; Wishart et al. 2003; Nguyen and Degos 1993; Montgomery Jr et al. 1999; Krauss et al. 2001; Torres et al. 2010). Results are consistent in showing that VIM DBS reduces tremor of about 50–60% in subjects with MS. The benefit can be sustained over time, at least up to 3 years after surgery (Wishart et al. 2003; Yap et al. 2007), but is most often transient, with possible recurrence as early as 3 months after the implant and poor long-term prognosis (Hassan et al. 2012).

Dual lead DBS of both the VIM and the VO nuclei has recently been attempted with a single-center controlled trial in 11 patients, reporting a mean 30% improvement (DBS failure in 3/11) at the 6 months follow-up, compared with 20% suppression obtained through single lead stimulation (Oliveria et al. 2017).

Finally, PSA/cZI might be superior to the VIM target for tremor control in MS. PSA DBS has shown potential for better suppression of proximal and axial involvement as well as greater tolerability thanks to lower intensity requirements compared to the VIM (Nandi and Aziz 2004; Kvernmo et al. 2022). However, decrement of effect after 12 months has been also reported with PSA/cZI DBS (Artusi et al. 2018), and further comparative studies are needed to establish superiority of one target over the other.

21.4.5 Orthostatic Tremor

Orthostatic tremor (OT) is a rare syndrome mainly characterized by high-frequency tremor of weight-bearing limbs, typically when standing and with isometric muscle activation. Many patients also suffer from tremor, at lower frequencies, of the face, hands, or trunk (Gerschlager and Brown 2011). The presence of a central aberrant oscillation, coherent with the tremor frequency and involving the primary motor cortex has been demonstrated, suggesting a potential role for thalamic DBS (Guridi et al. 2008).

There are only a limited number of case reports concerning DBS in OT. Espay and colleagues first reported outcomes in two patients who underwent, respectively, unilateral and bilateral VIM DBS for medically refractory OT. Both subjects significantly improved after surgery. However, while the patient implanted bilaterally remained responsive at the 18-month follow-up, the one implanted unilaterally returned to pre-surgical severity of symptoms shortly after surgery (Espay et al. 2008). A handful of case reports and small case series followed this first description.

In 2017, a multicenter registry was created, reporting the outcomes of 17 OT cases treated with VIM DBS across 11 different sites: the authors described a global functional improvement of 22% in activities of daily living, with significantly longer latencies to onset of symptoms in most patients, with a slow progressive decrement of benefit after 4 years of stimulation (Merola et al. 2017). Two additional cases of DBS failure were described, one due to resistance and the other due to development of disabling ataxia.

More recently, the largest case series (n. 5) from a single center has been published, indicating modest improvements in standing time and tremor-onset latency, translating to improved daily standing activities in all patients after VIM DBS (Hewitt et al. 2020).

The cZI is also a promising target for OT: two different groups have reported moderate and sustained clinical improvements with bilateral VIM-ZI or cZI DBS in seven patients collectively, with one case of failure due to infection (Athauda et al. 2017; Gilmore et al. 2019).

Association of OT with other tremor syndromes is particularly common. ET is concurrent in up to 23%, and parkinsonism in 9% of patients with OT (Hassan et al. 2016). Especially in the latter case, the presence of comorbidities and their relative weight in determining individual disability as well as the risk of side effects should be taken into consideration for DBS candidacy and target selection.

21.4.6 Primary Writing Tremor

Primary writing tremor (PWT) is the most frequent *task-specific tremor* and typically presents with a 5–7 Hz oscillation only during the act of writing (Bain et al. 1995). The pathophysiology of PWT is not clear. In particular, it is still debated whether its phenomenology represents a variant of ET, dystonia, a combination of both, or a separate entity (Bain 2011). DBS treatment of PWT has been recently reviewed by Datta et al. (2021): VIM DBS has been reported as a valid therapeutic option for PWT providing nearly complete relief of tremor in 8 patients from single case reports and one small case series, (Minguez-Castellanos et al. 1999; Racette et al. 2001; Ondo and Satija 2012; Lyons et al. 2013). One case of PSA DBS was also reported, with excellent results (Blomstedt et al. 2009).

However, given the low degree of disability engendered by this kind of task-specific tremor and the availability of effective and less invasive treatments such as botulinum toxin injections we believe that DBS candidate selection for this indication should be extremely selective.

21.4.7 Holmes Tremor

Holmes tremor (HT; midbrain tremor) is a coarse high amplitude, low frequency (<4–5 Hz) tremor affecting predominantly the proximal upper extremities. It is

present at rest, characterized by prominent postural and action components, and can occur after different lesions centered to the brainstem/cerebellum and thalamus. The dopaminergic nigrostriatal system, the cerebello-thalamic, dentato-rubro-olivary and possibly pallido-thalamic fibers can all be affected. Often, the choice of surgical target is limited by lesional anatomy, that needs to be taken into consideration for individual surgical planning. Remarkable and sustained benefit has been obtained with VIM DBS on Holmes tremor secondary to hemorrhage (Samadani et al. 2003; Goto and Yamada 2004; Lim et al. 2007), infarct (Nikkhah et al. 2004; Hertel et al. 2006), tumor, or abscess (Pahwa et al. 2002; Piette et al. 2004) also in young patients. Peker et al. reported a case of a 14-year-old girl who developed Holmes tremor due to a thalamic abscess and was successfully treated by thalamic DBS reaching 90% improvement at 2.5 years follow-up (Peker et al. 2008). Acar et al. (2010) described tremor suppression after VIM DBS in a young patient with drug resistant resting, action, and postural tremor in both arms and orolingual region due to a subarachnoid hemorrhage. Sanborn et al. (2009) described symptomatic and functional improvement after VIM DBS of Holmes-like left-upper-extremity tremor refractory to medical treatment due to a cystic degeneration of the brainstem. However, there is some indication that benefit from VIM DBS might be shortlived in some patients with HT, and specifically that the effect might wane after 2–3 years of treatment (Bargiotas et al. 2021). Therefore, other anatomical targets have been proposed as an alternative, or in conjunction with the VIM. Goto and Yamada managed to suppress tremor by means of a pallidotomy in a patient with reoccurrence 1 year after VIM implant (Goto and Yamada 2004). Afterwards, rescue GPi DBS providing moderate tremor suppression in one subject that poorly responded to VIM DBS was described (Lim et al. 2007). More recently, GPi DBS has been reported as potentially superior in two independent HT case series, with sustained benefit for more than 2 years after surgery (Espinoza Martinez et al. 2015; Kilbane et al. 2015). Interestingly, Kilbane et al. (2015) also performed GPi intraoperative recordings and identified a low-frequency oscillatory activity potentially related to tremor in their implanted patients. Transient benefit from DRTT DBS has been described as well, analogously to what observed for the VIM (Bargiotas et al. 2021). The STN might also be an effective target for rescue DBS after VIM DBS failure (Romanelli et al. 2003). In one patient with Benedikt syndrome post-midbrain infarction, DBS of the contralateral lenticular fasciculus has been employed with some efficacy on debilitating HT (Bandt et al. 2008). Lastly, stimulation of multiple targets could be a viable option to increase tremor control. Foote and colleagues performed two parallel lead insertions in the thalamus (VIM and Voa/Vop border) of three patients with proximal and distal tremor. Greatest benefit was described when both the VIM and Voa/Vop electrodes were active (Foote et al. 2006). Kobayashi et al. (2014) described additive effects of combining VIM with PSA stimulation in four patients, sustained at the 2 years follow-up.

21.4.8 Posttraumatic Tremor

Tremor has been described also as a possible consequence in about 5% of the patients after severe head injury (Krauss and Jankovic 2002). In this case tremor may appear weeks or months after injury and it is coarse and irregular, with a frequency of about 2–3.5 Hz. The most frequent clinical presentation is a Holmes tremor or a cerebellar tremor resulting from either hemorrhage or diffuse axonal injury at the level of midbrain. Most posttraumatic tremors resolve spontaneously, but some are persistent, refractory to medical therapy and result in severe disability. Only few case reports are available and the efficacy of DBS in posttraumatic tremor has been debated (Krauss and Jankovic 2002; Broggi et al. 1993; Nguyen and Degos 1993; Umemura et al. 2004). Surgical treatment in these cases aims to improve activities of daily living, rather than completely suppress tremor. Nguyen and Degos reported that stimulation of the lower part of the VIM was most effective in the distal component of the tremor, whereas its proximal component was specifically reduced by stimulation of its upper part (Nguyen and Degos 1993). Umemura et al. (2004) described better results when effective contacts were located in the middle part of VIM. Krauss et al. reported good outcomes from ZI and VIM/ZI DBS (Krauss et al. 1994). Combined neurostimulation of the VIM and STN has also been employed with encouraging results on posttraumatic tremor and hemiparkinsonism, even in the long term (Reese et al. 2011).

Thalamic tremor is a mixture of intentional tremor and dystonia, that can develop after lateral posterior thalamic stroke. Diederich and colleagues described mild but significant improvement after VIM DBS surgery in one patient with calcifications at the posterior edge of the right thalamus, abnormal collateralization of the posterior cerebral artery at the thalamic level, and mild hemiatrophy of the right mesencephalon. However, a second patient with post-stroke thalamic tremor did not improve after VIM DBS (Diederich et al. 2008). More recently, it has been suggested that larger volumes of stimulation encompassing also the pallidal afferent areas could be more effective than traditional VIM DBS. Indeed, Bagatti et al. (2019) reported striking and sustained benefit from combined DBS of the VOa/VOp and cZi using a single lead trajectory in a 23-year-old patient with dystonic tremor from a right thalamic stroke.

21.4.9 Tremor Secondary to Cerebellar Degeneration

Cerebellar tremor is mostly intentional (kinetic) and usually associated with other cerebellar signs, namely gait ataxia, dysmetria, and hypotonia, as well as speech impairment. DBS is often of limited utility in this context, considering the possibility of a detrimental effect (see below) on gait, segmental ataxia and dysarthria, to be carefully evaluated in patient selection.

Amongst cerebellar degeneration syndromes, the one for which DBS treatment is most commonly reported is Fragile X-associated tremor/ataxia syndrome (FXTAS). This is an X-linked neurodegenerative disorder characterized essentially by intention tremor, axial and segmental ataxia, parkinsonism, cognitive decline, and peripheral neuropathy (Hagerman et al. 2008). VIM DBS has been attempted in FXTAS, with encouraging outcomes in the short term (Artusi et al. 2018), inconsistently sustained over time (Weiss et al. 2015), and high risk of ataxia and speech worsening with bilateral procedures (Mehanna and Itin 2014). PSA/cZI DBS might be better tolerated (Oyama et al. 2014; Dos Santos Ghilardi et al. 2015).

DBS treatment has also been reported for tremor in spinocerebellar ataxias, a heterogeneous group of neurological disorders characterized by progressive ataxia and variable combinations of cerebral, basal ganglia, brainstem, spinal, and peripheral nervous system involvement. Only few case reports are available. Pirker et al. (2003) reported successful VIM-DBS in one patient with SCA-2 characterized by parkinsonism and severe, disabling resting and action tremor. Remarkable clinical improvement in severe postural tremor was also described in a second patient with SCA-2 treated with a combined PSA-thalamic DBS (Freund et al. 2007). More recently, cerebellar DBS of the dentate nucleus has been attempted in a small number of patients with heterogeneous ataxias including SCA-3, cerebellar stroke, and cerebral palsy with overall promising results on tremor improvement, that need to be confirmed in larger case series (Teixeira et al. 2015; Cury et al. 2021).

It should be noted that, while DBS might be effective on action tremor, in these patients ataxia and other cerebellar signs are usually the primary source of disability (Shimojima et al. 2005). On the other hand, especially in the wheelchair-bound stage, in which potential worsening of axial ataxia is less of a concern, DBS for tremor could help preserve the level of patients' behavioral expression and therefore positively impact quality of life and functional independence (Isobe et al. 2019; Hashimoto et al. 2018).

Finally, DBS application has been described in other rare cerebellar disorders. Schramm et al. (2005) reported a case of a 51-year-old man with a rare dominant inherited cerebellar ataxia and accompanying visual loss and tremor (CICALVT) resembling a Behr Syndrome variant. In this patient, tremor greatly improved after unilateral VIM DBS.

Another patient with phenylketonuria-induced cerebellar tremor experienced very satisfactory benefit on both intention and resting components immediately after surgery and at the 2 years follow-up (Payne et al. 2005).

21.4.10 Neuropathic Tremor

Neuropathic tremor is defined as tremor that develops in association with peripheral neuropathy when no other neurological condition associated with tremor is present. In neuropathic tremor, the incorrect or delayed proprioceptive input is believed to be responsible for a failure of cerebellar feedback mechanisms, associated to

maladaptive central motor processing manifesting as high cortico-EMG coherence at tremor frequency, amenable to VIM DBS (Weiss et al. 2011). Further indication of central involvement proceeds from the observation of single cell tremor-related activity in the VIM of patients with Charcot-Marie-Tooth syndrome type 2 and disabling unilateral limb tremor responsive to DBS (Cabañes-Martínez et al. 2017). However, as recently reviewed (Artusi et al. 2018), only 14 patients treated with DBS for this indication have been reported in literature, and therefore this has to be considered an investigational procedure (Ramirez-Zamora and Okun 2016). VIM DBS was used in 13 cases, and PSA DBS in the remaining one, with variable degrees of improvement ranging from 30% (Breit et al. 2009) to almost complete eradication (McMaster et al. 2009). Unilateral PSA DBS provided approximately 70% suppression of contralateral hand and head tremor (Blomstedt et al. 2009), and therefore might be more beneficial, although the presence of tremor at rest and involvement of the head in this specific case might suggest an overlap with a more common tremor syndrome, such as ET.

21.5 Adverse Events

21.5.1 Surgical Adverse Events

The most potentially serious neurologic adverse event is intracranial hemorrhage. The incidence of intracranial hemorrhage ranges between 2% and 5% with most of the traditional targets. Hemorrhages include subdural and intracerebral hematomas. Many intracerebral hematomas are asymptomatic, may be limited to a region along the electrode tract and are discovered only by postoperative brain imaging (Benabid et al. 1996; Koller et al. 1997; Limousin et al. 1999; Medtronic, Inc. 2002). Risk of severe complications (death or severe permanent deficits) accounts for less than 0.5% in larger series of experienced centers (Voges et al. 2006).

A higher risk for hemorrhage has been reported in initial comparative studies with single lead VIM/PSA DBS (Barbe et al. 2016; Bot et al. 2018) but this has not been confirmed by more recent work (Kvernmo et al. 2022).

Other adverse events related to stereotaxis, more common in patients with advanced age and comorbidities, include infections (0–15%), seizure (0–3%), stroke (0–2%), perielectrode edema (up to 13.5%), transient postoperative delirium (up to 13%) and headache (7%) (Bronstein et al. 2011; Lu et al. 2020; Charmley et al. 2021). Most of these side effects are transient and can usually be managed conservatively. As already discussed, patients with MS may be at increased risk of seizures and infections, as well as post-surgical MS relapse. It is generally recognized that the experience of the surgical team is a major determinant in lowering the risk of serious complications (Voges et al. 2006; Doshi et al. 2021; Jung et al. 2022).

21.5.2 Device Complications Including Lead Replacement

The most frequent hardware-related adverse events are open circuits and IPG malfunction, lead fractures, misplacements or migrations, lead erosions, lead infections, foreign body reactions, and cerebrospinal fluid leaks. Overall, 10–25% of the patients experience hardware-related complications (Oh et al. 2002; Joint et al. 2002; Kumar 2003; Voges et al. 2006). Useful references providing detailed methodology for troubleshooting hardware complications are available (Volkmann et al. 2002; Kumar 2003; Isaias and Tagliati 2008). Explantation of the intracerebral electrode is only occasionally necessary and is indicated in the presence of active infection or skin erosion unresponsive to medical management or skin grafting. In cases of VIM implants where explantation is required and reimplantation is not feasible, it may be possible to use the DBS electrode to generate a permanent lesion with radiofrequency prior to its removal (Oh et al. 2001; Kumar and McVicker 2000).

21.5.3 Stimulation-Related Adverse Events

Stimulation-related side effects are related to the implanted nucleus anatomy and the electrode location. The common mechanism for their generation is the unwanted spread of current to neighboring structures or fiber tracts, which can in turn influence more distant brain areas. As a general rule, stimulation-related adverse events are reversible when stimulation is turned off, sometimes requiring a prolonged washout period (Reich et al. 2016), and can be managed by optimization of stimulation parameters.

Regarding DBS of the GPi and STN in parkinsonian tremor, the overall side effect profile is similar between the two targets and the choice between one or the other should be based on individual patient characteristics. In general, spread of current to the internal capsule, medial to the GPi and lateral to the STN, can cause dysarthria, rarely dysphagia, and contralateral muscle contractions. Posteromedial spread of current to the lemniscal radiations with STN stimulation can evoke contralateral paresthesias. Gait and balance issues can complicate the advanced phase of disease and sometimes be worsened by DBS in both targets (St George et al. 2010). There is some indication that GPi DBS might be more favorable against the long-term worsening of speech and balance in PD (St George et al. 2010; Au et al. 2021), but this is still debated.

Cognitive deterioration is a possible outcome of both STN and GPi DBS in PD, albeit very heterogeneously reported in terms of severity and affected cognitive domains (Cernera et al. 2021). In this respect, VIM DBS appears to be better tolerated in this population (Voon et al. 2006; Troster et al. 1999; Troster and Fields 2003; Caparros-Lefebre et al. 1992), albeit mild deficits in verbal fluency have been documented (Benabid et al. 1996).

Specifically in dystonia, DBS of the GPi can be associated with the gradual development of contralateral hypokinesia (Berman et al. 2009; Huebl et al. 2015), including gait and postural difficulties (Schrader et al. 2011; Brecl Jakob et al. 2015; Wolf et al. 2016; Mahlknecht et al. 2018). This usually happens with ventral DBS contacts and can be ameliorated by dorsal steering of the stimulation volume and total energy reduction.

The most frequent side effect of VIM stimulation is paresthesia involving the contralateral limbs or the face (Dowsey-Limousin 2002; Schuurman et al. 2000), due to inclusion of the VC nucleus or the lemniscal radiation into the electrical field (Kiss et al. 2003). When paresthesias rapidly habituate they are of little concern, but if they persist (Alesch et al. 1995) alternative contacts or configurations should be explored (Isaias and Tagliati 2008).

Dysarthria (Pahwa et al. 2006) and gait ataxia with postural instability may also be induced by thalamic stimulation (Albanese et al. 1999; Schuurman et al. 2000; Alesch et al. 1995; Lyons et al. 2001; Obwegeser et al. 2001), especially with bilateral stimulation (Pahwa et al. 2006; Limousin et al. 1999; Benabid et al. 1996) or in patients that had undergone previous contralateral thalamotomy.

Delayed-onset gait disturbance is part of a chronic cerebellar syndrome observed in patients with ET and VIM implants and reversible after a prolonged washout of stimulation (Reich et al. 2016). It is thought to stem from a maladaptive response to stimulation-induced vestibulo-cerebellar dysfunction, caused by the antidromic spread of current along the fastigio-bulbar tract (Sprague and Chambers 1953). Due to the natural history of ET the worsening of gait ataxia is often interpreted as disease progression, and therefore it is challenging to establish its actual rate of occurrence, but it is important to take this entity into consideration given its reversibility. In fact, lowering stimulation pulse width from the usual standard value of 60 mcs to 30–40 mcs has shown promise in improving cerebellar symptoms without hampering tremor control (Reich et al. 2016).

Habituation, or variable waning of DBS benefit on tremor, is a frequent complication of thalamic DBS, particularly in ET and DT (Peters and Tisch 2021). The relationship between delayed-onset ataxia and habituation is unclear, but cooccurrence has been observed, along with a phenomenon of tremor rebound at stimulation withdrawal (Reich et al. 2016). This has to be taken into consideration during patient programming, allowing for sufficient time to evaluate the effects of changes in parameter settings.

The presence of rebound can also interfere with other proposed strategies for improving habituation, such as DBS holidays, on demand DBS, overnight withdrawal, and alternating weekly patterns of stimulation (Fasano and Helmich 2019).

It has been proposed that targeting of the PSA and DRTT might be advantageous against the development of ataxia and habituation (Reich et al. 2016; Peters and Tisch 2021). However, this has not been confirmed by a recent single-center large series of 93 patients with DBS targeting both VIM and PSA at the same time, in which gait ataxia and paresthesia were observed more frequently with contacts

located in the PSA, while dysarthria was mostly associated with VIM DBS (Kim et al. 2021).

In general, given its proximity to the VIM, PSA/cZI DBS can more or less replicate adverse events encountered with thalamic stimulation, paresthesia being the most common due to spread of current to the lemniscal radiations. Dysarthria, transient diplopia and ataxia are also commonly reported and likely represent involvement of the internal capsule, red nucleus and cerebellar fibers, respectively (Ramirez-Zamora et al. 2016). Nevertheless, given the lower energy requirements of PSA stimulation compared to VIM DBS, this target has the potential of being better tolerated due to more effective and selective delivery of current to functionally relevant fibers (Kim et al. 2021).

21.6 Future Directions: Adaptive Stimulation for Tremor

Conventional DBS, discussed above, delivers electrical pulses to the stimulated regions in a predefined and continuous fashion, irrespective of patient state or ongoing activity.

However, most patients experience fluctuations in symptoms throughout the day, particularly in the onset and severity of tremor. In PD, tremor fluctuations are mostly related to changes in medication levels and increased arousal due to anxiety or mental engagement (Isaias et al. 2011, 2012). In ET, they depend mainly on functional status, such as voluntary movement.

Recently available DBS devices allow on-demand stimulation delivery based on biomarkers carrying information about patient condition to trigger the stimulation, optimize its parameters (e.g., amplitude or frequency) or lock it (e.g., via phase-locking) to an acquired signal (adaptive DBS, aDBS) (Arlotti et al. 2019; Canessa et al. 2020; Vissani et al. 2020, 2021; Neumann et al. 2021; Thenaisie et al. 2021).

A first attempt of on demand stimulation for tremor was described by Brice and McLellan in 1980. They managed to successfully deliver thalamic stimulation triggered by electromyographic signals from the contralateral deltoid muscle (Brice and McLellan 1980).

Since then, wearable sensors including EMG and accelerometers have been used to trigger stimulation delivery based on motion detection (Yamamoto et al. 2013), tremor amplitude (Malekmohammadi et al. 2016; Cernera et al. 2021) or phase (Cagnan et al. 2017) of ongoing tremor, providing good symptom control with significantly lower energy consumption.

More recently, three independent groups were able to achieve stable and effective stimulation of the VIM triggered by a low frequency desynchronization detected by electrocorticography (ECoG) in the primary motor cortex (M1) and corresponding to the onset of a hand reaching movement. This provided comparable or superior benefit on tremor with respect to open-loop stimulation with lower total electrical energy delivered, allowing for reduced battery depletion (Herron et al. 2017; Opri et al. 2020; Ferleger et al. 2020; Fra Czek et al. 2021). One patient also reported

better response to closed-loop stimulation due to reduction of stimulation-induced speech dysfunction (Opri et al. 2020). ECoG has also been employed to detect neural signals related with tremor intensity, then used as an input for closed-loop stimulation with good clinical outcomes (Castaño-Candamil et al. 2020).

21.7 Deep Brain Stimulation and MRI-Guided Focused Ultrasound

As stated in the introduction of this chapter, DBS progressively replaced ablative surgery due to its non-lesional and reversible nature. However, ablative techniques continued to be employed and developed, representing a possible alternative for patients with medication-resistant tremors.

Traditional radiofrequency thalamotomy is performed through craniotomy, as DBS implants, and is generally regarded as comparably effective, albeit with a less favorable safety profile (Schuurman et al. 2000) essentially contraindicating bilateral procedures. Therefore, it gradually came to be considered mostly as a rescue modality after DBS failures, as in the case of lead infection (Oh et al. 2001; Kumar and McVicker 2000), or as a primary option in disadvantaged settings thanks to reduced costs and lower need for specialized follow-up.

Gamma knife (GK) radiosurgery was later developed as a non-invasive modality, having the advantage of not requiring skull penetration. It can be offered to patients who are not deemed good candidates for craniotomy due to bleeding diathesis, old age, or serious comorbidities, as well as those unwilling to experience brain surgery (Higuchi et al. 2017). Overall, the degree of tremor improvement after GK thalamotomy appears to be potentially comparable to that obtained with DBS, besides higher variability of therapeutic response (Lim et al. 2010; Young et al. 2010; Ohye et al. 2012; Witjas et al. 2015; Niranjan et al. 2017). However, this technique has three critical limitations: (i) the impossibility of assessing outcome intraprocedurally, (ii) a variable latency to the onset of benefit and side effects (Higuchi et al. 2017), and (iii) the unpredictable tissue response to ionizing radiation. A hyper-sensitivity to radiation injury, with unforeseen enlargement of the radiosurgical lesion beyond the target area, has been reported in up to 10.9% of GK thalamotomies (Ohye et al. 2012) as well as in pallidotomies (Okun et al. 2001) and subthalamotomies (Drummond et al. 2020), sometimes producing serious adverse events (Okun et al. 2001; Lim et al. 2010; Young et al. 2010; Drummond et al. 2020).

In recent years, a new incisionless alternative has become increasingly available: MRI-guided focused ultrasound (MRgFUS) is a lesioning technique that uses acoustic energy delivered to deep areas of the brain. Repeated sonications engender controlled tissue heating that is monitored with real-time MRI thermometry and intraprocedural clinical assessment, an important advantage compared to GK surgery. The first two prospective trials of MRgFUS thalamotomy for the treatment

of ET were published in 2013, reporting acute benefit of up to 89.4% at 1 month (Lipsman et al. 2013) and 75% at the 1 year follow-up (Elias et al. 2013). A prospective randomized sham-controlled study on 76 patients followed in 2016, reporting 47% improvement in the treatment group (Elias et al. 2016), which gained unilateral MRgFUS thalamotomy FDA approval for ET. Postpivotal studies confirmed effectiveness and tolerability of the procedure, demonstrating a 61.9% reduction of tremor scores, suggesting a learning curve in the involved centers (Krishna et al. 2020).

A favorable safety profile has been described for MRgFUS thalamotomy: most side effects are transient, peaking at 1 week after procedure and then gradually subsiding. The most common are sensory alterations, observed in 38% of cases, persisting in 14% at 12 months, and gait issues, manifesting in 36% of patients acutely and 9% at 12 months. Other cerebellar deficits such as dysmetria and ataxia, speech and swallowing difficulties, hypogeusia/dysgeusia, and contralateral weakness are also reported with much lower frequency (Elias et al. 2016; Fishman et al. 2018; Zaaroor et al. 2018; Sinai et al. 2019). Outcomes have been described as stable up to 5 years after thermal ablation (Halpern et al. 2019; Sinai et al. 2019) without delayed complications.

Since 2013, MRgFUS thalamotomy has also been used for treating tremor-predominant PD (Bond et al. 2017), ET-PD (Zaaroor et al. 2018), and for other indications including tremor associated with FXTAS (Fasano et al. 2016) and MS (Máñez-Miró et al. 2020). Furthermore, targets other than the thalamus are being explored, including the pallidothalamic tract (Magara et al. 2014), the GPi (Jung et al. 2018), the STN (Martínez-Fernández et al. 2020) and the DRTT (Schreglmann et al. 2017; Gallay et al. 2020).

Overall, MRgFUS has shown great potential as a safe and effective alternative to unilateral DBS, pending the evaluation of long-term follow-up data that will become available in the near future. Furthermore, the costs of a single MRgFUS are lower than DBS, even if they may increase in the case of repeat procedures for tremor recurrence (Ravikumar et al. 2017).

MRgFUS has, however, some contraindications. First, because MRgFUS is an MRI-guided procedure, patients who cannot undergo MRI are not suitable candidates. Also, the energy required for effective sonication is related to the ratio of cortical to cancellous bone in the skull (skull density ratio - SDR). All patients are screened with a head CT prior to MRgFUS, and the procedure is not recommended for SDRs less than 0.40 (Pouratian et al. 2020). Finally, the usual caveat of a higher intrinsic risk for bilateral lesioning procedures compared with DBS still applies, especially in younger patients potentially progressing over time, and patients with axial tremors requiring bihemispheric treatment, which is still a major contraindication (Pouratian et al. 2020). Nevertheless, the degree of precision achievable with this technique and the absence of delayed complications were so encouraging that a trial of bilateral thalamotomy was recently conducted, with promising results in terms of tolerability (Iorio-Morin et al. 2021), to be confirmed in larger patient cohorts.

Indeed, a recent systematic analysis shows that postoperative improvement is greater for bilateral DBS than thalamotomy with MRgFUS, but there is no difference between unilateral DBS and MRgFUS (Giordano et al. 2020; see also Huss et al. 2015). In terms of quality of life, the improvement appears greater for MRgFUS, but persistent complications are more common despite the higher risk of acute hemorrhage and hardware-related complications with DBS (Harary et al. 2019).

However, significant differences in the characteristics of the patient populations studied represent a critical limitation to the retrospective comparison between DBS and MRgFUS for ET. Indeed, cohorts treated with DBS are generally younger (Giordano et al. 2020) and affected by more severe tremor at baseline (Harary et al. 2019), which could impact treatment outcome and self-perception of quality of life. Head-to-head comparison studies in matched clinical populations are needed to reliably compare clinical efficacy and long-term outcomes and ultimately validate MRgFUS as a true alternative to DBS.

21.8 Final Remarks

DBS surgery is one of the best options for the treatment of medically intractable tremor across several clinical entities. The precise mechanism by which DBS affects its therapeutic response is still unknown. Therefore, the best DBS settings, the search for optimal targets, and the placement of multiple leads are open questions that need to be addressed systematically. New DBS systems (e.g., sensing DBS devices), electrodes with higher spatial selectivity, and neuroimaging advancements for functional network targeting will significantly contribute to a better understanding of tremor-related oscillatory networks for a more personalized (symptom-specific and task-related) DBS treatment.

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References

Acar G, Acar F, Bir LS, Kızılay Z, Cırak B. Vim stimulation in Holmes' tremor secondary to subarachnoid hemorrhage. Neurol Res. 2010;32(9):992–4.

Akram H, Dayal V, Mahlknecht P, Georgiev D, Hyam J, Foltynie T, Limousin P, De Vita E, Jahanshahi M, Ashburner J, Behrens T, Hariz M, Zrinzo L. Connectivity derived thalamic segmentation in deep brain stimulation for tremor. Neuroimage Clin. 2018;18:130–42.

Albanese A, Nordera GP, Caraceni T, et al. Longterm ventralis intermedius thalamic stimulation for parkinsonian tremor. Italian Registry for Neuromodulation in Movement disorders. Adv Neurol. 1999;80:631–4.

Alesch F, Pinter MM, Helscher RJ, Fertl L, Benabid AL, Koos WT. Stimulation of the ventral intermediate thalamic nucleus in tremor dominated Parkinson's disease and essential tremor. Acta Neurochir. 1995;136:75–81.

Al-Fatly B, Ewert S, Kübler D, Kroneberg D, Horn A, Kühn AA. Connectivity profile of thalamic deep brain stimulation to effectively treat essential tremor. Brain. 2019;142:3086–98.

Anderson T, Hu B, Pittman Q, Kiss ZH. Mechanisms of deep brain stimulation: an intracellular study in rat thalamus. J Physiol. 2004;559:301–13.

Anderson TR, Hu B, Iremonger K, Kiss ZH. Selective attenuation of afferent synaptic transmission as a mechanism of thalamic deep brain stimulation-induced tremor arrest. J Neurosci. 2006;26:841–50.

Anderson DN, Duffley G, Vorwerk J, Dorval AD, Butson CR. Anodic stimulation misunderstood: preferential activation of fiber orientations with anodic waveforms in deep brain stimulation. J Neural Eng. 2019;16(1):016026.

Arlotti M, Palmisano C, Minafra B, et al. Monitoring subthalamic oscillations for 24 hours in a freely moving Parkinson's disease patient. Mov Disord. 2019;34(5):757–9.

Artusi C, Farooqi A, Romagnolo A, Marsili L, Balestrino R, Sokol L, Wang L, Zibetti M, Duker A, Mandybur G, Lopiano L, Merola A. Deep brain stimulation in uncommon tremor disorders: indications, targets, and programming. J Neurol. 2018;265(11):2473.

Athauda D, Georgiev D, Aviles-Olmos I, et al. Thalamic-Caudal Zona Incerta deep brain stimulation for refractory orthostatic tremor: a report of 3 cases. Mov Disord Clin Pract. 2017;4(1):105–10.

Au KLK, Wong JK, Tsuboi T, Eisinger RS, Moore K, Lemos Melo Lobo Jofili Lopes J, Holland MT, Holanda VM, Peng-Chen Z, Patterson A, Foote KD, Ramirez-Zamora A, Okun MS, Almeida L. Globus Pallidus Internus (GPi) deep brain stimulation for Parkinson's disease: expert review and commentary. Neurol Ther. 2021;10(1):7–30.

Azghadi A, Rajagopal MM, Atkinson KA, Holloway KL. Utility of GPI+VIM dual-lead deep brain stimulation for Parkinson's disease patients with significant residual tremor on medication. J Neurosurg. 2021;10:1–7.

Azoulay-Zyss J, Roze E, Welter ML, et al. Bilateral deep brain stimulation of the pallidum for myoclonus-dystonia due to ε-sarcoglycan mutations: a pilot study. Arch Neurol. 2011;68(1):94–8.

Bagatti D, D'Ammando A, Franzini A, Messina G. Deep brain stimulation of the caudal zona incerta and motor thalamus for postischemic dystonic tremor of the left upper limb: case report and review of the literature. World Neurosurg. 2019;125:191–7.

Bain PG. Task-specific tremor. Handb Clin Neurol. 2011;100:711–8.

Bain PG, Findley LJ, Britton TC, et al.. MRC Human Movement, and Balance Unit, Institute of Neurology, London, UKPrimary writing tremor. Brain. 1995;118(6):1461–72.

Bandt SK, Anderson D, Biller J. Deep brain stimulation as an effective treatment option for post-midbrain infarction-related tremor as it presents with Benedikt syndrome. J Neurosurg. 2008;109:635–9.

Barbe MT, Franklin J, Kraus D, Reker P, Dembek TA, Allert N, Wirths J, Voges J, Timmermann L, Visser-Vandewalle V. Deep brain stimulation of the posterior subthalamic area and the thalamus in patients with essential tremor: study protocol for a randomized controlled pilot trial. Trials. 2016; 17: 476.

Bargiotas P, Nguyen TAK, Bracht T, et al. Long-term outcome and neuroimaging of deep brain stimulation in Holmes tremor: a case series. Neuromodulation. 2021;24(2):392–9.

Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol. 1987;50:344–6.

Benabid AL, Pollak P, Gao D, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg. 1996;84:203–14.

Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol. 2009;8:67–81.

Bergman NH, Wichmann T, Karmon B, DeLong MR. The primate sub-thalamic nucleus: II. Neuronal activity in the MPTP model of parkinsonism. J Neurophysiol. 1994;72:507–20.

Berk C, Honey CR. Bilateral thalamic deep brain stimulation for the treatment of head tremor. Report of two cases. J Neurosurg. 2002;96:615–8.

Berk C, Carr J, Sinden M, Martzke J, Honey CR. Thalamic deep brain stimulation for the treatment of tremor due to multiple sclerosis: a prospective study of tremor and quality of life. J Neurosurg. 2002;97:815–20.

Berman BD, Starr PA, Marks WJ Jr, Ostrem JL. Induction of bradykinesia with pallidal deep brain stimulation in patients with cranial-cervical dystonia. Stereotact Funct Neurosurg. 2009;87(1):37–44.

Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J Neurophysiol. 2001;85:1351–6.

Blomstedt P, Fytagoridis A, Tisch S. Deep brain stimulation of the posterior subthalamic area in the treatment of tremor. Acta Neurochir. 2009;151:31–6.

Blomstedt P, Sandvik U, Tisch S. Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor. Mov Disord. 2010;30(25):1350–6.

Blomstedt P, Sandvik U, Linder J, Fredricks A, Forsgren L, Hariz MI. Deep brain stimulation of the subthalamic nucleus versus the zona incerta in the treatment of essential tremor. Acta Neurochir. 2011;153:2329–35.

Blomstedt P, Fytagoridis A, Astrom M, Linder J, Forsgren L, Hariz MI. Unilateral caudal zona incerta deep brain stimulation for parkinsonian tremor. Parkinsonism Relat Disord. 2012;18:1062–6.

Bond AE, Shah BB, Huss DS, Dallapiazza RF, Warren A, Harrison MB, Sperling SA, Wang XQ, Gwinn R, Witt J, Ro S, Elias WJ. Safety and efficacy of focused ultrasound thalamotomy for patients with medication-refractory, tremor-dominant Parkinson disease: a randomized clinical trial. JAMA Neurol. 2017;74(12):1412–8.

Boogers A, Peeters J, Van Bogaert T, et al. Anodic and symmetric biphasic pulses enlarge the therapeutic window in deep brain stimulation for essential tremor. Brain Stimul. 2022;15(2):286–90.

Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. Proc Natl Acad Sci. 2010;107:8452–6.

Bot M, van Rootselaar F, Contarino MF, Odekerken V, Dijk J, de Bie R, Schuurman R, van den Munckhof P. Deep brain stimulation for essential tremor: aligning thalamic and posterior subthalamic targets in 1 surgical trajectory. Oper Neurosurg (Hagerstown). 2018;15(2):144–52.

Bouthour W, Wegrzyk J, Momjian S, Péron J, Fleury V, Tomkova Chaoui E, Horvath J, Boëx C, Lüscher C, Burkhard PR, Krack P, Zacharia A. Short pulse width in subthalamic stimulation in Parkinson's disease: a randomized, double-blind study. Mov Disord. 2018;33(1):169–73.

Brecl Jakob G, Pelykh O, Košutzká Z, et al. Postural stability under globus pallidus internus stimulation for dystonia. Clin Neurophysiol. 2015;126(12):2299–305.

Breit S, Wächter T, Schöls L, Gasser T, Nägele T, Freudenstein D, Krüger R. Effective thalamic deep brain stimulation for neuropathic tremor in a patient with severe demyelinating neuropathy. J Neurol Neurosurg Psychiatry. 2009;80(2):235–6.

Brice J, McLellan L. Suppression of intention tremor by contingent deep-brain stimulation. Lancet. 1980;1(8180):1221–2.

Broggi G, Brock S, Franzini A, Geminiani G. A case of posttraumatic tremor treated by chronic stimulation of the thalamus. Mov Disord. 1993;8:206–8.

Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol. 2011;68(2):165.

Butson CR, Cooper SE, Henderson JM, McIntyre CC. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. NeuroImage. 2007;34(2):661–70.

Cabañes-Martínez L, Del Álamo de Pedro M, de Blas Beorlegui G, Bailly-Bailliere IR. Long-term effective thalamic deep brain stimulation for neuropathic tremor in two patients with Charcot-Marie-Tooth disease. Stereotact Funct Neurosurg. 2017;95(2):102–6.

Cagnan H, Pedrosa D, Little S, et al. Stimulating at the right time: phase-specific deep brain stimulation. Brain. 2017;140(1):132–45.
Canessa A, Palmisano C, Isaias IU, Mazzoni A. Gait-related frequency modulation of beta oscillatory activity in the subthalamic nucleus of parkinsonian patients. Brain Stimul. 2020;13(6):1743–52.
Caparros-Lefebre D, Blond S, Pecheux N, Pasquier F, Petit H. Evaluation neuropsychologique avant et après stimulation thalamique chez 9 parkinsoniens. Rev Neurol. 1992;148:117–22.
Carpenter MA, Pahwa R, Miyawaki KL, Wilkinson SB, Searl JP, Koller WC. Reduction in voice tremor under thalamic stimulation. Neurology. 1998;50:796–8.
Carrillo-Ruiz JD, Velasco F, Jimenez F, Castro G, Velasco AL, Hernandez JA, Ceballos J, Velasco M. Bilateral electrical stimulation of prelemniscal radiations in the treatment of advanced Parkinson's disease. Neurosurgery. 2008;62:347–59.
Castaño-Candamil S, Ferleger BI, Haddock A, et al. A pilot study on data-driven adaptive deep brain stimulation in chronically implanted essential tremor patients. Front Hum Neurosci. 2020;14:541625.
Cernera S, Alcantara JD, Opri E, Cagle JN, Eisinger RS, Boogaart Z, Pramanik L, Kelberman M, Patel B, Foote KD, Okun MS. Wearable sensor-driven responsive deep brain stimulation for essential tremor. Brain Stimul. 2021;14(6):1434–43.
Charmley AR, Kimber T, Mahant N, Lehn A. Driving restrictions following deep brain stimulation surgery. BMJ Neurol Open. 2021;3(2):e000210.
Chen W, Hopfner F, Becktepe JS, Deuschl G. Rest tremor revisited: Parkinson's disease and other disorders. Transl Neurodegener. 2017;6:1–8.
Coenen VA, Allert N, Mädler B. A role of diffusion tensor imaging fiber tracking in deep brain stimulation surgery: DBS of the dentato-rubro-thalamic tract (drt) for the treatment of therapy-refractory tremor. Acta Neurochir. 2011;153(8):1579–85.
Coenen VA, Rijntjes M, Prokop T, Piroth T, Amtage F, Urbach H, Reinacher PC. One-pass deep brain stimulation of dentato-rubro-thalamic tract and subthalamic nucleus for tremor-dominant or equivalent type Parkinson's disease. Acta Neurochir. 2016;158(4):773–81.
Cury RG, Fraix V, Castrioto A, Pérez Fernández MA, Krack P, Chabardes S, Seigneuret E, Alho EJL, Benabid AL, Moro E. Thalamic deep brain stimulation for tremor in Parkinson disease, essential tremor, and dystonia. Neurology. 2017;89:1416–23.
Cury RG, França C, Duarte KP, et al. Safety and outcomes of dentate nucleus deep brain stimulation for cerebellar ataxia. Cerebellum. 2021. https://doi.org/10.1007/s12311-021-01326-8.
Datta A, Batra N, Pandey S. Primary writing tremor: current concepts. Ann Indian Acad Neurol. 2021;24(3):319–26.
De Roquemaurel A, Wirth T, Vijiaratnam N, Ferreira F, Zrinzo L, Akram H, Foltynie T, Limousin P. Stimulation sweet spot in subthalamic deep brain stimulation – myth or reality? A critical review of literature. Stereotact Funct Neurosurg. 2021;99(5):425–42.
Defazio G, Conte A, Gigante AF, et al. Is tremor in dystonia a phenotypic feature of dystonia? Neurology. 2015;84(10):1053–9.
Dembek TA, Petry-Schmelzer JN, Reker P, Wirths J, Hamacher S, Steffen J, Dafsari HS, Hövels M, Fink GR, Visser-Vandewalle V, et al. PSA and VIM DBS efficiency in essential tremor depends on distance to the dentatorubrothalamic tract. NeuroImage Clin. 2020;26:102235.
Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13(Suppl 3):2–23.
Deuschl G, Fogel W, Hahne M, Kupsch A, Muller D, Oechsner M, Sommer U, Ulm G, Vogt T, Volkmann J. Deep-brain stimulation for Parkinson's disease. J Neurol. 2002;249:36–39.
Diederich NJ, Verhagen Metman L, Bakay RA, Alesch F. Ventral intermediate thalamic stimulation in complex tremor syndromes. Stereotact Funct Neurosurg. 2008;86:167–72.
Dos Santos Ghilardi MG, Cury RG, dos Ângelos JS, et al. Long-term improvement of tremor and ataxia after bilateral DBS of VoP/zona incerta in FXTAS. Neurology. 2015;84:1904–6.
Doshi PK, Rai N, Das D. Surgical and hardware complications of deep brain stimulation-A single surgeon experience of 519 cases over 20 years. Neuromodulation. 2021. https://doi.org/10.1111/ner.13360.

Dowsey-Limousin P. Postoperative management of VIM DBS for tremor. Mov Disord. 2002;17 Suppl 3:208–11.

Drummond PS, Pourfar MH, Hill TC, Mogilner AY, Kondziolka DS. Subthalamic gamma knife radiosurgery in Parkinson's disease: a cautionary tale. Stereotact Funct Neurosurg. 2020;98(2):110–7.

Elias WJ, Huss D, Voss T, Loomba J, Khaled M, Zadicario E, Frysinger RC, Sperling SA, Wylie S, Monteith SJ, Druzgal J, Shah BB, Harrison M, Wintermark M. A pilot study of focused ultrasound thalamotomy for essential tremor. N Engl J Med. 2013;369(7):640–8.

Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, Schwartz M, Hynynen K, Lozano AM, Shah BB, Huss D, Dallapiazza RF, Gwinn R, Witt J, Ro S, Eisenberg HM, Fishman PS, Gandhi D, Halpern CH, Chuang R, Butts Pauly K, Tierney TS, Hayes MT, Cosgrove GR, Yamaguchi T, Abe K, Taira T, Chang JW. A randomized trial of focused ultrasound thalamotomy for essential tremor. N Engl J Med. 2016;375(8):730–9.

Elias GJB, Boutet A, Joel SE, et al. Probabilistic mapping of deep brain stimulation: insights from 15 years of therapy. Ann Neurol. 2021;89(3):426–43.

Espay AJ, Duker AP, Chen R, et al. Deep brain stimulation of the ventral intermediate nucleus of the thalamus in medically refractory orthostatic tremor: preliminary observations. Mov Disord. 2008;23(16):2357–62.

Espinoza Martinez JA, Arango GJ, Fonoff ET, et al. Deep brain stimulation of the globus pallidus internus or ventralis intermedius nucleus of thalamus for Holmes tremor. Neurosurg Rev. 2015;38(4):753–63.

Evidente VGH, Rokhlin P, Evidente MH, Lambert M, Garrett R, Ponce FA. Thalamic deep brain stimulation is effective in alleviating craniocervical dystonia. Mov Disord Clin Pract. 2021;8(5):778–81.

Fasano A, Sammartino F, Llinas M, Lozano AM. MRI-guided focused ultrasound thalamotomy in fragile X-associated tremor/ataxia syndrome. Neurology. 2016;87(7):736–8.

Fasano A, Helmich RC. Tremor habituation to deep brain stimulation: underlying mechanisms and solutions. Mov Disord. 2019;34(12):1761–1773.

Fayed I, Cobourn K, Pivazyan G, Torres-Yaghi Y, Pagan F, Lo S, Mandir A, Kalhorn C. Combination targeting of subthalamic nucleus and ventral intermediate thalamic nucleus with a single trajectory in deep brain stimulation for tremor-dominant Parkinson's disease. J Clin Neurosci. 2021;85:92–100.

Fenoy AJ, Schiess MC. Comparison of tractography-assisted to atlas-based targeting for deep brain stimulation in essential tremor. Mov Disord. 2018;33:1895–901.

Ferleger BI, Houston B, Thompson MC, et al. Fully implanted adaptive deep brain stimulation in freely moving essential tremor patients. J Neural Eng. 2020;17(5):056026.

Fishman PS, Elias WJ, Ghanouni P, Gwinn R, Lipsman N, Schwartz M, Chang JW, Taira T, Krishna V, Rezai A, Yamada K, Igase K, Cosgrove R, Kashima H, Kaplitt MG, Tierney TS, Eisenberg HM. Neurological adverse event profile of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor. Mov Disord. 2018;33(5):843–7.

Foote KD, Seignourel P, Fernandez HH, et al. Dual electrode thalamic deep brain stimulation for the treatment of posttraumatic and multiple sclerosis tremor. Neurosurgery. 2006;58(ONS Suppl 2):ONS-280–6.

Fra Czek TM, Ferleger BI, Brown TE, et al. Closing the loop with cortical sensing: the development of adaptive deep brain stimulation for essential tremor using the Activa PC+S. Front Neurosci. 2021;15:749705.

Freund HJ, Barnikol UB, Nolte D, et al. Subthalamic-thalamic DBS in a case with spinocerebellar ataxia type 2 and severe tremor—a unusual clinical benefit. Mov Disord. 2007;22:732–5.

Gallay MN, Moser D, Jeanmonod D. MR-guided focused ultrasound cerebellothalamic tractotomy for chronic therapy-resistant essential tremor: anatomical target reappraisal and clinical results. J Neurosurg. 2020;7:1–10.

Geny C, Nguyen JP, Pollin B, et al. Improvement of severe postural cerebellar tremor in multiple sclerosis by chronic thalamic stimulation. Mov Disord. 1996;11:489–94.

Gerschlager W, Brown P. Orthostatic tremor – a review. Handb Clin Neurol. 2011;100:457–62.

Gilmore G, Murgai A, Nazer A, et al. Zona incerta deep-brain stimulation in orthostatic tremor: efficacy and mechanism of improvement. J Neurol. 2019;266(11):2829–37.
Giordano M, Caccavella VM, Zaed I, Foglia Manzillo L, Montano N, Olivi A, Polli FM. Comparison between deep brain stimulation and magnetic resonance-guided focused ultrasound in the treatment of essential tremor: a systematic review and pooled analysis of functional outcomes. J Neurol Neurosurg Psychiatry. 2020;91(12):1270–8.
Goto S, Yamada K. Combination of thalamic Vim stimulation and GPi pallidotomy synergistically abolishes Holmes' tremor. J Neurol Neurosurg Psychiatry. 2004;75:1200–7.
Groppa S, Herzog J, Falk D, Riedel C, Deuschl G, Volkmann J. Physiological and anatomical decomposition of subthalamic neuro- stimulation effects in essential tremor. Brain. 2014;137(1):109–21.
Gruber D, Kühn AA, Schoenecker T, et al. Pallidal and thalamic deep brain stimulation in myoclonus-dystonia. Mov Disord. 2010;25:1733–43.
Guridi J, Rodriguez-Oroz MC, Arbizu J, et al. Successful thalamic deep brain stimulation for orthostatic tremor. Mov Disord. 2008;23:1808–11.
Hacker ML, DeLong MR, Turchan M, Heusinkveld LE, Ostrem JL, Molinari AL, Currie AD, Konrad PE, Davis TL, Phibbs FT, Hedera P, Cannard KR, Drye LT, Sternberg AL, Shade DM, Tonascia J, Charles D. Effects of deep brain stimulation on rest tremor progression in early stage Parkinson disease. Neurology. 2018;91(5):e463.
Hacker ML, Turchan M, Heusinkveld LE, et al. Deep brain stimulation in early-stage Parkinson disease: five-year outcomes. Neurology. 2020;95(4):e393–401.
Hacker M, Cannard G, Turchan M, et al. Early subthalamic nucleus deep brain stimulation in Parkinson's disease reduces long-term medication costs. Clin Neurol Neurosurg. 2021;210:106976.
Hagerman RJ, Hall DA, Coffey S, et al. Treatment of fragileX-associated tremor ataxia syndrome (FXTAS) and related neurological problems. Clin Interv Aging. 2008;3(2):251–62.
Hallett M. Tremor: pathophysiology. Parkinsonism Relat Disord. 2014;20S1:118–22.
Halpern CH, Santini V, Lipsman N, Lozano AM, Schwartz ML, Shah BB, Elias WJ, Cosgrove GR, Hayes MT, McDannold N, Aldrich C, Eisenberg HM, Gandhi D, Taira T, Gwinn R, Ro S, Witt J, Jung NY, Chang JW, Rosenberg J, Ghanouni P. Three-year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor. Neurology. 2019;93(24):e2284–93.
Hamani C, Florence G, Heinsen H, Plantinga BR, Temel Y, Uludag K, Alho E, Teixeira MJ, Amaro E, Fonoff ET. Disorders of the nervous system subthalamic nucleus deep brain stimulation: basic concepts and novel perspectives. ENeuro. 2017;2017:0140–17.
Harary M, Segar DJ, Hayes MT, Cosgrove GR. Unilateral thalamic deep brain stimulation versus focused ultrasound thalamotomy for essential tremor. World Neurosurg. 2019;126:e144–52.
Hariz MI, Shamsgovara P, Johansson F, Hariz GM, Fodstad H. Tolerance and tremor rebound following long-term chronic thalamic stimulation for parkinsonian and essential tremor. Stereotact Funct Neurosurg. 1999;72:208–18.
Hariz MI, Krack P, Alesch F, et al. Multicentre European study of thalamic stimulation for parkinsonian tremor: a 6 year follow-up. J Neurol Neurosurg Psychiatry. 2008;79:694–9.
Hashimoto T, Muralidharan A, Yoshida K, et al. Neuronal activity and outcomes from thalamic surgery for spinocerebellar ataxia. Ann Clin Transl Neurol. 2018;5(1):52–63.
Hassan A, Ahlskog JE, Rodriguez M, Matsumoto JY. Surgical therapy for multiple sclerosis tremor: a 12-year follow-up study. Eur J Neurol. 2012;19:764–8.
Hassan A, Ahlskog JE, Matsumoto JY, et al. Orthostatic tremor: clinical, electrophysiologic, and treatment findings in 184 patients. Neurology. 2016;86:458–64.
Hassler R. Introduction to stereotaxis with an atlas of the human brain. Stuttgart: Thieme; 1959.
Hassler R, Riechert T, Mundinger F, Umbach W, Ganglberger JA. Physiological observations in stereotaxic operations in extrapyramidal motor disturbances. Brain. 1960;83:337–50.
Hedera P, Phibbs FT, Dolhun R, et al. Surgical targets for dystonic tremor: considerations between the globus pallidus and ventral intermediate thalamic nucleus. Parkinsonism Relat Disord. 2013;19(7):684–6.

Helmich RC, Janssen MJR, Oyen WJG, Bloem BR, Toni I. Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. Ann Neurol. 2011;69(2):269–81.
Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation [published correction appears in J Neurophysiol. 2020 Mar 1;123(3):1277]. J Neurophysiol. 2016;115(1):19–38.
Herron JA, Thompson MC, Brown T, Chizeck HJ, Ojemann JG, Ko AL. Chronic electrocorticography for sensing movement intention and closed-loop deep brain stimulation with wearable sensors in an essential tremor patient. J Neurosurg. 2017;127(3):580–7.
Hertel F, Züchner M, Decker C, et al. Unilateral Holmes tremor, clearly responsive to cerebrospinal fluid release, in a patient with an ischemic midbrain lesion and associated chronic hydrocephalic ventricle enlargement. J Neurosurg. 2006;104:448–51.
Herzog J, Hamel W, Wenzelburger R, et al. Kinematic analysis of thalamic versus subthalamic neurostimulation in postural and intention tremor. Brain. 2007;130:1608–25.
Hewitt AL, Klassen BT, Lee KH, et al. Deep brain stimulation for orthostatic tremor: a single-center case series. Neurol Clin Pract. 2020;10(4):324–32.
Higuchi Y, Matsuda S, Serizawa T. Gamma knife radiosurgery in movement disorders: indications and limitations. Mov Disord. 2017;32(1):28–35.
Hirai T, Jones EG. A new parcellation of the human thalamus on the basis of histochemical staining. Brain Res Rev. 1989;14:1–34.
Hirai T, Miyazaki M, Nakajima H, et al. The correlation between tremor characteristics and the predicted volume of effective lesions in stereotaxic nucleus ventralis intermedius thalamotomy. Brain. 1983;106:1001–18.
Holsheimer J, Demeulemeester H, Nuttin B, de Sutter P. Identification of the target neuronal elements in electrical deep brain stimulation. Eur J Neurosci. 2000;12:4573–7.
Horn A, Li N, Dembek TA, et al. Lead-DBS v2: towards a comprehensive pipeline for deep brain stimulation imaging. NeuroImage. 2019;184:293–316.
Hubble JP, Busenbark KL, Wilkinson S, et al. Effects of thalamic deep brain stimulation based on tremor type and diagnosis. Mov Disord. 1997;12:337–41.
Huebl J, Brücke C, Schneider GH, Blahak C, Krauss JK, Kühn AA. Bradykinesia induced by frequency-specific pallidal stimulation in patients with cervical and segmental dystonia. Parkinsonism Relat Disord. 2015;21(7):800–3.
Huss DS, Dallapiazza RF, Shah BB, Harrison MB, Diamond J, Elias WJ. Functional assessment and quality of life in essential tremor with bilateral or unilateral DBS and focused ultrasound thalamotomy. Mov Disord. 2015;30(14):1937–43.
Hutchison WD, Lozano AM, Tasker RR, Lang AE, Dostrovsky JO. Identification and characterization of neurons with tremor-frequency activity in human globus pallidus. Exp Brain Res. 1997;113:557–63.
Ikramuddin S, Brinda AM, Hill M, Butler R, Aman J, Vitek J, Schrock L, Cooper S, Johnson M, Matsumoto J. Low stimulation amplitude is associated with improved tremor outcome in VIM DBS for ET. Neurology. 2022;98 Suppl 18:346.
Iorio-Morin C, Yamamoto K, Sarica C, Zemmar A, Levesque M, Brisebois S, Germann J, Loh A, Boutet A, Elias GJB, Azevedo P, Adam E, Patel U, Lenis M, Kalia SK, Hodaie M, Fasano A, Lozano AM. Bilateral focused ultrasound thalamotomy for essential tremor (BEST-FUS phase 2 trial). Mov Disord. 2021;36(11):2653–62.
Isaias I, Tagliati M. Deep brain stimulation programming. In: Tarsy D, Vitek JL, Starr P, Okun M, editors. Deep brain stimulation in neurological and psychiatric disorders. Totowa: Humana; 2008. p. 362–97.
Isaias IU, Marotta G, Hirano S, et al. Imaging essential tremor. Mov Disord. 2010;25(6):679–86.
Isaias IU, Marotta G, Pezzoli G, et al. Enhanced catecholamine transporter binding in the locus coeruleus of patients with early Parkinson disease. BMC Neurol. 2011;11:88.
Isaias IU, Marzegan A, Pezzoli G, et al. A role for locus coeruleus in Parkinson tremor. Front Hum Neurosci. 2012;5:179.
Isobe T, Sato H, Goto T, et al. Long-term suppression of disabling tremor by thalamic stimulation in a patient with spinocerebellar ataxia type 2. Stereotact Funct Neurosurg. 2019;97(4):241–3.

Joint C, Nandi D, Parkin S, Gregory R, Aziz T. Hardware-related problems of deep brain stimulation. Mov Disord. 2002;17(Suppl 3):175–80.

Jones EG. Correlation and revised nomenclature of ventral nuclei in the thalamus of human and monkey. Stereotact Funct Neurosurg. 1990;54–55:1–20.

Jones MW, Tasker RR. The relationship of documented destruction of specific cell types to complications and effectiveness in thalamotomy for tremor in Parkinson's disease. Stereotact Funct Neurosurg. 1990;55:207–11.

Jung NY, Park CK, Kim M, Lee PH, Sohn YH, Chang JW. The efficacy and limits of magnetic resonance-guided focused ultrasound pallidotomy for Parkinson's disease: a Phase I clinical trial. J Neurosurg. 2018;1:1–9.

Jung IH, Chang KW, Park SH, Chang WS, Jung HH, Chang JW. Complications after deep brain stimulation: a 21-year experience in 426 patients. Front Aging Neurosci. 2022;14:819730.

Kilbane C, Ramirez-Zamora A, Ryapolova-Webb E, et al. Pallidal stimulation for Holmes tremor: clinical outcomes and single-unit recordings in 4 cases. J Neurosurg. 2015;122(6):1306–14.

Kim HJ, Jeon BS, Paek SH, Lee JY, Kim HJ, Kim CK, Kim DG. Bilateral subthalamic deep brain stimulation in Parkinson disease patients with severe tremor. Neurosurgery. 2010;67:626–32.

Kim MJ, Chang KW, Park SH, Chang WS, Jung HH, Chang JW. Stimulation-induced side effects of deep brain stimulation in the ventralis intermedius and posterior subthalamic area for essential tremor. Front Neurol. 2021;12:678592.

Kirsch AD, Hassin-Baer S, Matthies C, Volkmann J, Steigerwald F. Anodic versus cathodic neurostimulation of the subthalamic nucleus: a randomized-controlled study of acute clinical effects. Parkinsonism Relat Disord. 2018;55:61–7.

Kiss ZH, Mooney DM, Renaud L, Hu B. Neuronal response to local electrical stimulation in rat thalamus: physiological implications for mechanisms of deep brain stimulation. Neuroscience. 2002;113:137–43.

Kiss ZH, Anderson T, Hansen T, Kirstein D, Suchowersky O, Hu B. Neural substrates of microstimulation-evoked tingling: a chronaxie study in human somatosensory thalamus. Eur J Neurosci. 2003;18:728–32.

Kitagawa M, Murata J, Kikuchi S, et al. Deep brain stimulation of subthalamic area for severe proximal tremor. Neurology. 2000;55:114–6.

Kitagawa M, Murata J, Uesugi H, Kikuchi S, Saito H, Tashiro K, Sawamura Y. Two-year follow-up of chronic stimulation of the posterior subthalamic white matter for tremor-dominant Parkinson's disease. Neurosurgery. 2005;56:281–9.

Kobayashi K, Katayama Y, Oshima H, et al. Multitarget, dual-electrode deep brain stimulation of the thalamus and subthalamic area for treatment of Holmes' tremor. J Neurosurg. 2014;120(5):1025–32.

Koch M, Mostert J, Heersema D, De Keyser J. Tremor in multiple sclerosis. J Neurol. 2007;254(2):133–45.

Koller W, Pahwa R, Busenbark K, et al. High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Ann Neurol. 1997;42:292–9.

Koller WC, Lyons KE, Wilkinson SB, Pahwa R. Efficacy of unilateral deep brain stimulation of the VIM nucleus of the thalamus for essential head tremor. Mov Disord. 1999;14:847–50.

Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov Disord. 2001;16:464–8.

Krack P, Benazzouz A, Pollak P, et al. Treatment of tremor in Parkinson's disease by subthalamic nucleus stimulation. Mov Disord. 1998;13:907–14.

Krack P, Dostrovsky J, Ilinsky I, et al. Surgery of the motor thalamus: problems with the present nomenclatures. Mov Disord. 2002;17 Suppl 3:2–8.

Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003;349:1925–34.

Krauss JK, Jankovic J. Head injury and posttraumatic movement disorders. Neurosurgery. 2002;50:927–39.

Krauss JK, Mohadjer M, Nobbe F, Mundinger F. The treatment of posttraumatic tremor by stereotactic surgery. Symptomatic and functional outcome in a series of 35 patients. J Neurosurg. 1994;80:810–9.

Krauss JK, Simpson RK Jr, Ondo WG, Pohle T, Burgunder JM, Jankovic J. Concepts and methods in chronic thalamic stimulation for treatment of tremor: technique and application. Neurosurgery. 2001;48(3):535–41.

Kremer NI, Pauwels RWJ, Pozzi NG, Lange F, Roothans J, Volkmann J, Reich MM. Deep brain stimulation for tremor: update on long-term outcomes, target considerations and future directions. J Clin Med. 2021;10:3468.

Krishna V, Sammartino F, Cosgrove R, Ghanouni P, Schwartz M, Gwinn R, Eisenberg H, Fishman P, Chang JW, Taira T, Kaplitt M, Rezai A, Rumià J, Gedroyc W, Igase K, Kishima H, Yamada K, Ohnishi H, Halpern C. Predictors of outcomes after focused ultrasound thalamotomy. Neurosurgery. 2020;87(2):229–37.

Krüger MT, Avecillas-Chasin JM, Tamber MS, et al. Tremor and quality of life in patients with advanced essential tremor before and after replacing their standard deep brain stimulation with a directional system. Neuromodulation. 2021;24(2):353–60.

Kübler D, Kroneberg D, Al-Fatly B, Schneider GH, Ewert S, van Riesen C, Gruber D, Ebersbach G, Kühn AA. Determining an efficient deep brain stimulation target in essential tremor: cohort study and review of the literature. Parkinsonism Relat Disord. 2021;89:54–62.

Kumar R. Methods of programming and patient management with deep brain stimulation. In: Tarsy D, Lozano AM, Vitek JL, editors. Surgical treatment of parkinson's disease and other movement disorders. Totowa: Humana; 2003. p. 189–212.

Kumar R, McVicker JM. Radiofrequency lesioning through an implanted deep brain stimulating electrode: treatment of tolerance to thalamic stimulation in essential tremor. Mov Disord. 2000;15 Suppl 3:69.

Kumar R, Lozano AM, Kim YJ, Hutchison WD, Sime E, Halket E, Lang AE. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology. 1998;51:850–5.

Kvernmo N, Konglund AE, Reich MM, Roothans J, Pripp AH, Dietrichs E, Volkmann J, Skogseid IM. Deep Brain Stimulation for Arm Tremor: A Randomized Trial Comparing Two Targets. Ann Neurol. 2022;91(5):585–601.

Laitinen LV. Pallidotomy for Parkinson's disease. Neurosurg Clin NArn. 1995;6:105–12.

Lange F, Steigerwald F, Malzacher T, et al. Reduced programming time and strong symptom control even in chronic course through imaging-based DBS programming. Front Neurol. 2021;12:785529.

Lee JY, Lao-Kaim NP, Pasquini J, Deuschl G, Pavese N, Piccini P. Pallidal dopaminergic denervation and rest tremor in early Parkinson's disease: PPMI cohort analysis. Parkinsonism Relat Disord. 2018;51:101–4.

Lenz FA, Tasker RR, Kwan HC, et al. Single unit analysis of the human ventral thalamic nuclear group: correlation of thalamic "tremor cells" with the 3-6 Hz component of parkinsonian tremor. J Neurosci. 1988;8:754–64.

Lenz FA, Kwan HC, Martin RL, Tasker RR, Dostrovsky JO, Lenz YE. Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. Brain. 1994;117:531–43.

Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. J Neurosci. 2000;20:7766–75.

Lim DA, Khandhar SM, Heath S, Ostrem JL, Ringel N, Starr P. Multiple target deep brain stimulation for multiple sclerosis related and poststroke Holmes' tremor. Stereotact Funct Neurosurg. 2007;85:144–9.

Lim SY, Hodaie M, Fallis M, Poon YY, Mazzella F, Moro E. Gamma knife thalamotomy for disabling tremor: a blinded evaluation. Arch Neurol. 2010;67(5):584–8.

Limousin P, Speelman JD, Gielen F, et al. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry. 1999;66:289–96.

Lipsman N, Schwartz ML, Huang Y, Lee L, Sankar T, Chapman M, Hynynen K, Lozano AM. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. Lancet Neurol. 2013;12(5):462–8.

Liu LD, Prescott IA, Dostrovsky JO, Hodaie M, Lozano AM, Hutchison WD. Frequency-dependent effects of electrical stimulation in the globus pallidus of dystonia patients. J Neurophysiol. 2012;108:5–17.

Low HL, bin Mohd Ismail MN, Taqvi A, Deeb J, Fuller C, Misbahuddin A. Comparison of posterior subthalamic area deep brain stimulation for tremor using conventional landmarks versus directly targeting the dentatorubrothalamic tract with tractography. Clin Neurol Neurosurg. 2019;185:105466.

Lu G, Luo L, Liu M, Zheng Z, Zhang B, Chen X, et al. Outcomes and adverse effects of deep brain stimulation on the ventral intermediate nucleus in patients with essential tremor. Neural Plast. 2020;2486065.

Lund-Johansen M, Hugdahl K, Wester K. Cognitive function in patients with Parkinson's disease undergoing stereotaxic thalamotomy. J Neurol Neurosurg Psychiatry. 1996;60:564–71.

Lyons KE, Koller WC, Wilkinson SB, Pahwa R. Long term safety and efficacy of unilateral deep brain stimulation of the thalamus for Parkinson tremor. J Neurol Neurosurg Psychiatry. 2001;71:682–4.

Lyons M, Shneyder N, Evidente V. PWT responds to unilateral thalamic deep brain stimulation. Turk Neurosurg. 2013;23:122–4.

Lyons KE, Pahwa R, Comella CL, Eisa MS, Rodger J, Elble RJ, Fahn S, Jankovic J, Juncos JL, Koller WC, Ondo WG, Sethi KD, Stern MB, Tanner CM, Tintner R, Watts RL. Benefits and risks of pharmacological treatments for essential tremor. Drug Saf. 2003;26(7):461–81.

Magara A, Bühler R, Moser D, Kowalski M, Pourtehrani P, Jeanmonod D. First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease. J Ther Ultrasound. 2014;2:11.

Magariños-Ascone C, Pazo JH, Macadar O, Buno W. High-frequency stimulation of the subthalamic nucleus silences subthalamic neurons: a possible cellular mechanism in Parkinson's disease. Neuroscience. 2002;115:1109–17.

Magnin M, Morel A, Jeanmonod D. Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. Neuroscience. 2000;96:549–64.

Mahlknecht P, Georgiev D, Akram H, Brugger F, Vinke S, Zrinzo L, Hariz M, Bhatia KP, Hariz GM, Willeit P, Rothwell JC. Parkinsonian signs in patients with cervical dystonia treated with pallidal deep brain stimulation. Brain. 2018;141(10):3023–34.

Malekmohammadi M, Herron J, Velisar A, et al. Kinematic adaptive deep brain stimulation for resting tremor in Parkinson's disease. Mov Disord. 2016;31(3):426–8.

Máñez-Miró JU, Martínez-Fernández R, Del Alamo M, Pineda-Pardo JA, Fernández-Rodríguez B, Alonso-Frech F, Álvarez-Cermeño JC, Obeso JA. Focused ultrasound thalamotomy for multiple sclerosis-associated tremor. Mult Scler. 2020;26(7):855–8.

Martínez-Fernández R, Máñez-Miró JU, Rodríguez-Rojas R, Del Álamo M, Shah BB, Hernández-Fernández F, Pineda-Pardo JA, Monje MHG, Fernández-Rodríguez B, Sperling SA, Mata-Marín D, Guida P, Alonso-Frech F, Obeso I, Gasca-Salas C, Vela-Desojo L, Elias WJ, Obeso JA. Randomized trial of focused ultrasound subthalamotomy for Parkinson's disease. N Engl J Med. 2020;383(26):2501–13.

Mason XL, Cross KA, Arac A, Bordelon Y, Wu AD. Vim-thalamic deep brain stimulation for cervical dystonia and upper-limb tremor: quantification by markerless-3D kinematics and accelerometry. Tremor Other Hyperkinet Mov (N Y). 2022;12:5.

McIntyre CC, Grill WM, Sherman DL, Thakor NV. Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. J Neurophysiol. 2004a;91:1457–69.

McIntyre CC, Mori S, Sherman DL, Thakor NV, Vitek JL. Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. Clin Neurophysiol. 2004b;115(3):589–95.

McMaster J, Gibson G, Castro-Prado F, Vitali A, Honey CR. Neurosurgical treatment of tremor in anti-myelin-associated glycoprotein neuropathy. Neurology. 2009;73(20):1707–8.

Medtronic, Inc. Deep brain stimulation for the treatment of tremor using the Medtronic Model 3387 DBSTM lead and the Itrel® II Model 7424 implantable pulse generator. Final Report. 2002.

Mehanna R, Itin I. Which approach is better: bilateral versus unilateral thalamic deep brain stimulation in patients with fragile X-associated tremor ataxia syndrome. Cerebellum. 2014;13:222–5.

Merola A, Fasano A, Hassan A, et al. Thalamic deep brain stimulation for orthostatic tremor: a multicenter international registry. Mov Disord. 2017;32(8):1240–4.

Middlebrooks EH, Tuna IS, Almeida L, Grewal SS, Wong J, Heckman MG, Lesser ER, Bredel M, Foote KD, Okun MS, Holandah VM. Structural connectivity–based segmentation of the thalamus and prediction of tremor improvement following thalamic deep brain stimulation of the ventral intermediate nucleus. Neuroimage Clin. 2018;20:1266–73.

Middlebrooks EH, Okromelidze L, Wong JK, Eisinger RS, Burns MR, Jain A, Lin HP, Yu J, Opri E, Horn A, Goede LL, Foote KD, Okun MS, Quiñones-Hinojosa A, Uitti RJ, Grewal SS, Tsuboi T. Connectivity correlates to predict essential tremor deep brain stimulation outcome: evidence for a common treatment pathway. Neuroimage Clin. 2021;32:102846.

Milosevic L, Kalia SK, Hodaie M, Lozano AM, Fasano A, Popovic MR, et al. Neuronal inhibition and synaptic plasticity of basal ganglia neurons in Parkinson's disease. Brain. 2017;141:177–90.

Milosevic L, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD. Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. Brain. 2018;141(7):2142–55.

Minguez-Castellanos A, Carnero-Pardo C, Gómez-Camello A, et al. Primary writing tremor treated by chronic thalamic stimulation. Mov Disord. 1999;14:1030–3.

Moldovan AS, Hartmann CJ, Trenado C, Meumertzheim N, Slotty PJ, Vesper J, Schnitzler A, Groiss SJ. Less is more - Pulse width dependent therapeutic window in deep brain stimulation for essential tremor. Brain Stimul. 2018;11(5):1132–9.

Montgomery EB. Deep brain stimulation programming: principles and practice. Oxford, UK: Oxford University Press; 2010.

Montgomery EB, Gale JT. Mechanisms of action of deep brain stimulation (DBS). Neurosci Biobehav Rev. 2008;32(3):388–407.

Montgomery EB Jr, Baker KB, Kinkel RP, Barnett G. Chronic thalamic stimulation for the tremor of multiple sclerosis. Neurology. 1999;53:625–8.

Morishita T, Foote KD, Haq IU, Zeilman P, Jacobson CE, Okun MS. Should we consider Vim thalamic deep brain stimulation for select cases of severe refractory dystonic tremor. Stereotact Funct Neurosurg. 2010;88:98–104.

Moro E, Poon YY, Lozano AM, et al. Subthalamic nucleus stimulation: improvements in outcome with reprogramming. Arch Neurol. 2006;63:1266–72.

Moro E, Lozano AM, Pollak P, Agid Y, Rehncrona S, Volkmann J, Kulisevsky J, Obeso JA, Albanese A, Hariz MI, et al. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. Mov Disord. 2010;25:578–86.

Morrison MA, Lee AT, Martin AJ, Dietiker C, Brown EG, Wang DD. DBS targeting for essential tremor using intersectional dentato-rubro-thalamic tractography and direct proton density visualization of the VIM: technical note on 2 cases. J Neurosurg. 2021;1:1–9.

Mundinger F. Results of 500 subthalamotomies in the region of the zona incerta. In: Third symposium on Parkinson's disease. Edinburgh: E & S Livingstone; 1969. p. 261–5.

Munhoz RP, Cerasa A, Okun MS. Surgical treatment of dyskinesia in Parkinson's disease. Front Neurol. 2014;5:1–9.

Murata J, Kitagawa M, Uesugi H, et al. Electrical stimulation of the posterior subthalamic area for the treatment of intractable proximal tremor. J Neurosurg. 2003;99:708–15.

Mure H, Hirano S, Tang CC, et al. Parkinson's disease tremor-related metabolic network: characterization, progression, and treatment effects. NeuroImage. 2011;54(2):1244–53.

Nandi D, Aziz TZ. Deep brain stimulation in the management of neuropathic pain and multiple sclerosis tremor. J Clin Neurophysiol. 2004;21:31–9.

Neumann WJ, Memarian Sorkhabi M, Benjaber M, et al. The sensitivity of ECG contamination to surgical implantation site in brain computer interfaces. Brain Stimul. 2021;14(5):1301–6.
Nguyen JP, Degos JD. Thalamic stimulation and proximal tremor: a specific target in the nucleus ventrointermedius thalami. Arch Neurol. 1993;50:498–500.
Nikkhah G, Prokop T, Hellwig B, Lücking CH, Ostertag CB. Deep brain stimulation of the nucleus ventralis intermedius for Holmes (rubral) tremor and associated dystonia caused by upper brainstem lesions. J Neurosurg. 2004;100:1079–83.
Niranjan A, Raju SS, Kooshkabadi A, Monaco E 3rd, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for essential tremor: retrospective analysis of a 19-year experience. Mov Disord. 2017;32(5):769–77.
Nishio M, Korematsu K, Yoshioka S, et al. Long-term suppression of tremor by deep brain stimulation of the ventral intermediate nucleus of the thalamus combined with pallidotomy in hemiparkinsonian patients. J Clin Neurosci. 2009;16:1489–91.
Novak KE, Dalvi A, Nenonene EK, Bernstein LP. Surgical treatment of tremor. Dis Mon. 2011;57:142–59. 0011-5029/2011
Nowacki A, Barlatey S, Al-Fatly B, Dembek T, Bot M, Green AL, Kübler D, Lachenmayer ML, Debove I, Segura-Amil A, Horn A, Visser-Vandewalle V, Schuurman R, Barbe M, Aziz TZ, Kühn AA, Nguyen TAK, Pollo C. Probabilistic mapping reveals optimal stimulation site in essential tremor. Ann Neurol. 2022;91(5):602–12.
Obwegeser AA, Uitti RJ, Turk MF, Strongosky AJ, Wharen RE. Thalamic stimulation for the treatment of midline tremors in essential tremor patients. Neurology. 2000;54:2342–4.
Obwegeser AA, Uitti RJ, Witte RJ, Lucas JA, Turk MF, Wharen RE Jr. Quantitative and qualitative outcome measures after thalamic deep brain stimulation to treat disabling tremors. Neurosurgery. 2001;48:274–84.
Oh MY, Hodaie M, Kim SH, Alkhani A, Lang AE, Lozano AM. Deep brain stimulator electrodes used for lesioning: proof of principle. Neurosurgery. 2001;49:363–9.
Oh MY, Abosch A, Kim SH, Lang AE, Lozano AM. Long-term hardware-related complications of deep brain stimulation. Neurosurgery. 2002;50:1268–76.
Ohye C, Higuchi Y, Shibazaki T, Hashimoto T, Koyama T, Hirai T, Matsuda S, Serizawa T, Hori T, Hayashi M, Ochiai T, Samura H, Yamashiro K. Gamma knife thalamotomy for Parkinson disease and essential tremor: a prospective multicenter study. Neurosurgery. 2012 Mar;70(3):526–35.
Okun MS, Stover NP, Subramanian T, Gearing M, Wainer BH, Holder CA, Watts RL, Juncos JL, Freeman A, Evatt ML, Schuele SU, Vitek JL, DeLong MR. Complications of gamma knife surgery for Parkinson disease. Arch Neurol. 2001;58(12):1995–2002.
Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines. Neurology. 2001;56:S1–S88.
Oliveria SF, Rodriguez RL, Bowers D, Kantor D, Hilliard JD, Monari EH, Scott BM, Okun MS, Foote KD. Safety and efficacy of dual-lead thalamic deep brain stimulation for patients with treatment-refractory multiple sclerosis tremor: a single-centre, randomised, single-blind, pilot trial. Lancet Neurol. 2017;16(9):691–700.
Ondo WG, Satija P. Task-specific writing tremor: clinical phenotypes, progression, treatment outcomes, and proposed nomenclature. Int J Neurosci. 2012;122:88–91.
Ondo W, Almaguer M, Jankovic J, Simpson RK. Thalamic deep brain stimulation: comparison between unilateral and bilateral placement. Arch Neurol. 2001;58:218–22.
Opri E, Cernera S, Molina R, Eisinger RS, Cagle JN, Almeida L, Denison T, Okun MS, Foote KD, Gunduz A, Crayton Pruitt J. Chronic embedded cortico-thalamic closed-loop deep brain stimulation for the treatment of essential tremor. Sci Transl Med. 2020;12(572):eaay7680.
Oyama G, Umemura A, Shimo Y, et al. Posterior subthalamic area deep brain stimulation for fragile X-associated tremor/ataxia syndrome. Neuromodulation. 2014;17:721–3.
Pahwa R, Lyons KE, Wilkinson SB, et al. Comparison of thalamotomy to deep brain stimulation of the thalamus in essential tremor. Mov Disord. 2001;16:140–3.
Pahwa R, Lyons KE, Kempf L, Wilkinson SB, Koller WC. Thalamic stimulation for midbrain tremor after partial hemangioma resection. Mov Disord. 2002;17:404–7.

Pahwa R, Lyons KL. Essential tremor: differential diagnosis and current therapy. Am J Med. 2003;115(2):134–42.
Pahwa R, Lyons K, Wilkinson SB, et al. Long-term evaluation of deep brain stimulation of the thalamus. J Neurosurg. 2006;104:506–12.
Papavassiliou E, Rau G, Heath S, et al. Thalamic deep brain stimulation for essential tremor: relation of lead location to outcome. Neurosurgery. 2004;54:1120–30.
Patriat R, Cooper SE, Duchin Y, Niederer J, Lenglet C, Aman J, Park MC, Vitek JL, Harel N. Individualized tractography-based parcellation of the globus pallidus pars interna using 7T MRI in movement disorder patients prior to DBS surgery. NeuroImage. 2018;178:198–209.
Payne MS, Brown BL, Rao J, Payne BR. Treatment of phenylketonuria-associated tremor with deep brain stimulation: case report. Neurosurgery. 2005;56:E868.
Peker S, Isik U, Akgun Y, Ozek M. Deep brain stimulation for Holmes' tremor related to a thalamic abscess. Childs Nerv Syst. 2008;24:1057–62.
Peters J, Tisch S. Habituation after deep brain stimulation in tremor syndromes: prevalence, risk factors and long-term outcomes. Front Neurol. 2021;12:696950.
Petry-Schmelzer JN, Dembek TA, Steffen JK, et al. Selecting the most effective DBS contact in essential tremor patients based on individual tractography [published correction appears in Brain Sci. 2021 Dec 31;12(1):]. Brain Sci. 2020;10(12):1015.
Piette T, Mescola P, Henriet M, Cornil C, Jacquy J, Vanderkelen B. A surgical approach to Holmes' tremor associated with high-frequency synchronous bursts. Rev Neurol. 2004;160:707–11.
Pirker W, Back C, Gerschlager W, Laccone F, Alesch F. Chronic thalamic stimulation in a patient with spinocerebellar ataxia type 2. Mov Disord. 2003;18:222–5.
Plaha P, Ben-Shlomo Y, Patel NK, Gill SS. Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. Brain. 2006;129:1732–1747.
Plaha P, Patel NK, Gill SS. Stimulation of the subthalamic region for essential tremor. J Neurosurg. 2004;101:48–54.
Plaha P, Khan S, Gill SS. Bilateral stimulation of the caudal zona incerta nucleus for tremor control. J Neurol Neurosurg Psychiatry. 2008;79:504–13.
Pollak P, Fraix V, Krack P, et al. Treatment results: Parkinson's disease. Mov Disord. 2002;17 Suppl 3:S75–83.
Pouratian N, Baltuch G, Elias WJ, Gross R. American Society for Stereotactic and Functional Neurosurgery Position statement on magnetic resonance-guided focused ultrasound for the management of essential tremor. Neurosurgery. 2020;87(2):E126–9.
Putzke JD, Wharen RE Jr, Wszolek ZK, Turk MF, Strongosky AJ, Uitti RJ. Thalamic deep brain stimulation for tremor-predominant Parkinson's disease. Parkinsonism Relat Disord. 2003;10:81–8.
Putzke JD, Wharen RE Jr, Obwegeser AA, et al. Thalamic deep brain stimulation for essential tremor: recommendations for long-term outcome analysis. Can J Neurol Sci. 2004;31:333–42.
Putzke JD, Uitti RJ, Obwegeser AA, Wszolek ZK, Wharen RE. Bilateral thalamic deep brain stimulation: midline tremor control. J Neurol Neurosurg Psychiatry. 2005;76:684–90.
Racette BA, Dowling J, Randle J, Mink JW. Thalamic stimulation for primary writing tremor. J Neurol. 2001;248:380–2.
Ramirez-Zamora A, Okun MS. Deep brain stimulation for the treatment of uncommon tremor syndromes. Expert Rev Neurother. 2016;16(8):983–97.
Ramirez-Zamora A, Smith H, Kumar V, Prusik J, Phookan S, Pilitsis JG. Evolving concepts in posterior subthalamic area deep brain stimulation for treatment of tremor: surgical neuroanatomy and practical considerations. Stereotact Funct Neurosurg. 2016;94:283–97.
Rammo RA, Ozinga SJ, White A, et al. Directional stimulation in Parkinson's disease and essential tremor: the Cleveland Clinic experience [published online ahead of print, 2021 Mar 18]. Neuromodulation. 2022;25(6):829–35.
Ravikumar VK, Parker JJ, Hornbeck TS, Santini VE, Pauly KB, Wintermark M, Ghanouni P, Stein SC, Halpern CH. Cost-effectiveness of focused ultrasound, radiosurgery, and DBS for essential tremor. Mov Disord. 2017;32(8):1165–73.

Rebelo P, Green AL, Aziz TZ, et al. Thalamic Directional Deep Brain Stimulation for tremor: spend less, get more. Brain Stimul. 2018;11(3):600–6.

Reese R, Herzog J, Falk D, et al. Successful deep brain stimulation in a case of posttraumatic tremor and hemiparkinsonism. Mov Disord. 2011;26(10):1954–5.

Rehncrona S, Johnels B, Widner H, et al. Long-term safety and efficacy of thalamic deep brain stimulation of the thalamus for parkinsonian tremor. J Neurol Neurosurg Psychiatry. 2001;71:682–4.

Rehncrona S, Johnels B, Widner H, Tornqvist AL, Hariz M, Sydow O. Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. Mov Disord. 2003;18:163–70.

Reich MM, Steigerwald F, Sawalhe AD, Reese R, Gunalan K, Johannes S, et al. Short pulse width widens the therapeutic window of subthalamic neurostimulation. Ann Clin Transl Neurol. 2015;2:427–32.

Reich MM, Brumberg J, Pozzi NG, Marotta G, Roothans J, Åström M, Musacchio T, Lopiano L, Lanotte M, Lehrke R, Buck AK, Volkmann J, Isaias IU. Progressive gait ataxia following deep brain stimulation for essential tremor: adverse effect or lack of efficacy. Brain. 2016;139:2948–56.

Reich MM, Horn A, Lange F, et al. Probabilistic mapping of the anti-dystonic effect of pallidal neurostimulation: a multicentre imagingstudy. Brain. 2019;142:1386–98.

Riskin-Jones HH, Kashanian A, Sparks H, Tsolaki E, Pouratian N. Increased structural connectivity of thalamic stimulation sites to motor cortex relates to tremor suppression. Neuroimage Clin. 2021;30:102628.

Rodriguez MC, Guridi OJ, Alvarez L, Mewes K, Macias R, Vitek J, DeLong MR, Obeso JA. The subthalamic nucleus and tremor in Parkinson's disease. Mov Disord. 1998;13(S3):111–8.

Romanelli P, Bronte-Stewart H, Courtney T, Heit G. Possible necessity for deep brain stimulation of both the ventralis intermedius and subthalamic nuclei to resolve Holmes tremor. J Neurosurg. 2003;99:566–71.

Samadani U, Umemura A, Jaggi JL, Colcher A, Zager EL, Baltuch GH. Thalamic deep brain stimulation for disabling tremor after excision of a midbrain cavernous angioma. J Neurosurg. 2003;98:888–90.

Sammartino F, Krishna V, King NKK, Lozano AM, Schwartz ML, Huang Y, Hodaie M. Tractography-based ventral intermediate nucleus targeting: novel methodology and intraoperative validation. Mov Disord. 2016;31:1217–25.

Sanborn MR, Danish SF, Ranalli NJ, Grady MS, Jaggi JL, Baltuch GH. Thalamic deep brain stimulation for midbrain tremor secondary to cystic degeneration of the brainstem. Stereotact Funct Neurosurg. 2009;87:128–33.

Sandvik U, Lars-Owe K, Anders L, Patric B. Thalamic and subthalamic DBS for essential tremor: where is the optimal target? Neurosurgery. 2011;70(4):840–5.

Savica R, Matsumoto JY, Josephs KA, et al. Deep brain stimulation in benign tremulous parkinsonism. Arch Neurol. 2011;68:1033–6.

Schrader C, Capelle HH, Kinfe TM, et al. GPi-DBS may induce a hypokinetic gait disorder with freezing of gait in patients with dystonia. Neurology. 2011;77(5):483–8.

Schramm P, Scheihing M, Rasche D, Tronnier VM. Behr syndrome variant with tremor treated by VIM stimulation. Acta Neurochir. 2005;147:679–83.

Schreglmann SR, Bauer R, Hägele-Link S, Bhatia KP, Natchev P, Wegener N, Lebeda A, Werner B, Martin E, Kägi G. Unilateral cerebellothalamic tract ablation in essential tremor by MRI-guided focused ultrasound. Neurology. 2017;88(14):1329–33.

Schulder M, Sernas T, Mahalick D, Adler R, Cook S. Thalamic stimulation in patients with multiple sclerosis. Stereotact Funct Neurosurg. 1999;72:196–201.

Schulder M, Sernas TJ, Karimi R. Thalamic stimulation in patients with multiple sclerosis: long-term follow-up. Stereotact Funct Neurosurg. 2003;80:48–55.

Schüpbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med. 2013;368(7):610–22.

Schüpbach WM, Rau J, Houeto JL, et al. Myths and facts about the EARLYSTIM study. Mov Disord. 2014;29(14):1742–50.
Schuurman PR, Bosch DA, Bossuyt PM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med. 2000;342:461–8.
Shimojima Y, Hashimoto T, Kaneko K, et al. Thalamic stimulation for disabling tremor in a patient with spinocerebellar degeneration. Stereotact Funct Neurosurg. 2005;83:131–4.
Sinai A, Nassar M, Eran A, Constantinescu M, Zaaroor M, Sprecher E, Schlesinger I. Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience. J Neurosurg. 2019;5:1–8.
Soh D, ten Brinke TR, Lozano AM, Fasano A. Therapeutic window of deep brain stimulation using cathodic monopolar, bipolar, semi-bipolar, and anodic stimulation. Neuromodulation. 2019;22(4):451–5.
Speelman JD, Bosch DA. Resurgence of functional neurosurgery for Parkinson's disease: a historical perspective. Mov Dis. 1998;13(3):582–8.
Sprague JM, Chambers WW. Regulation of posture in intact and de- cerebrate cat. I. Cerebellum, reticular formation, vestibular nuclei. J Neurophysiol. 1953;16:451–63.
Steigerwald F, Müller L, Johannes S, Matthies C, Volkmann J. Directional deep brain stimulation of the subthalamic nucleus: a pilot study using a novel neurostimulation device. Mov Disord. 2016;31(8):1240–3.
St George RJ, Nutt JG, Burchiel KJ, Horak FB. A meta-regression of the long-term effects of deep brain stimulation on balance and gait in PD. Neurology. 2010;75(14):1292–9.
Stellar S, Cooper IS. Mortality and morbidity in cryothalamectomy for parkinsonism. A statistical study of 2,868 consecutive operations. J Neurosurg. 1968;28:459–67.
Sydow O, Thobois S, Alesch F, Speelman JD. Multicentre European study of thalamic stimulation in essential tremor: a six year follow up. J Neurol Neurosurg Psychiatry. 2003;74:1387–91.
Tarsy D, Norregaard T, Hubble J. Thalamic deep brain stimulation for Parkinson's disease and essential tremor. In: Tarsy D, Lozano AM, Vitek JL, editors. Surgical treatment of parkinson's disease and other movement disorders. Totowa: Humana; 2003. p. 153–61.
Tarsy D, Scollins L, Corapi K, O'Herron S, Apetauerova D, Norregaard T. Progression of Parkinson's disease following thalamic deep brain stimulation for tremor. Stereotact Funct Neurosurg. 2005;83:222–7.
Tasker RR. Deep brain stimulation is preferable to thalamotomy for tremor suppression. Surg Neurol. 1998;49:145–54.
Teixeira MJ, Cury RG, Galhardoni R, et al. Deep brain stimulation of the dentate nucleus improves cerebellar ataxia after cerebellar stroke. Neurology. 2015;85(23):2075–6.
Thenaisie Y, Palmisano C, Canessa A, et al. Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. J Neural Eng. 2021;18(4). https://doi.org/10.1088/1741-2552/ac1d5b.
Torres CV, Moro E, Lopez-Rios AL, et al. Deep brain stimulation of the ventral intermediate nucleus of the thalamus for tremor in patients with multiple sclerosis. Neurosurgery. 2010;67:646–51.
Troster AI, Fields JA. The role of neuropsychological evaluation in the neurosurgical treatment of movement disorders. In: Tarsy D, Lozano AM, Vitek JL, editors. Surgical treatment of Parkinson's disease and other movement disorders. Totowa: Humana; 2003. p. 213–40.
Troster AI, Fields JA, Pahwa R, et al. Neuropsychological and quality of life outcome after thalamic stimulation for essential tremor. Neurology. 1999;53:1174–780.
Tsuboi T, Jabarkheel Z, Zeilman PR, Barabas MJ. Foote KD, Okun MS, Shukla AW. Longitudinal follow-up with VIM thalamic deep brain stimulation for dystonic or essential tremor. Neurology. 2020; 10;94(10):e1073–e1084.
Tsuboi T, Wong JK, Eisinger RS, et al. Comparative connectivity correlates of dystonic and essential tremor deep brain stimulation. Brain. 2021;144(6):1774–86.
Umemura A, Samadani U, Jaggi JL, Hurtig HI, Baltuch GH. Thalamic deep brain stimulation for posttraumatic action tremor. Clin Neurol Neurosurg. 2004;106:280–3.

Veerappan V, Anderson S, Safarpour D, Hiller AL. Role of directional configuration in deep brain stimulation for essential tremor: a single center experience. Tremor Other Hyperkinet Mov (N Y). 2021;11:47.

Velasco F, Velasco M, Ogarrio C, Olvera A. Neglect induced by thalamotomy in humans: a quantitative appraisal of the sensory and motor deficits. Neurosurgery. 1986;19:744–51.

Velasco F, Jimenez F, Perez ML, et al. Electrical stimulation of the prelemniscal radiation in the treatment of Parkinson's disease: an old target revised with new techniques. Neurosurgery. 2001;49:293–306.

Vidailhet M, Vercueil L, Houeto JL, et al. Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. Lancet Neurol. 2007;6:223–9.

Vissani M, Isaias IU, Mazzoni A. Deep brain stimulation: a review of the open neural engineering challenges. J Neural Eng. 2020;17(5):051002.

Vissani M, Palmisano C, Volkmann J, et al. Impaired reach-to-grasp kinematics in parkinsonian patients relates to dopamine-dependent, subthalamic beta bursts. NPJ Parkinsons Dis. 2021;7(1):53.

Voges J, Waerzeggers Y, Maarouf M, et al. Deep-brain stimulation: longterm analysis of complications caused by hardware and surgery-experiences from a single centre. J Neurol Neurosurg Psychiatry. 2006;77:868–72.

Volkmann J, Herzog J, Kopper F, Deuschl G. Introduction to the programming of deep brain stimulators. Mov Disord. 2002;17 Suppl 3:S181–7.

Voon V, Kubu C, Krack P, Houeto JL, Troster AI. Deep brain stimulation: neuropsychological and neuropsychiatric issues. Mov Disord. 2006;21 Suppl 14:305–27.

Waldthaler J, Bopp M, Kühn N, et al. Imaging-based programming of subthalamic nucleus deep brain stimulation in Parkinson's disease. Brain Stimul. 2021;14(5):1109–17.

Walker AE. Normal and pathological physiology of the human thalamus. In: Schaltenbrand G, Walker AE, editors. Stereotaxy of the human brain: anatomical, physiological, and clinical applications. Stuttgart: Thieme; 1982. p. 181–217.

Wang ZM, Wei PH, Shan Y, Han M, Zhang M, Liu H, Gao JH, Lu JH. Identifying and characterizing projections from the subthalamic nucleus to the cerebellum in humans. NeuroImage. 2020;210:116573.

Weiss D, Govindan RB, Rilk A, et al. Central oscillators in a patient with neuropathic tremor: evidence from intraoperative local field potential recordings. Mov Disord. 2011;26(2):323–7.

Weiss D, Mielke C, Wächter T, et al. Long-term outcome of deep brain stimulation in fragile X-associated tremor/ataxia syndrome. Parkinsonism Relat Disord. 2015;21:310–3.

Wertheimer P, Bourret J, Lapraz C. Apropos of the treatment of a dyskinesia by stereotaxic leucotomy. Rev Neurol. 1960;102:481–6.

Wishart HA, Roberts DW, Roth RM, et al. Chronic deep brain stimulation for the treatment of tremor in multiple sclerosis: review and case reports. J Neurol Neurosurg Psychiatry. 2003;74:1392–7.

Witjas T, Carron R, Krack P, Eusebio A, Vaugoyeau M, Hariz M, Azulay JP, Régis J. A prospective single-blind study of Gamma Knife thalamotomy for tremor. Neurology. 2015;85(18):1562–8.

Wolf ME, Capelle HH, Bäzner H, Hennerici MG, Krauss JK, Blahak C. Hypokinetic gait changes induced by bilateral pallidal deep brain stimulation for segmental dystonia. Gait Posture. 2016;49:358–63.

Wong JK, Cauraugh JH, Ho KWD, et al. STN vs GPi deep brain stimulation for tremor suppression in Parkinson disease: a systematic review and meta-analysis. Parkinsonism Relat Disord. 2019;58:56–62.

Yamamoto T, Katayama Y, Ushiba J, et al. On-demand control system for deep brain stimulation for treatment of intention tremor. Neuromodulation. 2013;16(3):230–5.

Yap L, Kouyialis A, Varma TR. Stereotactic neurosurgery for disabling tremor in multiple sclerosis: thalamotomy or deep brain stimulation? Br J Neurosurg. 2007;21:349–54.

Young RF, Li F, Vermeulen S, Meier R. Gamma Knife thalamotomy for treatment of essential tremor: long-term results. J Neurosurg. 2010;112(6):1311–7.

Zaaroor M, Sinai A, Goldsher D, Eran A, Nassar M, Schlesinger I. Magnetic resonance-guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. J Neurosurg. 2018;128(1):202–10.

Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2011;77:1752–5.

Chapter 22
Mechatronic Devices for Upper Limb Tremor

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Abstract Pathological tremor, such as parkinsonian and essential tremor, can significantly affect the quality of life of the individuals who suffer from it. Traditional medicines may be ineffective, induce side effects, and surgery is invasive with significant risks. The emergence of wearable technology has led to the externally worn mechatronic tremor suppression device as a potential alternative approach for tremor management. Although end users have not widely adopted wearable tremor suppression devices (WTSDs) due to the lack of commercially available devices, there is increasing evidence that these can suppress up to 99% of the user's tremor. There are four core components in the design of a WTSD. These are the motion sensing system, the tremor estimation/prediction algorithm, the actuation system, and the control system. In this chapter, each of the four core components is reviewed separately, followed by the state-of-the-art for WTSDs.

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22.1 Introduction

Advances in assistive technologies are revolutionizing the health care system. In particular, mechatronic devices are uniquely positioned to have a significant impact on the quality of care, as demonstrated by the surgical devices, wearable exoskeletons, and rehabilitation robots that have been developed in recent years. Mechatronics appears at the intersection of four engineering disciplines: mechanical, computer, electrical, and controls (Fig. 22.1). Although there are assistive technologies at the intersection of any two or three of these areas, the intersection of all four is what defines the term mechatronics as we know it today. The combination of these fields can be applied to the challenge of suppressing upper-limb tremor, leading to novel solutions that can be tailored to the characteristics of each individual.

There are two main types of pathological tremor that can be treated with wearable devices. These are Parkinsonian tremor (PT), associated with Parkinson's disease (PD), and essential tremor (ET), an isolated tremor disorder. For both PT and ET, a mechatronic system can be attached to the body, intelligently measure the tremorous motion, and act to suppress observed tremor in an effective manner. The individual components of a mechatronic system within a tremor suppression device are described below:

- The mechanical system corresponds to the physical device that is attached to the body to support motion. This can be, for example, a glove or a brace-like orthotic. It is defined by the number of degrees of mobility (active or passive)

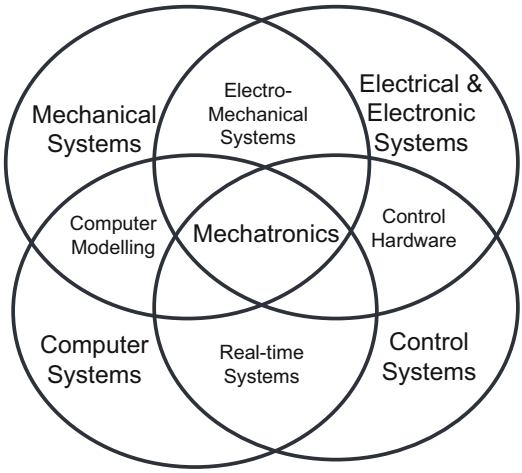

Fig. 22.1 Mechatronics lies at the intersection of four main disciplines

that it supports, the materials that it is made from, and the way that it is attached to the body.
- The electrical system has two key components: sensors and actuators. Sensors are used to measure motion (including tremor motion, voluntary motion, and the motion of the device itself), as well as other signals necessary to improve awareness and operation of the device, for example, muscle activity sensors or temperature sensors to tune the system. Actuators are used to produce the motion of the device, be it for suppressing tremorous motion or for tracking voluntary motion.
- The computer system is closely tied to the electrical system, and includes the data acquisition, filtering, and analog-to-digital conversion hardware, as well as any interface required for the user to communicate with the device.
- Finally, the control system determines appropriate actions based on the sensor data to provide the device with some form of autonomy. The more advanced the control system is, the more intelligent the device becomes, and the better it can adjust to the particular tremor characteristics of a user.

The motion of the upper limb is complex and unpredictable. Simple tremor suppression systems that do not adapt to each individual, or that are unable to distinguish tremorous motion from the user's intended motion, have been shown to be successful to a limited degree, but result in increased stress and fatigue for the wearer. The following sections will review in detail the state-of-the-art of tremor suppression mechatronic systems for the upper limb, focusing on the individual components as described above.

22.2 Tremor Signal Sensing and Estimation

22.2.1 Tremor Signal Sensing Technology

Sensors are one of the essential components of a mechatronic tremor suppression device. Their purpose is to detect physical changes in their environment, such as the device or the user, and transfer the information to the main controller. In most of the existing devices, biological signals of the users were measured as the first step of the tremor estimation process. Based on the nature of the signals, they can be categorized into biomechanical signals, such as joint motion and torque, and physiological signals, such as surface electromyography (sEMG) and electroencephalography (EEG).

Biomechanical signals refer to the outward mechanical information that is conveyed through human body dynamics, such as the acceleration, velocity, displacement, and force generated by a human joint. The sensors that are commonly used to measure biomechanical signals include inertial measurement units (IMU), encoders, potentiometers, and force sensitive resistors (FSR) (Fraden 2016). An IMU is a collection of measurement tools that consist of an accelerometer for

capturing linear acceleration, a gyroscope for capturing angular velocity, and/or a magnetometer for measuring the Earth's magnetic field for orientation. An encoder is an electro-mechanical device that converts the velocity and displacement of the human body into electrical signals that can be read by the control device. A potentiometer is commonly seen as a three-terminal resistor in which the position of one terminal is rotated or slid across a uniform resistance. Similar to an encoder, a potentiometer can directly measure positional information; however, this type of sensor has a limited range of motion and limited life due to wear. Lastly, an FSR is a resistor that changes its resistance according to the applied force. It is often used to measure the interaction force between a user's body and a mechatronic device.

Nguyen and Luu, in 2021, reviewed 13 existing mechatronic tremor suppression devices (Nguyen and Luu 2021). The majority of the devices incorporated IMUs to measure motion at the elbow (Case et al. 2015; Huen et al. 2016; Matsumoto et al. 2013), wrist (Case et al. 2015; Huen et al. 2016; Loureiro et al. 2005; Yi et al. 2019; Zahedi et al. 2021a, b; Zamanian and Richer 2019), and fingers (Zhou et al. 2018c, 2021), two devices incorporated force sensors (Herrnstadt and Menon 2016b; Herrnstadt et al. 2019), one device combined IMU and potentiometer sensors (Herrnstadt and Menon 2012), and one device combined IMU and force sensors (Rocon et al. 2007a). In addition to the 13 reviewed devices, Taheri (2013) and Herrnstadt and Menon (2016a) developed elbow tremor suppression devices that utilize encoders to measure the angular position/velocity. The use of these sensors does not require skin contact; hence, they are often integrated within a wearable tremor suppression device (WTSD). Although most of the existing WTSDs use biomechanical signals as the feedback modality to their control systems because the corresponding sensors are inexpensive, self-contained, compact, and allow flexible placement, the pitfall of using these sensors in a WTSD is that they can only measure tremor motion after the tremorgenic signal has reached the corresponding muscles from the cerebral cortex. This inherently causes a delay that a control system must be able to handle when suppressing tremor.

To address the issue above, physiological sensing may be used in a WTSD to measure the tremorgenic activities before the initiation of biomechanical activities. sEMG (Ando et al. 2012; Dideriksen et al. 2017; Dosen et al. 2015; Gallego et al. 2012, 2013a; Hao et al. 2017; Hosseini 2019; Jitkritsadakul et al. 2015; Maneski et al. 2011; Rocon et al. 2010; Widjaja et al. 2008, 2011; Zhang and Ang 2007; Zhang et al. 2011) and EEG (Gallego et al. 2012, 2013a; Rocon et al. 2010) are two commonly used signals in a WTSD that uses physiological sensing. sEMG is the measurement of the electrical activities of muscles at the surface of the skin. Conventionally, these signals are recorded by a pair of conductive electrodes that are placed over the muscle of interest. EEG is the measurement of the electrical activities produced in the brain and measured at the scalp (Ang and Guan 2016; Nazmi et al. 2015). Commonly, a large number of electrodes are used in one EEG headset to record signals across the cerebral lobe of interest and to provide higher spatial resolution. Due to the noisy nature of physiological signals, both recorded EMG and EEG signals are required to be conditioned, preprocessed, filtered, and amplified before they can be used by a control system (Merletti and Parker 2004).

The selection of sensing technology in wearable mechatronic devices is often limited by the application, e.g., the use of biomechanical sensing is viable if the user can produce motion in the joint of interest, and the use of physiological sensing is acceptable if the application does not have a strict requirement on control accuracy and computational complexity. To date, both sensing modalities have been used successfully in mechatronic tremor suppression devices. It has been shown that both the unwanted tremor activities and the user's voluntary activities can be measured using inexpensive commercially available sensors. This encouraging evidence provides a higher degree of freedom to researchers and manufacturers when choosing the optimal sensor(s) for a WTSD.

22.2.2 Tremor Estimation Techniques

Sensors enable a mechatronic device to perceive the world through the digitization of elements of the physical process with which it intends to interact. Although the information obtained through the sensors reflects the process, an algorithm is required to interpret the data. In the development of a mechatronic tremor suppression device, an intelligent algorithm is often used as part of the control system to distinguish tremorous motion from the voluntary motion of the user. This intelligent algorithm is often named a tremor estimator or tremor predictor.

Considering that the frequency of tremor is typically higher than the frequency of voluntary motion, classic filters, such as low-pass filters (Ando et al. 2012; Gonzalez et al. 1995; Riley and Rosen 1987) and high-pass filters (Herrnstadt and Menon 2012; Taheri et al. 2013b), were widely adopted by most of the early studies in the field that aimed prove the feasibility of suppressing tremor using mechatronic devices. These algorithms are computationally inexpensive and can be implemented on cost-effective microcontrollers; however, the drawbacks of these filters include the inherent phase delay and amplitude attenuation.

To reduce the estimation error caused by the above drawbacks, a number of techniques have been studied. For example, a pair of cascaded low-pass and high-pass Infinite Impulse Response filters (Ang et al. 2006) were proposed that compensate for the phase lag caused by the low-pass filter by introducing a phase lead through the high-pass filter. In another example, a backstepping-sliding mode control algorithm (Taheri 2013) was proposed to estimate the muscle torque, thereby reducing the time delay between the muscle torque, and the resulting tremor in the joint. Finally, an adaptive band-pass filter (Popović et al. 2010) that reduces the phase lag by updating the center frequency of the filter according to the input signals was also suggested. Since the tremor motion is often at a higher frequency than the voluntary motion, a notch filter has been used to suppress those signals at tremor frequency rather than all frequencies beyond a certain point (Avizzano et al. 1999; Hsu et al. 1996; Prochazka et al. 1992; Rocon et al. 2005a, 2007a). This results in lower distortion of the filtered signal. This type of filter works well on signals with fixed frequency; however, the frequency of tremor is time-varying, and therefore a

notch filter with a fixed frequency cannot capture the tremor motion without losing features.

Considering the drawbacks of the aforementioned filters, it is important to include adaptability in the design of a tremor estimator. A Fourier Linear Combiner (FLC) was proposed by Vaz et al. (Vaz and Thakor 1989; Vaz et al. 1994) based on the assumption that tremor can be simplified to a roughly periodic signal. This suggests that tremor can be modeled by a sinusoidal or Fourier series. The FLC estimates tremor based on a known frequency. The Least Mean Square (LSM) algorithm was incorporated to update the parameters of the estimator. It has a low computational workload (Vaz et al. 1994) and surpasses any common filter with its zero-phase feature (Vaz and Thakor 1989). Based on similar principles, an adaptive FLC-based Modified Least Mean Kurtosis algorithm (Mengüç 2021) was developed to improve the estimation accuracy; however, since tremor is not a periodic signal, the performance of this estimator was limited.

Based on the design of the FLC, Riviere et al. (1998) proposed a Weighted-frequency Fourier Linear Combiner (WFLC), which functions as an adaptive notch filter that adjusts the notch depth and notch frequency according to the input tremor signal. Specifically, this estimator was built on the FLC with a modified tremor frequency estimation using the LSM algorithm. Given that Riviere's WFLC only controls the notch depth and frequency, Nho (2006) developed an enhanced WFLC that also controls the notch bandwidth. Although these WFLCs have been proven to work, they do not consider directional couplings when used to estimate tremor in multiple directions. To address this issue, Adhikari et al. (2016) proposed and evaluated a quaternion-based WFLC. The use of the gradient descent algorithm allows the WFLC to adapt to the frequency and amplitude of tremor with zero-phase shift (Poulo 2008); however, it can only adapt to a single-harmonic signal without degrading its performance (Riviere et al. 2001; Zhou et al. 2016).

To overcome the drawbacks of the WFLC, Veluvolu et al. proposed a Bandlimited Multiple Fourier Linear combiner (BMFLC) (Veluvolu et al. 2007). The principle of the BMFLC for estimating signals with multiple frequencies is to incorporate multiple FLCs. Each FLC estimates a particular frequency band and the combination of all FLCs produces a reconstructed signal of the signal of interest. The main drawback of the BMFLC is that it requires prior knowledge of the frequency, and it works only on signals with fixed frequencies. To compensate for these drawbacks, Veluvolu et al. proposed a double adaptive BMFLC (Veluvolu et al. 2010), Wang et al. proposed an adaptive sliding BMFLC (Wang et al. 2014), and Atashzar et al. proposed an enhanced BMFLC (Atashzar et al. 2016). All of these modified BMFLCs possess the advantages of the BMFLC, and incorporate adaptive methods for the selection of the frequency band.

The FLC-based tremor estimators discussed above extract the tremor signal based on an estimate of the gradient of the mean square error using a truncated Fourier series with prior knowledge of the input signal, i.e., the tremor frequency range. In contrast, the Kalman Filter (KF) does not require any a priori assumption and it computes the optimal solution by minimizing the covariance of the a posteriori estimation error (Gallego et al. 2010). In addition, the KF is more robust for

nonperiodic motions, such as parkinsonian tremor. Recent studies on the use of the KF and its derivative algorithms have shown better accuracy in tremor estimation than the gradient descent methods. These include the extended KF (Bó et al. 2008), WFLC-KF (Gallego et al. 2010), the enhanced high-order WFLC-KF (Zhou et al. 2016, 2018b), the BMFLC-KF (Veluvolu and Ang 2011), wavelet decomposition coupled with an Adaptive Kalman filter (Shahtalebi et al. 2019b), and the least squares support vector machine Kalman filter (Dai et al. 2020).

Other than the above widely adopted tremor estimators, additional tremor estimators include the filtered-X least mean square algorithm (Ou 2012), Empirical Mode Decomposition and the Hilbert-Huang Transform (Zhang et al. 2008), Quaternion Variant for Extreme Learning Machines (Wang et al. 2018), and the Enhanced Moving Window Recursive Singular Spectrum Analysis-Extreme Learning Machine Algorithm (Adhikari et al. 2022).

The majority of the algorithms developed to date can only extract tremor signals from a known set of measured signals. The major limitation of these types of algorithms is the inherent time delay that they produce between the time when the signal is measured by the sensors, and the time when the tremor signal is extracted. This delay, together with the delay generated by the actuation system of a mechatronic tremor suppression device, makes it impossible to achieve zero-phase real-time suppression of the tremor motion. Therefore, to maximize the tremor suppression performance of a mechatronic tremor suppression device, the concept of tremor prediction is gaining interest among researchers. Shahtalebi et al. (2019a, 2020) developed a tremor predictor using a recurrent neural network, and Ibrahim et al. (2020, 2021) developed and tested several tremor predictors using different deep neural network models, including a one-dimensional convolutional-multilayer perceptron model (1D-CNN-MLP), a long-short term memory model (LSTM), a gated recurrent unit model (GRU), a bidirectional LSTM, and a bidirectional GRU. Both algorithms can predict tremor ahead of time to compensate for the time delay generated in the control system; however, their computational complexity is high, making them impractical to implement on a cost-effective microcontroller. This pitfall significantly limits the application of tremor predictors in a mechatronic WTSD, and it is expected to be a limitation until the capabilities of low-cost microcontrollers improve significantly, or cloud computing is utilized.

22.3 Actuation

Apart from the sensors, the other components of the electrical system of a mechatronic WTSD refer to the devices that produce motion to suppress the tremor, i.e., the actuators. This section will focus on both the mechanical actuation of the joints, and the direct stimulation of the muscles and sensory nerves to produce motion.

22.3.1 Mechanical Joint Actuation

The selection of the appropriate actuator is critical, since this will determine the amount of torque that the final design can deliver, the operating bandwidth, the efficiency, and the overall weight of the design. For tremor suppression, these properties, among many others such as speed, form factor, and actuation direction, all need to meet the design specifications and constraints of the desired application. Since actuators can be defined as any mechanism that can turn one form of energy into mechanical motion, choosing the right actuator for any unique set of design constraints is not a trivial task. Note that the type of suppression used to attenuate involuntary tremor harmonics can be classified into two groups: active and semi active.

Active suppression involves driving the actuator to actively oppose involuntary motion while supporting voluntary motion. These types of systems can provide additional forces to the system to supplement the forces produced by biological muscles. Semi-active suppression, on the other hand, does not produce any additional forces, but instead takes advantage of the energy dissipation properties of certain materials to increase the system's damping coefficient and absorb unwanted disturbances. The remainder of this section will describe some of the most common actuators used to provide both active and semi-active tremor suppression, as well as their advantages, disadvantages, and design considerations such as mounting location and mechanical transmission techniques.

Active Suppression

With active suppression, the actuator must be able to provide a mechanical torque to the targeted joint, which must overcome gravitational forces, resistance, and damping forces produced by the musculoskeletal system, and the muscular contractions caused by the tremor harmonics. The actuator must also be able to provide these opposing forces at frequencies at or above the typical voluntary motion frequency and the maximum tremor frequency.

Electric Motors

Electric motors are the most widely used actuator for tremor suppression since they can be operated at frequencies far exceeding that of pathological tremor. This, along with high positioning accuracy, allows for fast reaction times and highly effective and repeatable attenuation of involuntary tremor motion. Additionally, electric motors have relatively high efficiency, operate with low audible noise, have high power output, and are commercially available in many different specifications. One of the earlier designs utilizing electric motors, called the Wearable Orthosis for Tremor Assessment and Suppression (WOTAS), provided a tremor power reduction of 50% (Rocon et al. 2007a). The efficacy of these electric motor-based designs has since improved, where one design showed a 99.4% reduction in tremor power with only a 0.34% reduction to the voluntary motion component (Herrnstadt and Menon 2017).

Although electric motors possess many desirable characteristics, their torque and angular speed need to be matched to the joint specifications, which require a transmission system using either belts and pulleys, or gear trains. Additionally, the rigid form factor of both linear and rotary motors makes them difficult to couple to the complex surface geometry of the human body. Biological coupling is especially difficult with the cylindrical shell and rotational output of rotary motors since musculoskeletal systems are made up of compounded synovial joints that are comprised of complex internal structures such as bone ends, ligaments, and cartilage. In addition to this, their size can make them socially disconcerting, and studies have revealed that individuals are unwilling to wear bulky active devices due to these concerns. To date, the size, weight, and form factor, of electric motor-based tremor suppression devices has impeded clinical adoption (Fromme et al. 2019).

There are many examples of designs that implement reduction systems directly at the targeted joint using gears, which can not only be highly effective but can also make the system protrude far from the user's arm (Herrnstadt and Menon 2017; Rocon 2007a; Kiguchi and Hayashi 2013; Ando et al. 2012). As well, their rigid housing requires stiff mechanical joints that make their integration with soft human tissue difficult to achieve at an acceptable level of comfort. The addition of these mechanical components also increases the cost and complexity of the system, while adding volume and weight, which decreases the overall wearability. Because of this, it is difficult to design a system with electric motors that a user would want to wear every day; however, researchers have found ways to combat these drawbacks using tendon-based transmission systems.

Tendon-based transmission systems have been used to relocate the mass and bulk of the driving mechanisms to a more convenient location on the body. Typically, they would be placed away from the targeted joint, at a location that is supported by larger body parts. The Wearable Tremor Suppression Glove developed by Zhou et al. (2018a, b, c) and the Soft Exosuit by Kobayashi et al. (2021) are examples of designs that have implemented this feature with acceptable levels of tremor suppression. Positioning the actuator in this manner will typically reduce the weight placed on the supporting joints, thus reducing the strain on the wearer, while improving comfort and mobility. Another benefit of using tendon-based transmission is that the rotational output from the motor is converted into translational motion that can be connected to anchor points on the limbs connected to the joint. The cables used to drive the joints can also be tensioned to eliminate backlash that may be introduced by imperfections in gear or pulley reduction systems. However, to transfer mechanical power to the joint, the cables must pass through guides, which can add friction, thereby reducing efficiency and power output. Furthermore, if the cables need to pass through multiple joints to reach the target joint, then the movement of all joints can affect the final forces and displacements, which requires close attention when designing the control system.

Since tremor can affect multiple joints at once, it is desirable to actively control all affected joints simultaneously. However, due to the size, cost, and form factor or electric motors, adding and controlling multiple ones in parallel can be a complex problem to solve, and could add too much weight to a distal joint. Systems

that incorporate multiplexing are another example of electric motor development. For example, a multi-channel mechatronic splitter (MMS) can be incorporated to support multiple control outputs from a single input source (Zhou et al. 2017).

Pneumatic Actuators

Different from electric motors, pneumatic actuators utilize the high power-density of pressurized air to create motion, which can help to reduce the total weight of wearable devices. To achieve the necessary pressures, air compressors are used, which can be both bulky and noisy; however, these limitations can be mitigated by using pre-compressed air stored in high pressure tanks. Typically, pneumatic actuators are made from dual chamber metal cylinders that can be driven bidirectionally depending on which chamber is pressurized, such as those used in the design proposed by Taheri (2013). However, soft pneumatic actuators have been devised that make them more suitable for wearable applications.

McKibben-type pneumatic actuators are made from an inflatable inner tube situated inside a braided mesh and clamped at both ends. When the inner tube is pressurized, it expands inside the braided mesh. The geometry of the mesh translates the radial expansion of the tube into a linear contraction. This type of soft actuator has stress–strain profiles that are similar to human muscles, while being lightweight, easy to fabricate, and retaining the high power-density of traditional pneumatic actuators. Skaramagkas et al. utilized this type of soft pneumatic muscle connected to a tendon-based transmission system to suppress tremor in the fingers (Skaramagkas et al. 2021). One downside to their design is that the actuation can only be applied in a single direction, which limits the system's ability to suppress tremor. For this reason, they are typically found in an antagonistic configuration, providing bidirectional control of a joint.

Electroactive Polymers

Another noteworthy actuation method that could be used to suppress tremor includes the use of electroactive polymers (EAPs). There are various materials from which EAPs can be made, but dielectric elastomers are commonly used. The biggest advantages of EAPs are that they are relatively compliant and lightweight, allowing them to conform to the human body; however, these benefits come at the cost of low mechanical output strains, high excitation voltages, viscoelasticity, and low manufacturability. To make EAPs usable, the low output strains can be amplified by stacking multiple layers in series and then using closed loop feedback to eliminate the nonlinear viscoelastic effects (Kelley and Kauffman 2020). It is important to note that the results of current studies still require specialized equipment and non-standardized manufacturing techniques (Lidka et al. 2018). Although these actuators are still in the early stages of development in the realm of tremor suppression, further research may improve their feasible use in wearable applications.

Semi-Active Suppression

Contrary to active suppression, semi-active suppression uses materials that absorb unwanted disturbances. The damping magnitude of actuators used for semi-active tremor suppression can be actively adjusted to be much more effective than purely

passive mechanisms, which have fixed damping coefficients. Since all of the energy being put into the system comes from the contraction of biological muscles, it is unlikely that the wearer of a semi-active orthosis could hurt themselves. This simplifies the process of acquiring health and safety approvals. Examples of semi-active suppression actuation systems are presented below.

Magnetorheological Fluid Actuators

Magnetorheological fluids (MRFs) have been used in several designs as semi-active actuators (Yi et al. 2019; Loureiro et al. 2005; Zahedi 2021a, b). MRFs consist of magnetic particles suspended in oil that, when placed near a magnetic field, will clump together due to magnetic attractive forces, thus increasing the fluid's viscosity. The resistive and damping forces of an MRF actuator can be actively adjusted by controlling the magnetic field acting on the fluid. One study found that this method attenuated the magnitude of the tremor's angular velocity and acceleration by 61.55% and 61.68%, respectively (Zahedi 2021b).

Piezoelectric Actuators

Smart textiles utilizing the piezoelectric effect have also been considered for tremor suppression. Piezoelectric materials are made from ceramics that can generate energy when mechanically deformed but can also produce mechanical strain when supplied with an excitation voltage. This allows them to be used as both an energy harvesting mechanism and an actuator. Conventional piezoelectric ceramic materials are rigid and tend to be made in a block-like form factor, which limits their suitability for wearable devices. One study developed a piezoelectric fiber composite that could harvest the excess mechanical energy from the movement of the body while maintaining semi-active tremor suppression (Swallow and Siores 2009).

Smart Materials

Other popular smart materials that have potential for tremor suppression applications are shape memory alloys (SMAs) and twisted coiled actuators (TCAs), which rely on the thermal–mechanical properties of certain materials to contract. SMAs are made from metal alloys that can transition between two material states when heated. On the other hand, TCAs are made from polymer threads that have been tightly twisted into helical structures and contract when heated (Haines et al. 2014). Both are similar in terms of performance since they both rely on converting electrical energy into heat, and heat into mechanical force.

These thermally activated actuators have been shown to provide high power densities in a small, lightweight, and compliant package. However, due to the slow nature of heat transfer through these materials and the low efficiencies associated with the conversion of electrical heating and thermomechanical activation, their operating bandwidths and mechanical power capabilities are significantly limited when compared to conventional actuators such as electric motors. The operating bandwidths can be improved at the expense of efficiency, by operating these actuators in environments with lower thermal resistance and higher thermal capacitance. Some systems have been designed to actively control the flow of a fluid in an

enclosed environment to benefit from the enhanced thermal characteristics while conserving efficiency, albeit at the expense of greater complexity. Nonetheless, even with active cooling methods, the maximum operating frequency is still far lower than conventional electric motors in both SMAs and TCAs (Cheng and Desai 2015; Edmonds 2020; Daemi et al. 2021), and is not enough to effectively eliminate all types of tremors. It is possible that future implementations could utilize them to vary compliance to make tremor suppression devices that can automatically adjust their stiffness based on conditions that change infrequently, such as the ambient environment or to certain tasks that produce different tremor frequencies.

In this section, common actuators used for both active and semi-active tremor suppression in wearable devices were presented. Among the devices that employ active suppression, rotary electric motors are the most widely used. Their main disadvantage is that their output cannot be directly applied to human joints due to the complex arrangement of bones and tendons that create a moving axis of rotation. Additionally, the output of electric motors typically requires a gear reduction to increase torque, as well as a tendon-based transmission system that requires additional pulleys, all of which decrease the efficiency and increase the complexity of the system. On the other hand, due to their popularity, electric motors provide flexibility in terms of power output, so designs can be rapidly developed using off-the-shelf components and well-known control schemes. Among the actuators used in semi-active suppression, the most common are MRF actuators. This can be attributed to their ability to rapidly adjust their mechanical damping coefficient by generating an electromagnetic field. This method of semi-active suppression is inherently bidirectional, giving it a large advantage over smart materials that rely on antagonistic forces to operate effectively.

Overall, each type of actuator has a set of unique benefits that provide some advantages over others and have all shown effectiveness in tremor suppression. However, some disadvantages have rendered certain actuation methods unsatisfactory for use in wearable devices. For instance, pneumatic actuation requires a high-pressure source either in the form of a loud and bulky compressor or a high-pressure tank, both of which are impractical and pose a significant safety risk. Despite this, pneumatic actuators in the form of McKibben cables provide a significant advantage over electric motors by offering high power densities in a soft and flexible shell, making them a viable option for applications that permit an adjoining high-pressure source. Smart materials are gaining popularity due to their ability to directly deform without requiring a shell or casing, which allows them to provide adequate power density in a smaller form factor. However, each type of smart material has its own set of unique disadvantages that depend on the material properties and the method of transduction from the control input to the mechanical output. For instance, EAPs require high voltages to operate and output small total deformations, so designs implementing EAPs must include special considerations such as electrical insulation and mechanical limitations.

22.3.2 Actuation of the Muscles and Sensory Nerves

Despite the effectiveness of mechanical actuators for managing tremor, they tend to make the devices uncomfortable and have not gained acceptance among users. As an alternative, research has explored the development of tremor reduction techniques using electrical stimulation. Functional Electrical Stimulation (FES) uses modulated electrical signals to activate muscle fibers and produce a motion to suppress tremor. Co-contraction and out-of-phase stimulation are the two main strategies used to apply FES for tremor suppression. In both approaches, the stimulation intensity is above the motor threshold.

The co-contraction strategy is based on manipulating the target joint impedance by applying stimulation to a pair of antagonistic muscles, and therefore increasing the joint stiffness to counteract tremor. As the dynamic response of the muscle to tremor is comparable to a low-pass filter, the increased joint stiffness and viscosity decreases the cutoff frequency and consequently filters out the tremorous movement.

Grimaldi et al. (2011) and Gallego et al. (2013b) showed the usefulness of the co-contraction method for tremor suppression by achieving $35 \pm 9\%$ and $52.3 \pm 25.5\%$ tremor suppression levels, respectively. The second study concludes that FES can be useful for both ET and PD groups despite their different etiology and symptomatology (Gallego et al. 2013b).

From a straightforward on/off open-loop configuration strategy, Bó et al. (2014) concluded that tremor attenuation is not always immediate and clear, despite the simplicity of the method compared to other FES-based devices. Therefore, a prior adaptation and training phase may be necessary to improve suppression. Lastly, Jitkritsadakul et al. (2015, 2017), showed a reduction in the UPDRS score, peak amplitude and RMS value of the angular velocity in PD participants using the co-contraction strategy. These studies are summarized in Table 22.1.

Compared to the co-contraction approach, in the out-of-phase method, electrical stimulation is applied to the antagonist of the muscle that generates tremor. To be effective, the applied stimulation must have sufficient intensity to generate forces that oppose the tremor.

Several studies (Prochazka et al. 1992; Javidan et al. 1992; Gillard et al. 1999; Maneski et al. 2011) showed the effectiveness of the out-of-phase stimulation on participants with tremor using different control approaches. Further explorations conducted by Widjaja et al. (2011) and Dosen et al. (2015) aimed to compensate for electromechanical delays and improve the prediction of tremor. These studies used EMG signals for detection of tremor onset in advance, giving the system enough time to calculate and generate an appropriate stimulation for out-of-phase tremor suppression. Table 22.2 summarizes studies that use the out-of-phase method for tremor suppression.

While electrical stimulation with an intensity above the motor threshold has shown effectiveness in tremor reduction, several limitations are associated with this approach, such as muscle selectivity, non-adaptive control systems, and muscle

Table 22.1 Summary of studies using the co-contraction method for tremor suppression

Reference	Target muscles/joint	Participants	Detail(s)	Efficacy
Grimaldi et al. (2011)	Flexor carpi radialis, extensor carpi radialis, biceps and triceps	1 ET, 1 PD, 1 cerebellar syndrome	Constant frequency and pulse width, pulse intensity based on the subject's comfort	$35 \pm 9\%$ (Suppression ratio)
Gallego et al. (2013a, b)	Wrist	9 ET, 3 PD	Stimulation intensity adapted to the tremor frequency and amplitude in real-time	$52.3 \pm 25.5\%$ (Amplitude reduction)
Bó et al. (2014)	Wrist or fingers	10 ET	Joint with higher tremor amplitude selected for stimulation. Stimulation frequency: 40 Hz, Pulse width: 150 μs, pulse amplitude based on the patient's comfort and muscle contraction levels Results showed tremor amplitude reduction in eight subjects and no positive response in two subjects	$60 \pm 27\%$ (Average suppression ratio using the RMS of the tremor amplitude)
Jitkritsadakul et al. (2015)	Abductor pollicis brevis and interosseus muscles	34 PD	Constant stimulation frequency and pulse width, Pulse intensity below 20 mA	$49.6 \pm 38.89\%$ (Angular velocity peak amplitude) $43.8 \pm 33.2\%$ (RMS value for resting tremor)
Jitkritsadakul et al. (2017)		30 PD	Similar stimulation approach using a designed glove. Dividing participants into the glove and sham group ($n = 15$)	Reduction in UPDRS score

Table 22.2 Summary of studies using the out-of-phase method for tremor suppression

Reference	Target muscles/joint	Participants	Detail(s)	Efficacy
Prochazka et al. (1992); Javidan et al. (1992)	Triceps and biceps brachii	3 ET, 4 PD, 6 cerebellar syndrome	Using a closed-loop system to filter out the tremor motion with greater frequencies	ET: 73%, PD: 62%, CS: 38% (Amplitude reduction)
Gillard et al. (1999)	Wrist or finger flexor and extensor muscles	3 PD	Compared the performance of the proposed approach in (Prochazka et al. 1992) using analog and digital filters	84% digital, 65% analog (Mean attenuation ratio)
Maneski et al. (2011)	Wrist	5 healthy, 4 PD, 3 ET	Pulse width: 250 μs, pulse frequency: 40 Hz, pulse intensity was set to the minimal value that can produce full extension and flexion motion Variable number of pulses, controlled according to the tremor amplitude Used a multichannel system with adaptive sensor-driven control. Initial experiments on healthy individuals Tremor reduction in six out of seven tremor participants, with no improvements in one ET subject	67 ± 13% (Amplitude reduction)
Widjaja et al. (2011)	Wrist flexors and extensors	1 ET	Pulse width: 200 μs, pulse frequency: 25 Hz, pulse intensity: 23 mA Simple on-off control used	57% (Power reduction ratio)
Dosen et al. (2015)	Wrist and finger flexors and extensors	2 ET, 4 PD	Stimulation above motor threshold	60% ± 14% (Suppression ratio

fatigue due to the artificially induced contractions. Results from (Dosen et al. 2015) showed that stimulation below the motor threshold can manipulate and reduce tremor. An average tremor reduction of $42 \pm 5\%$ was achieved for five participants in this study when using sensory stimulations. While these results are promising for reducing muscle fatigue, inconsistency in tremor suppression suggested that further studies were required. Therefore, other studies focused on the effect of low-level stimulations and the relationship between the activation of afferent pathways and tremor generation and reduction. The underlying neurophysiological mechanism of tremor suppression using sensory stimulation is still unclear; however, the hypothesis is that activating sensory afferent pathways may generate a response in the central nervous system (CNS) that modulates the tremor motion.

Following the study from Dosen et al., other researchers studied the effectiveness of sensory stimulation in wrist tremor suppression using surface and intramuscular electrodes (Dideriksen et al. 2017; Muceli et al. 2019; Pascual-Valdunciel et al. 2021), and the stimulation of cutaneous afferents in participants with PD (Xu et al. 2016; Hao et al. 2017). Heo et al. achieved tremor reduction for postural and action tremor in ET participants during and within 5 minutes after the sensory stimulation, while inconsistent results were achieved with resting tremor in PD participants and patients with scans without evidence of dopaminergic deficits (SWEDDs) (Heo et al. 2015, 2016, 2018, 2019). Further work in four studies led by Delp (Lin et al. 2018; Pahwa et al. 2019; Isaacson et al. 2020; Yu et al. 2020), studied the effect of stimulation of the wrist median and radial nerves in ET participants. Lastly, in another study by Kim et al. (2020), variable tremor suppression results with different stimulation parameters suggests the need for an optimization algorithm to obtain stimulation parameters. Table 22.3 summarizes the above-mentioned studies, which use sensory stimulation methods for tremor suppression.

Another method for tremor reduction found in the literature is the use of mechanical vibration. Kazi et al. (2010) developed a vibration glove using piezoelectric actuators to suppress PD postural tremor. Even though the experimental results showed tremor reduction, the small sample size is insufficient to validate the method.

In another study, Lora-Millán et al. (2019) achieved inconsistent results by activating afferent pathways using mechanical vibration and therefore, concluded that the method could not systematically suppress tremor in subjects with ET. Lastly, Liu et al. (2020), used the phenomenon of tonic vibration reflex (TVR)—defined as the involuntary sustained contraction of the stimulated muscle using vibration stimulation and reciprocal relaxation of its antagonist muscle—to generate a counter-phase motion of the ET for tremor reduction. In three experiments on healthy individuals, the group showed that the method can generate the counter-phase motion of the periodic pronation-supination motion; however, the study did not provide any support for tremor suppression in real subjects with ET. Table 22.4 summarizes studies that have investigated vibration methods for tremor suppression.

Table 22.3 Summary of studies using sensory stimulation methods for tremor suppression

Reference	Target muscles/joint	Participants	Detail(s)	Efficacy
Dosen et al. (2015)	Wrist and finger flexors and extensors	2 ET, 4 PD	Stimulation below motor threshold	42 ± 5% (Suppression ratio)
Dideriksen et al. (2017)	Wrist flexor/extensors	4 ET, 5 PD	Used intra-muscular and surface electrodes Variable stimulation intensity, Pulse frequency: 100 Hz, pulse width: 400 μs Effective tremor suppression in six participants	52% (Average suppression level based on the joint angle)
Muceli et al. (2019)	Wrist flexor/extensors	3 Healthy, 2 ET, 4 PD	Same strategy as (Dosen et al. 2015) for sensory stimulation and data recording Used a newly designed multichannel intramuscular electrode Results for tremor suppression are only for one PD subject	58% (Average suppression level based on the joint angle)
Pascual-Valdunciel et al. (2021)	Wrist flexor/extensors	9 ET	Using intramuscular electrodes from (Muceli et al. 2019) Two stimulation strategies used and compared Tremor power used to calculate tremor score for reporting the suppression level Prolonged tremor reduction resulting from the sensory stimulation was observed in four patients	32% with selective and adaptive timely stimulation.
				No improvement with continuous stimulations.

(continued)

Table 22.3 (continued)

Reference	Target muscles/joint	Participants	Detail(s)	Efficacy
Heo et al. (2015, 2016, 2018, 2019)	Flexor Carpi Radialis, extensor carpi radialis, Biceps brachii, and triceps brachii	18 ET, 14 PD, 9 SWEDD	Pulse frequency:100 Hz, pulse width: 300 μs 50–71% of PD participants showed a decrease in tremor amplitude No significant tremor reduction among SWEDD participants	ET: (RMS average) During stimulation: MP: 60%, Wrist: 40% After 5 minutes: MP: 67%, Wrist: 45% PD (Hand tremor reduction ratio) During stimulation: 62.1 ± 20% After stimulation: 58.6 ± 29.9%
Xu et al. (2016)	Superficial radial nerves	2 PD	Stimulation to the dorsal side of the hand, near the MP joint of the index finger, using a stimulation amplitude of 1.5–1.75 times the radiating threshold Tremorous motion monitored for 5 seconds before, during, and after stimulations	Verification only
Hao et al. (2017)		8 PD	61.56% (peak spectral amplitude) 47.97% (EMG)	
Lin et al. (2018)	Median and radial nerves at the wrist	23 ET	Calibrated stimulation frequency based on the participant's tremor frequency Treatment group ($n = 10$) Stimulation duration: 40 minutes	60 ± 8.4% Tremor amplitude
Pahwa et al. (2019)		77 ET	Treatment group ($n = 40$)	49% BF-ADL score (subject-rated Bain and Findley Activities of the Daily Life)

Isaacson et al. (2020)		205 ET	Evaluated the effect of this neuromodulation therapy over the long term, using a repeated therapy protocol at home for 3 months Tremor reduction for 92% of patients, with 54% of patients experiencing improvements in tremor power of more than 50%	62% TETRAS 68% BF-ADL scores
Yu et al. (2020)		15 ET	Studied the duration of tremor reduction after the treatment session	Tremor reduction effect lasts for at least 60 minutes after the therapy for 80% of participants.
Kim et al. (2020)	Wrist (radial nerve)	9 ET	Design and development of a wireless wearable device Using an open and closed loop stimulation system, with multiple sets of parameters	$42.17 \pm 3.09\%$, (tremor power reduction rate)

Table 22.4 Summary of studies using vibration methods for tremor suppression

Reference	Target muscles/joint	Participants	Specification(s)	Efficacy
Kazi et al. (2010)	Wrist	1 PD	Used three different vibration frequencies	7 Hz: 34.50% 8 Hz: 63.39% 9 Hz: 76.16% (From displacement signal results)
Lora-Millán et al. (2019)	Fingers, the back of the hand, below the wrist and below the elbow.	18 ET	Stimulation frequencies ranging from 50 to 450 Hz	Increase in tremor amplitude for 50–72% of cases, and reduction in 5–22% of the patients, depending on the strategy
			Seven piezoelectric actuators were used	
Liu et al. (2020)	Wrist pronation/supination	5 healthy subjects	Three experiments conducted to investigate the idea, and compared ET tremor with generated vibrations	No support for tremor suppression in real subjects with ET

22.4 Control Systems

As presented in previous sections, mechatronic tremor suppression devices work by exerting a controllable force on the target joints (Rocon et al. 2007b; Taheri et al. 2014). This complex task requires determining the necessary power delivery, modeling the geometry of the human upper limb, and computing the required force for tremor suppression. Furthermore, since the tremor motion needs to be reduced with minimal resistance against the user's voluntary movements, not having a priori knowledge of the user's voluntary movements increases the difficulty of developing a suitable control system in comparison to traditional stabilization or tracking control methods.

Although several studies have been conducted to develop tremor suppression algorithms for different orthoses, qualification methods for suppression effectiveness have not been standardized in the literature, making it harder to compare the performance of control systems that have been used in proposed suppression algorithms. A review of wearable technologies for tremor suppression and the different metrics used to validate these devices has been conducted by Lora-Millán et al. (2021). However, in most of the literature, the performance of the control systems was evaluated by considering the spectral and temporal metrics of the suppression systems (Herrnstadt and Menon 2016b).

This section reviews the control systems developed for several wearable technologies that manage upper limb tremors by adjusting limb biomechanics or applying counteracting forces. A general block diagram that outlines a typical closed-loop controller used for WTSDs is shown in Fig. 22.2.

Early research evaluated the application of viscous resistive forces to the upper limb to reduce tremor motions by considering various levels of velocity-dependent force feedback (Morrice et al. 1990; Arnold et al. 1993; Rosen et al. 1995). These nonadaptive systems did not employ quantitative performance criteria during the design of the feedback control system. Instead, they dealt with the question of

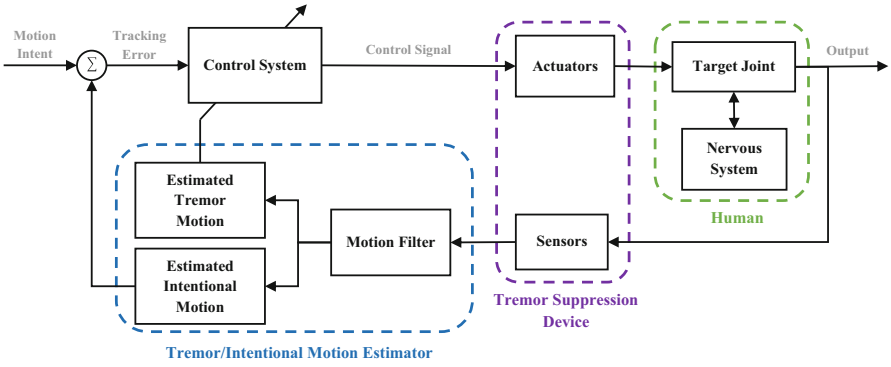

Fig. 22.2 The general block diagram of closed-loop control systems for tremor suppression

whether velocity-dependent resistive forces (damping) could effectively attenuate tremorous motions, without worrying about causing a statistical reduction of voluntary movements.

Impedance control systems have been considered as a practical strategy to alter the frequency response of human–machine systems given that closed-loop systems have a higher impedance in the high-frequency region (Pledgie et al. 2000; Hashemi et al. 2004). The impedance of a system consists of stiffness, damping, and inertia characterized by a second-order model that includes all of the components that affect the biomechanical characteristics of tremor in the upper limb (Hogan 1984; Adelstein 1981). Pledgie et al. (2000) designed an impedance controller to attenuate pathological tremor power in the forearms using a PHANToM manipulator. The impedance controller modified the frequency response of the human–machine system by considering position, velocity, and acceleration feedback in a kinetic model of the system. The performance of the impedance controller was highly dependent on the accuracy of the human–machine kinetic equations and the required feedback states of the systems. In 2007, Manto et al. implemented an impedance control strategy on a wearable orthosis to evaluate essential tremor suppression in the elbow and wrist. They used an error cancellation algorithm to discriminate the tremorous component from voluntary motions in real time. The results showed that employing tremor estimation algorithms, such as the WFLC algorithm, instead of direct sensors, can increase the performance of the impedance controllers; however, the controllers remain sensitive to the kinetic model of the system. Furthermore, under high tremor attenuation ratios, intentional motions are adversely affected by the orthotic devices.

Rocon et al. (2007a) developed two control strategies, one passive and one active, for the WOTAS robotic exoskeleton. Specifically, the control strategies were (i) an impedance controller to change the stiffness, damping, and mass properties of the upper limb to counteract tremor motions (passive), and (ii) notch filtering at the tremor frequency based on noise cancelation techniques (active). In both control strategies, tremorous motions were identified and distinguished from intentional movements in order to establish an appropriate physical interaction for adjusting the combined human–exoskeleton articular impedance or to apply forces to oppose the tremor. Note that the tremor force, position, velocity, and acceleration were needed for implementation of both control strategies. In testing, WOTAS showed a 40% tremor power suppression in wrist flexion/extension and pronation/supination, and in elbow flexion/extension. A detailed analysis of the results demonstrated that the active controller had a higher level of tremor suppression compared to the passive one.

A robust controller that applies the backstepping method to compute an appropriate torque value in a tremor suppression orthosis for the wrist joint was introduced in (Taheri et al. 2011b). The goal of the tremor suppression algorithm was to attenuate motions with frequencies higher than 3 Hz (tremor motions) as disturbances, without affecting voluntary movements with frequencies lower than 2 Hz. However, the proposed suppression algorithm showed undesirable phase lag over voluntary motions due to the use of a robust stabilizer to suppress any movement with a

frequency over 3 Hz. To deal with this problem, a procedure was proposed in (Taheri et al. 2013b) to tune some relevant parameters in order to reach the desired tremor energy suppression level, while reducing the impact on voluntary movements as much as possible. In addition, a band-pass filter was added to the output of the robust stabilizer to compensate for the undesirable closed-loop phase lag in the frequency range of intentional motions. A kinetic model of an arm joint was calculated by considering the joint stiffness and damping parameters. To estimate the tremor motions in the feedback term, a high-pass filter was used, in which the output of the system was stabilized by a recursive design procedure based on the backstepping technique. Finding suitable parameters during the tuning process to meet closed-loop stability criteria and provide the required suppression torque is one of the main challenges in designing the backstepping control system. Note that the global asymptotic stability of the robust controller was investigated using the Lyapunov method (Liapunov 1892). It was demonstrated that the proposed controller is robust against parametric uncertainties and unmodeled nonlinear terms of the kinetic model. The experimental results (Taheri et al. 2013b) showed a 97.5–99.2% reduction of tremor motions with minimal impact on voluntary movements.

In another study, an adaptive tremor suppression algorithm was proposed by Taheri et al. (2014) to compute the forces that needed to be applied to the arm by pneumatic actuators while estimating fundamental tremor frequencies instead of tremor motions. The proposed adaptive algorithm components included a tremor suppression controller, a tremor frequency estimator, and a pneumatic actuator module. The tremor suppression controller required the joint angular velocity and the fundamental tremor frequency estimated in real time by the tremor frequency estimator to apply an equal and opposite tremor muscle torque. In the pneumatic actuator module, a sliding mode integral controller was used to control pneumatic actuators (Khalil 2002) and to calculate the desired force of the actuators as a function of the desired tremor suppression torque and the orthosis geometry. The closed-loop stability was evaluated for a range of joint damping and stiffness values by considering the closed-loop poles and the positive correlation between the joint damping and stiffness (Flash and Mussa-Ivaldi 1990; Stroeve 1999). The mean resistance force to the voluntary movement was 0.7 N, while the mean position error was 2.08%. The testbench results of the adaptive algorithm showed a 98.1% tremor reduction for datasets from ten patients with ET or PT (Taheri et al. 2014). In contrast with impedance controllers, the proposed adaptive algorithm did not require an accurate kinetic human–machine system model and could be robust against parametric uncertainties of the model.

As'arry et al. (2013) examined a hybrid proportional-integral (PI) with active force control (AFC) strategy for improving hand tremor suppression. To design the hybrid controller, an iterative learning control method was incorporated into the active force control to estimate the inertial and mass parameters of a dummy hand model. Note that the AFC theory (Johnson 1971; Davison 1976) is based on the principle of invariance and Newton's second law of motion, which guarantees the stability and robustness of systems, even in the presence of disturbances or adverse operating conditions. The main drawback of this control theory is the calculation

of the estimated inertia matrix required in the AFC feedforward loop; however, in 1998, Mailah demonstrated the effectiveness of using a learning algorithm as an online parameter estimator for AFC (1998; Priyandoko et al. 2009). Thus, the intelligent AFC designed for tremor reduction by As'arry et al. continuously computes the estimated inertia matrix of the hand using an appropriate learning algorithm. The intelligent AFC forces a suppression device to execute voluntary movements accurately even in the presence of tremor motions. The integral absolute error (IAE) was used to evaluate the performance of the proposed controller. The experimental results showed that the hybrid PI with intelligent AFC decreased hand tremor by 98.25%, compared to the benchmark PI controller (92.47%) and a PI controller with AFC (97.59%). The main concern about the proposed controller for tremor suppression devices is that it is susceptible to instability due to over learning.

Herrnstadt and Menon (2016b) designed an admittance controller cooperating with a velocity control system to approximate intentional movements and remove any disturbance. The control system was comprised of an outer admittance feedback loop and an inner velocity feedback loop, while a state feedback loop was added to enhance the velocity tracking. The admittance and speed controllers utilized a proportional-integral-derivative (PID) controller and a PI controller, respectively. The main goal of the control system was to track a zero force in order to minimize the measured interaction force between the human and the mechanical suppression orthosis (Duchaine et al. 2012). The performance of the admittance control system was compared with two impedance controllers presented in (Taheri et al. 2014; Hashemi et al. 2004) through the Power Spectral Density (PSD) of the velocity signal. The selected attenuation performance metric was the ratio of the signal power with and without suppression. The experimental results on a benchtop tremor simulation device demonstrated a 99% reduction of the tremor signal while less than a 0.2% impact on the intentional movement was reported.

Shamroukh et al. (2017) compared two different control strategies to evaluate the performance of intelligent controllers for a semi-active orthosis to reduce pathological tremors. In that study, a PI controller was considered as a benchmark to investigate the feasibility of a fuzzy logic PID controller (Lee 1990). An experimental setup was used to simulate a tremorous forearm in order to collect data for system modeling using the MATLAB System Identification Toolbox. A second-order transfer function obtained from the system identification was used as the plant in MATLAB/Simulink. Then, several fuzzy rules were established to tune the fuzzy logic PID controller gains, aiming to reduce velocity errors in the joint. Finally, the two integral square error (ISE) and IAE metrics were selected to investigate the fuzzy logic PID controller performance compared to the PI controller. Although the fuzzy logic controller showed better performance in suppressing tremor motions, the stability of the controllers was not discussed.

A model-based controller was proposed (Wang and Barry 2020) to reduce tremor in the coupled wrist flexion–extension and radial-ulnar deviation motions by considering the kinematics and dynamics of a tremor alleviating wrist exoskeleton (TAWE). The proposed control system consisted of two nonlinear feedforward and feedback control terms to modify the inertia and internal forces of the system. To

this aim, modeling of the kinetic equations and necessary control conditions of the TAWE was conducted. A kinematic model estimator was used in the feedback control term, approximating the Jacobian matrices of the system states to control the forces exerted by the TAWE on the wrist. The control framework included voluntary motion-filtering algorithms in the feedback term to serve as reference inputs to the control system. The performance of the active model-based controller was compared to a passive proportional-derivative (PD) controller. Although the results showed that the proposed controller had better performance, uncertainties in the model resulted in the tremor not being entirely suppressed. It should be mentioned that the functionality of the TAWE and the performance of the proposed control system were significantly affected by the accuracy of the wrist kinematics.

22.5 State of the Art: Wearable Mechatronic Tremor Suppression Devices

The components reviewed in previous sections come together as mechatronic tremor suppression devices, such as the one presented in Fig. 22.3. These are complex systems that incorporate a sensing system, a tremor estimation algorithm, a control system, an electronic system, an actuation and transmission system, and a user interface. Due to the side effects of traditional treatments and facilitated by the development of mechatronic technology, mechatronic tremor suppression devices have become a promising alternative approach for tremor management.

Tremor suppression technology that utilizes mechanical loading is the most popular and studied technology, which can be classified into three categories, as out-

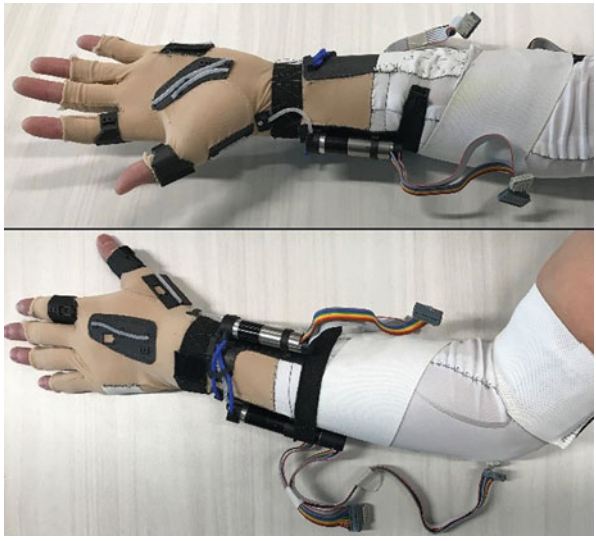

Fig. 22.3 A wearable tremor suppression glove (Zhou et al. 2021) that suppresses tremor the index finger metacarpophalangeal (MCP) joint, the thumb MCP joint, and the wrist

Table 22.5 Existing WTSDs that use the mechanical loading method

Research group	Supp. type	Supp. mechanism	Target joint(s)	Supp. ratio	Weight (kg)
Pons et al.	Active	DC motor	WFE, FPS, EFE	40% (P)	0.85
Fujie et al.	Active	DC motor	EFE	50–80% (A)	0.41
Richer et al.	Active	Pneumatic actuator	WFE, FPS, EFE, WRD	98.8% (P)	0.38
Kalaiarasi et al.	Active	Pneumatic actuator	WFE, WRD	30% (A)	N.R.
Menon et al.	Active	DC motor	EFE	99.8% (P)	0.88
Huen et al.	Active	DC motor	WFE, FPS	77% (A)	0.35
Zhou et al.	Active	DC motor	IFFE, TFE, WFE	60–85.5% (P)	0.58
Awantha et al.	Active	Layer jamming actuator	IFFE	78.3% (A)	N.R.
Skaramagkas et al.	Active	Pneumatic artificial muscles	IFFE, WFE	89% (A)	0.43
Richer et al.	Semi-active	Magnetorheological damper	EFE, FPS, WRD, WFE	96.3% (P)	N.R.
Loureiro et al.	Semi-active	Double viscous beam	WFE, WRD	98% (P)	0.38
Hernstadt et al.	Semi-active	Electromagnetic brake	EFE	88% (P)	0.94
Yi et al.	Semi-active	Magnetorheological damper	WFE	60.4% (A)	0.26

Note that WFE, FPS, EFE, WRD, IFFE, and TFE stands for wrist flexion–extension, forearm pronation–supination, elbow flexion–extension, wrist radial deviation, index finger flexion–extension, and thumb flexion–extension. "P" indicates tremor power suppression ratio, and "A" indicates tremor amplitude suppression ratio. Information not reported is labeled as N.R.

lined in Sect. 22.2.1, i.e., active suppression, semi-active suppression, and passive suppression. The features of these devices are listed in Table 22.5. The evolution of mechatronic tremor suppression devices developed with these modalities are presented in chronological order in Fig. 22.4.

The mechatronic tremor suppression devices that use an active suppression strategy create a dynamic interaction between the device and the user. These devices often use actuators that can produce motion and force by electric current, pneumatic pressure, or hydraulic fluid pressure. Pons et al. (Belda-Lois et al. 2007; Rocon et al. 2004, 2005a, b, 2006, 2007a, 2014; Rocon and Pons 2011; Manto et al. 2007) developed a three degree-of-freedom (DOF) WOTAS. This device employs both active and passive suppression strategies using electric motors to suppress tremor with minimal impact on the user's voluntary motion. WOTAS supports tremor suppression in the directions of elbow flexion–extension, forearm adduction–abduction, and wrist flexion–extension. Validation of the WOTAS was conducted on 10 individuals living with tremor with an average suppression in the tremor power of 40%. The total weight of the WOTAS is 0.85 kg.

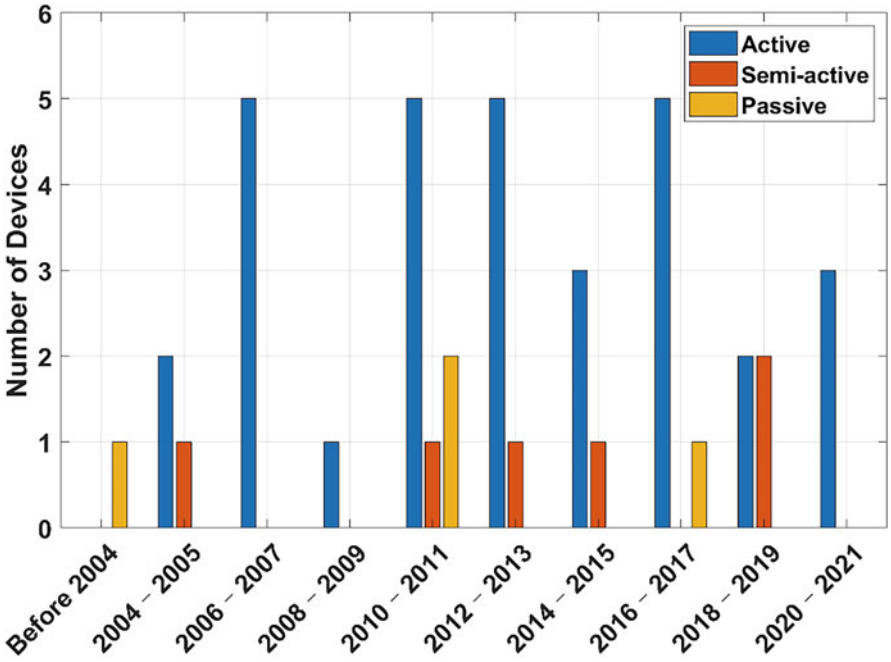

Fig. 22.4 Chronological development of upper-limb mechatronic tremor suppression devices

Fujie et al. (Ando et al. 2009, 2012; Seki et al. 2011a, b) developed an active elbow tremor suppression exoskeleton device that suppresses tremor using an electric motor. This device estimates elbow tremor in the direction of flexion–extension using EMG signals acquired from the user's biceps and triceps. The total weight of the device is 0.33 kg. Although the device has been developed, no efficacy study has been conducted to evaluate the performance of this device when suppressing tremor. Following the development of this device, a second prototype (Matsumoto et al. 2013, 2014) was developed by the same research group to improve the wearability of the first prototype. A change in the mounting mechanism of the device increased the total weight to 0.41 kg. The prototype was tested on one subject with ET and showed a 50–80% reduction in the tremor amplitude.

Richer et al. (Taheri et al. 2011a, 2013a, 2014; Taheri 2013) investigated the use of pneumatic cylinders for suppressing wrist tremor in the directions of flexion–extension and radial–ulnar deviation. The control system was tested on a benchtop setup with 10 recorded tremor datasets. The result showed an average of 98.8% reduction in tremor power. Similarly, Kalaiarasi and Kumar (2018) introduced a two-DOF tremor suppression device assisted with a pneumatic mechanism. In comparison with the pneumatic tremor suppression device developed by Richer's group, the tremor amplitude was only suppressed by 30%. Zamanian and Richer (2017) also proposed another tremor suppression device that uses a permanent

magnet linear motor. This device is lighter in weight (0.315 kg), and it does not require a compressed air source. The benchtop validation showed an average of 97.6% reduction in tremor power.

Herrnstadt and Menon (2016a, b, 2017) developed an active elbow tremor suppression orthosis that suppresses elbow tremor using electric motors with a gear transmission system. This device was tested on a benchtop setup with a recorded elbow tremor signal in the direction of flexion–extension. The result showed a 99.8% reduction in the tremor power. The total weight of the device is 0.875 kg.

Lastly, Huen et al. (2016) proposed a two DOF forearm robotic device for suppressing tremor in the directions of forearm pronation–supination and wrist flexion–extension. This device was validated on six healthy volunteers with simulated tremor motion generated by mechanical vibration. The results showed an average of 77% reduction in tremor amplitude. The total weight of the device including the electric motors is 0.35 kg.

A recent study (Zhou et al. 2018a, b, c) on the use of mechatronic devices for tremor suppression concluded that it is not enough to suppress tremor only in the proximal joints, such as the elbow and the wrist, but that it is also necessary to suppress tremor in the fingers, as it found that applying mechanical suppression to the proximal joints would increase the magnitude of tremor in the distal joints. Following this finding, Zhou et al. (2018a, b, c, 2021) developed a wearable tremor suppression glove that suppresses tremor in the thumb metacarpophalangeal (MCP) joint, index finger MCP joint, and the wrist using brushless DC motors. This glove was tested and assessed on a participant living with parkinsonian tremor. This study showed an overall suppression of 80.7%, 73.1%, and 85.5% in resting tremor; 79.5%, 70.2%, and 81% in postural tremor; and 58.7%, 60.0%, and 65.0% in kinetic tremor in the thumb MCP joint, the index finger MCP joint, and the wrist, respectively. The total weight of this glove is 0.58 kg. Awantha et al. (2020) designed and evaluated a soft glove for suppressing finger tremor using layer jamming actuators. The performance of the soft glove was evaluated on a simulated tremor generator. A maximum of 78.32% tremor reduction was obtained. Finally, Skaramagkas et al. (2020) developed a soft exoskeletal glove for suppressing essential hand tremor using pneumatic artificial muscles. The experimental evaluation achieved an 89% reduction in tremor amplitude. The total weight of the prototype was 280 g when it was configured to suppress tremor in the index finger and 430 g when configured for wrist tremor.

In addition to active suppression devices, a semi-active mechatronic tremor suppression device applies a controllable damping force to the target joint. Since this strategy does not generate motion of the target joint, it is considered safer than the active strategy. Richer et al. (Case et al. 2011, 2015) developed a semi-active tremor suppression device using magnetorheological dampers (MRDs). The MRD compensates for the drawbacks of conventional dampers by using MRFs to actively control the damper viscosity. The concept of the proposed device includes suppression of elbow flexion–extension, forearm pronation–supination, wrist ulnar–radial deviation, and wrist flexion–extension. A benchtop validation with 10 tremor datasets showed an average of 96.3% and 74.3% reduction in the tremor's first and

second harmonics, respectively. Loureiro et al. (2005) tested the feasibility of the proposed device on one subject with tremor. This study achieved a 98% tremor suppression rate in the direction of wrist flexion–extension. In addition, Herrnstadt and Menon (2012) validated a semi-active elbow suppression brace on three healthy volunteers with simulated tremor. The result showed an average 88% reduction in tremor power. Lastly, Yi et al. (2019) developed a wrist tremor suppression device using an MRD. The total weight of the system is 262 g and the maximum tremor reduction ratio is 60.39%.

In comparison with the active and semi-active suppression devices, passive suppression technology applies constant damping force to the target joint(s) using mechanical damper(s). This type of technology does not require a tremor suppression device to incorporate a sensing system, control system, electronic system, or power source. Therefore, a tremor suppression device that uses passive suppression technology is not considered to be a mechatronic device.

While the application of mechanical loading to suppress tremor has been the major technique used in available mechatronic tremor suppression devices, other techniques have been explored as well, such as using mechanical vibration. LeBlanc (2005) and Lavu and Gupta (2009) developed and validated two vibration-based tremor suppression devices. The proposed vibration devices were controlled to vibrate at a fixed frequency to counterbalance the tremor generated by a simulator. Although the results of both studies indicated that the use of vibration can reduce the magnitude of the simulated tremor, the vibration suppression systems of both studies were fixed to the ground and may not achieve the same level of performance when the vibrator is worn by a human. Therefore, the use of mechanical vibration in a WTSD still requires further validation.

22.6 Discussion: Challenges and Opportunities

As demonstrated by the work reviewed in the preceding sections, mechatronic devices can be used to provide an effective treatment for pathological tremor in the upper limb. While there has been some demonstrated success, the approach is still quite new. Most devices have focused on the larger joints of the elbow and wrist, with only a handful addressing the complexities of treating tremor of the fingers, and none are able to suppress tremor of the entire upper limb. Further, the majority of devices have only been tested on a small number of individuals. None have made the transition from the lab to become commercially available and therefore cannot yet benefit the millions of individuals who suffer from PT or ET.

At the core, effective tremor suppression requires good data, robust control algorithms, and responsive actuators. To be a useful aid throughout the day, the device itself must be compact, lightweight, comfortable, and able to control tremor in enough joints that activities may be conducted with ease. The ergonomics of the device are particularly important. Existing designs meet some of these requirements;

however, there are many opportunities for further exploration and refinement of the technologies, techniques, and systems that comprise WTSDs.

To start, the integration of multiple sensing modalities may be used to obtain a better understanding of the device operation, the user, and the environment than is possible with the biomechanical or physiological signals that are used by existing devices. The additional data may reflect features that can be used to develop improved tremor estimation and prediction techniques and more robust controllers. Given that existing tremor estimation algorithms extract the tremor signal based on the frequency difference from the voluntary motion, they are ineffective for voluntary motion that is closer in frequency to the tremor frequency, such as playing a musical instrument. Additional tremor features may help to extend the range of voluntary motions that can be accommodated. Developing motion estimation algorithms to distinguish tremorous motions from voluntary human movements efficiently and robustly is critical to improved suppression performance. Further, more comprehensive kinematic and kinetic models of the human–machine system (Daemi et al. 2020) will enable impedance and intelligent control strategies to adapt to the inertia and internal dynamic properties of the system better.

The challenge with increasing the amount of sensor data and implementing improved tremor estimation and prediction algorithms is that computational resources, particularly those found in embedded devices, are a currently a limiting factor. Determining optimal sensor combinations and sampling rates, combined with the development of more efficient algorithms, will help to mitigate this issue.

The choice of actuator used for a WSTD has a significant impact on its size, weight, and ability to adequately generate the motions and forces necessary to suppress tremor. Unfortunately, none of the currently available actuators offer the right combination of power output and form factor. Electric motors used in combination with a tendon-based transmission system are effective for tremor suppression but are still too bulky, while newer actuators suffer from low power output or poor response times. The use of direct electrical stimulation holds some promise as a compact alternative; however, further work is required to manage the muscle fatigue and discomfort that results from extended periods of tremor suppression. One avenue for exploration is a device that combines mechanical actuation and FES to balance the strengths and weaknesses of each approach. Overall, the development of new actuation technologies has the potential to have the greatest impact on the future success of WTSDs.

22.7 Final Remarks

In this chapter, the pillars of a mechatronic tremor suppression device were presented, including tremor signal sensing and estimation, actuation, and control. In addition, the state-of-the-art for wearable tremor suppression devices was reviewed. All of the presented devices were designed for a limited number of joints; however, a recent study (Zhou et al. 2018a, b, c) indicated that suppressing tremor in only

a few joints may be insufficient. A device covering the entire upper limb may be more beneficial to the users. In the future, more focus needs to be placed on the optimization of the mechatronic design and on the real-world performance evaluation of these devices when assisting end users with the activities of daily living.

References

Adelstein BD. Peripheral mechanical loading and the mechanism of abnormal intention tremor. Master's dissertation. Massachusetts Institute of Technology; 1981.

Adhikari K, Tatinati S, Ang WT, Veluvolu KC, Nazarpour K. A quaternion weighted Fourier linear combiner for modeling physiological tremor. IEEE Trans Biomed Eng. 2016;63(11):2336–46.

Adhikari K, Tatinati S, Veluvolu KC, Chambers JA. Physiological tremor filtering without phase distortion for robotic microsurgery. IEEE Trans Autom Sci Eng. 2022;19(1):497–509.

Ando T, Watanabe M, Fujie MG. Extraction of voluntary movement for an EMG controlled exoskeltal robot of tremor patients. In: Proceedings of the 4th international IEEE/EMBS conference on neural engineering; 2009 Apr 29–May 2. Antalya, Turkey. p. 120–3.

Ando T, Watanabe M, Nishimoto K, Matsumoto Y, Seki M, Fujie MG. Myoelectric-controlled exoskeletal elbow robot to suppress essential tremor: extraction of elbow flexion movement using STFTs and TDNN. J Rob Mechatron. 2012;24(1):141–9.

Ang KK, Guan C. EEG-based strategies to detect motor imagery for control and rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2016;25(4):392–401.

Ang WT, Krichane M, Sim T. Zero phase filtering for active compensation of periodic physiological motion. In: Proceedings of the first IEEE/RAS-EMBS international conference on biomedical robotics and biomechatronics; 2006 Feb 20–22. Pisa, Italy. p. 182–7.

Arnold AS, Rosen MJ, Aisen ML. Evaluation of a controlled-energy-dissipation orthosis for tremor suppression. J Electromyogr Kinesiol. 1993;3(3):131–48.

As'arry A, Md Zain MZ, Musa M, Hussein M. Hybrid learning control for improving suppression of hand tremor. In: Proceedings of the Institution of Mechanical Engineers. Part H: Journal of Engineering in Medicine. 2013;227(11):1171–1180.

Atashzar SF, Shahbazi M, Samotus O, Tavakoli M, Jog MS, Patel RV. Characterization of upper-limb pathological tremors: application to design of an augmented haptic rehabilitation system. IEEE J Sel Top Sign Proces. 2016;10(5):888–903.

Avizzano CA, Rogni A, Bergamasco M. Application of filtering strategies to Multiple Sclerosis tremor: analysis of results. In: Proceedings of the 8th IEEE international workshop on robot and human interaction; 1999 Sept 27–29. Pisa, Italy. p. 254–60.

Awantha WV, Wanasinghe AT, Kavindya AG, Kulasekera AL, Chathuranga DS. A novel soft glove for hand tremor suppression: evaluation of layer jamming actuator placement. In: Proceedings of the 3rd IEEE international conference on soft robotics; 2020 May 15–July 15. New Haven, CT, USA. p. 440–445.

Belda-Lois JM, Martinez-Reyero AI, Castillo A, Rocon E, Pons JL, Loureiro R, Manto M, Normie L, Soede M. Controllable mechanical tremor reduction. Assessment of two orthoses. Technol Disabil. 2007;19(4):169–78.

Bó APL, Poignet P, Widjaja F, Ang WT. Online pathological tremor characterization using extended Kalman filtering. In: Proceedings of the 30th annual international conference of the IEEE Engineering in Medicine and Biology Society; 2008 Aug 20–24. Vancouver, BC, Canada. p. 1753–6.

Bó APL, Azevedo-Coste C, Geny C, Poignet P, Fattal C. On the use of fixed-intensity functional electrical stimulation for attenuating essential tremor. Artif Organs. 2014;38(11):984–91.

Case D, Taheri B, Richer E. Design and characterization of a small-scale magnetorheological damper for tremor suppression. IEEE/ASME Trans Mechatron. 2011;18(1):96–103.

Case D, Taheri B, Richer E. Active control of MR wearable robotic orthosis for pathological tremor suppression. In: Proceedings of the dynamic systems and control conference; 2015 Oct 28–30. Columbus, Ohio, USA. p. V003T42A004.

Cheng SS, Desai JP. Towards high frequency actuation of SMA spring for the neurosurgical robot-MINIR-II. In: Proceedings of the IEEE international conference on robotics and automation; 2015 May 26–30. Seattle, Washington, USA. p. 2580–5.

Daemi P, Zhou Y, Inzunza K, Naish MD, Price AD, Trejos AL. Kinematic modeling and characterization of a wearable tremor suppression device for pathological tremor reduction. In: Proceedings of the 8th IEEE RAS/EMBS international conference for biomedical robotics and biomechatronics; 2020 Nov 29–Dec 3. New York, USA. p. 1236–41.

Daemi P, Kamel M, Gharibo J, Naish MD, Trejos AL, Price AD. Control of twisted-coiled actuators via multi-DOF PID. In: Proceedings of the electroactive polymer actuators and devices XXIII. Virtual, vol 11587; 2021 Mar 22–26. p. 115870M.

Dai J, Du Z, Yan Z, Liang Y. Least squares support vector machine Kalman filter for physiological tremor suppression in minimally invasive surgical robot. J Harbin Inst Technol. 2020;27:22–8.

Davison E. Multivariable tuning regulators: the feedforward and robust control of a general servomechanism problem. IEEE Trans Autom Control. 1976;21(1):35–47.

Dideriksen JL, Laine CM, Dosen S, Muceli S, Rocon E, Pons JL, Benito-Leon J, Farina D. Electrical stimulation of afferent pathways for the suppression of pathological tremor. Front Neurosci. 2017;11:178.

Dosen S, Muceli S, Dideriksen JL, Romero JP, Rocon E, Pons J, Farina D. Online tremor suppression using electromyography and low-level electrical stimulation. IEEE Trans Neural Syst Rehabil Eng. 2015;23(3):385–95.

Duchaine V, St-Onge BM, Gao D, Gosselin C. Stable and intuitive control of an intelligent assist device. IEEE Trans Haptic. 2012;5(2):148–59.

Edmonds BP. Feasibility of twisted coiled polymer actuators for use in upper limb wearable rehabilitation devices. Doctoral dissertation. University of Western Ontario; 2020.

Flash T, Mussa-Ivaldi F. Human arm stiffness characteristics during the maintenance of posture. Exp Brain Res. 1990;82(2):315–26.

Fraden J. Handbook of modern sensors: physics, designs, and applications. 5th ed. Cham: Springer; 2016.

Fromme NP, Camenzind M, Riener R, Rossi RM. Need for mechanically and ergonomically enhanced tremor-suppression orthoses for the upper limb: a systematic review. J Neuroeng Rehabil. 2019;16(1):1–5.

Gallego JA, Rocon E, Roa JO, Moreno JC, Pons JL. Real-time estimation of pathological tremor parameters from gyroscope data. Sensors. 2010;10(3):2129–49.

Gallego JÁ, Ibanez J, Dideriksen JL, Serrano JI, del Castillo MD, Farina D, Rocon E. A multimodal human–robot interface to drive a neuroprosthesis for tremor management. IEEE Trans Syst Man Cybern Part C Appl Rev. 2012;42(6):1159–68.

Gallego JA, Rocon E, Belda-Lois JM, Koutsou AD, Mena S, Castillo A, Pons JL. Design and validation of a neuroprosthesis for the treatment of upper limb tremor. In: Proceedings of the 35th annual international conference of the IEEE Engineering in Medicine and Biology Society; 2013a July 3–7. Osaka, Japan. p. 3606–9.

Gallego JÁ, Rocon E, Belda-Lois JM, Pons JL. A neuroprosthesis for tremor management through the control of muscle co-contraction. J Neuroeng Rehabil. 2013b;10(1):36.

Gillard DM, Cameron T, Prochazka A, Gauthier MJA. Tremor suppression using functional electrical stimulation: a comparison between digital and analog controllers. IEEE Trans Rehabil Eng. 1999;7(3):385–8.

Gonzalez JG, Heredia EA, Rahman T, Barner KE, Arce GR. Filtering involuntary motion of people with tremor disability using optimal equalization. In: Proceedings of the IEEE international conference on systems, man and cybernetics. Intelligent systems for the 21st century; 1995 Oct 22–25. Vancouver, BC, Canada. p. 2402–7.

Grimaldi G, Camut S, Manto M. Functional electrical stimulation effect on upper limb tremor. Int J Bioelectromagn. 2011;13(3):123–4.

Haines CS, Lima MD, Li N, Spinks GM, Foroughi J, Madden JD, Kim SH, Fang S, De Andrade MJ, Göktepe F, Göktepe Ö. Artificial muscles from fishing line and sewing thread. Science. 2014;343(6173):868–72.

Hao MZ, Xu SQ, Hu ZX, Xu FL, Niu CX, Xiao Q, Lan N. Inhibition of Parkinsonian tremor with cutaneous afferent evoked by transcutaneous electrical nerve stimulation. J Neuroeng Rehabil. 2017;14(1):1–3.

Hashemi SM, Golnaraghi MF, Patla AE. Tuned vibration absorber for suppression of rest tremor in Parkinson's disease. Med Biol Eng Comput. 2004;42(1):61–70.

Heo JH, Kim JW, Kwon Y, Lee SK, Eom GM, Kwon DY, et al. Sensory electrical stimulation for suppression of postural tremor in patients with essential tremor. Biomed Mater Eng. 2015;26:S803–9.

Heo J-H, Kwon Y, Jeon H-M, Kwon D-Y, Lee C-N, Park K-W, et al. Suppression of action tremor by sensory electrical stimulation in patients with essential tremor. J Mech Med Biol. 2016;16(08):1640026.

Heo JH, Jeon HM, Choi EB, Kwon DY, Eom GM. Continuous sensory electrical stimulation for the suppression of parkinsonian rest tremor. J Mech Med Biol. 2018;18(7):1840006.

Heo JH, Jeon HM, Choi EB, Kwon DY, Eom GM. Effect of sensory electrical stimulation on resting tremors in patients with Parkinson's disease and SWEDDs. J Mech Med Biol. 2019;19(7):1940033.

Herrnstadt G, Menon C. On-off tremor suppression orthosis with electromagnetic brake. Int J Mech Eng Mechatron. 2012;1(2):7–14.

Herrnstadt G, Menon C. Voluntary-driven elbow orthosis with speed-controlled tremor suppression. Front Bioeng Biotechnol. 2016a;4:29.

Herrnstadt G, Menon C. Admittance-based voluntary-driven motion with speed-controlled tremor rejection. IEEE/ASME Trans Mechatron. 2016b;21(4):2108–19.

Herrnstadt G, Menon C. Elbow orthosis for tremor suppression–a torque based input case. In: Proceedings of the international conference on bioinformatics and biomedical engineering; 2017 Apr 26–28. Granada, Spain. p. 292–302.

Herrnstadt G, McKeown MJ, Menon C. Controlling a motorized orthosis to follow elbow volitional movement: tests with individuals with pathological tremor. J Neuroeng Rehabil. 2019;16(1):1–4.

Hogan N. Impedance control: an approach to manipulation. In: Proceedings of the American control conference; 1984 June 6–8. San Diego, CA, USA. p. 304–13.

Hosseini SM. Tremor suppression in the human hand and forearm. Doctoral dissertation. University of Technology Sydney; 2019.

Hsu DS, Huang WM, Thakor NV. StylPen: on-line adaptive canceling of pathological tremor for computer pen handwriting. In: Proceedings of the IEEE 22nd annual Northeast bioengineering conference; 1996 Mar 14–15. New Brunswick, NJ, USA. p. 113–4.

Huen D, Liu J, Lo B. An integrated wearable robot for tremor suppression with context aware sensing. In: Proceedings of the IEEE 13th international conference on wearable and implantable body sensor networks; 2016 June 14–17. San Francisco, CA, USA. p. 312–7.

Ibrahim A, Zhou Y, Jenkins ME, Trejos AL, Naish MD. The design of a Parkinson's tremor predictor and estimator using a hybrid convolutional-multilayer perceptron neural network. In: Proceedings of the 42nd annual international conference of the IEEE Engineering in Medicine & Biology Society; 2020 July 20–24. Montreal, QC, Canada. p. 5996–6000.

Ibrahim A, Zhou Y, Jenkins ME, Trejos AL, Naish MD. Real-time voluntary motion prediction and Parkinson's tremor reduction using deep neural networks. IEEE Trans Neural Syst Rehabil Eng. 2021;29:1413–23.

Isaacson SH, Peckham E, Tse W, Waln O, Way C, Petrossian MT, et al. Prospective home-use study on non-invasive neuromodulation therapy for essential tremor. Tremor Other Hyperkinet Mov. 2020;10(29):1–16.

Javidan M, Elek J, Prochazka A. Attenuation of pathological tremors by functional electrical stimulation II: clinical evaluation. Ann Biomed Eng. 1992;20(2):225–36.
Jitkritsadakul O, Thanawattano C, Anan C, Bhidayasiri R. Exploring the effect of electrical muscle stimulation as a novel treatment of intractable tremor in Parkinson's disease. J Neurol Sci. 2015;358(1–2):146–52.
Jitkritsadakul O, Thanawattano C, Anan C, Bhidayasiri R. Tremor's glove-an innovative electrical muscle stimulation therapy for intractable tremor in Parkinson's disease: a randomized sham-controlled trial. J Neurol Sci. 2017;381:331–40.
Johnson C. Accomodation of external disturbances in linear regulator and servomechanism problems. IEEE Trans Autom Control. 1971;16(6):635–44.
Kalaiarasi A, Kumar LA. Sensor based portable tremor suppression device for stroke patients. Acupunct Electrother Res. 2018;43(1):29–37.
Kazi S, As'Arry A, Zain MM, Mailah M, Hussein M. Experimental implementation of smart glove incorporating piezoelectric actuator for hand tremor control. WSEAS Trans Syst Control. 2010;5(6):443–53.
Kelley CR, Kauffman JL. Towards wearable tremor suppression using dielectric elastomer stack actuators. Smart Mater Struct. 2020;30(2):025006.
Khalil HK. Nonlinear Systems. 3rd ed. Upper Saddle River: Prentice-Hall; 2002.
Kiguchi K, Hayashi Y. Upper-limb tremor suppression with a 7DOF exoskeleton power-assist robot. In: Proceedings of the 35th annual international conference of the IEEE Engineering in Medicine and Biology Society; 2013 July 3–7. Osaka, Japan. p. 6679–82.
Kim J, Wichmann T, Inan OT, De Weerth SP. A wearable system for attenuating essential tremor based on peripheral nerve stimulation. IEEE J Transl Eng Health Med. 2020;8:1–11.
Kobayashi Y, Matsumoto Y, Kawasaki M, Kato A, Ando T, Nagaoka M, Fujie MG. Development of a Soft Exosuit for suppressing essential tremor. IEEE Trans Med Rob Bionics. 2021;3(3):783–90.
Lavu SS, Gupta A. Active vibration control of essential tremor. In: Proceedings of the 14th national conference on machines and mechanisms; 2009 Dec 17–18. Durgapur, India. p. 446–9.
LeBlanc J. Design proposal for a mechanical tremor suppression device. Doctoral dissertation. Tufts University; 2005.
Lee CC. Fuzzy logic in control systems: fuzzy logic controller. I. IEEE Trans Syst Man Cybern. 1990;20(2):404–18.
Liapunov AM. On the general problem of stability of motion. Soviet Union: Kharkov Mathematical Society; 1892.
Lidka M, Price AD, Trejos AL. Development and evaluation of dielectric elastomer actuators for assistive wearable devices. In: Proceedings of the 2018 IEEE Canadian conference on electrical & computer engineering (CCECE); 2018 May 13–16. Quebec, QC, Canada. p. 1–4.
Lin PT, Ross EK, Chidester P, Rosenbluth KH, Hamner SR, Wong SH, et al. Noninvasive neuromodulation in essential tremor demonstrates relief in a sham-controlled pilot trial. Mov Disord. 2018;33(7):1182–3.
Liu W, Kai T, Kiguchi K. Tremor suppression with mechanical vibration stimulation. IEEE Access. 2020;8:226199–212.
Lora-Millán JS, López-Blanco R, Gallego JÁ, Méndez-Guerrero A, de la Aleja JG, Rocon E. Mechanical vibration does not systematically reduce the tremor in essential tremor patients. Sci Rep. 2019;9(1):16476.
Lora-Millán JS, Delgado-Oleas G, Benito-León J, Rocon E. A review on wearable technologies for tremor suppression. Front Neurol. 2021;12:700600.
Loureiro RC, Belda-Lois JM, Lima ER, Pons JL, Sanchez-Lacuesta JJ, Harwin WS. Upper limb tremor suppression in ADL via an orthosis incorporating a controllable double viscous beam actuator. In: Proceedings of the 9th international conference on rehabilitation robotics; 2005 June 28–July 1. Chicago, IL, USA. p. 119–22.
Mailah M. Intelligent active force control of a rigid robot arm using neural network and iterative learning algorithms. Doctoral dissertation. University of Dundee; 1998.

Maneski LP, Jorgovanović N, Ilić V, Došen S, Keller T, Popović MB, Popović DB. Electrical stimulation for the suppression of pathological tremor. Med Biol Eng Comput. 2011;49(10):1187–93.
Manto M, Rocon E, Pons J, Belda JM, Camut S. Evaluation of a wearable orthosis and an associated algorithm for tremor suppression. Physiol Meas. 2007;28(4):415.
Matsumoto Y, Seki M, Ando T, Kobayashi Y, Nakashima Y, Iijima H, Nagaoka M, Fujie MG. Development of an exoskeleton to support eating movements in patients with essential tremor. J Rob Mechatron. 2013;25(6):949–58.
Matsumoto Y, Amemiya M, Kaneishi D, Nakashima Y, Seki M, Ando T, Kobayashi Y, Iijima H, Nagaoka M, Fujie MG. Development of an elbow-forearm interlock joint mechanism toward an exoskeleton for patients with essential tremor. In: Proceedings of the IEEE/RSJ international conference on intelligent robots and systems; 2014 Sept 14–18. Chicago, IL, USA. p. 2055–62.
Mengüç EC. Adaptive Fourier linear combiner based on modified least mean Kurtosis algorithm for the processing of sinusoidal signals. Trans Inst Meas Control. 2021;43(5):1039–47.
Merletti R, Parker PJ, editors. Electromyography: physiology, engineering, and non-invasive applications. Wiley; 2004.
Morrice BL, Becker WJ, Hoffer JA, Lee RG. Manual tracking performance in patients with cerebellar incoordination: effects of mechanical loading. Can J Neurol Sci. 1990;17(3):275–85.
Muceli S, Poppendieck W, Hoffmann KP, Dosen S, Benito-León J, Barroso FO, et al. A thin-film multichannel electrode for muscle recording and stimulation in neuroprosthetics applications. J Neural Eng. 2019;16(2):026035.
Nazmi N, Rahman MA, Mazlan SA, Zamzuri H, Mizukawa M. Electromyography (EMG) based signal analysis for physiological device application in lower limb rehabilitation. In: Proceedings of the 2nd international conference on biomedical engineering; 2015 Mar 30–31. Penang, Malaysia. p. 1–6.
Nguyen HS, Luu TP. Tremor-suppression orthoses for the upper limb: current developments and future challenges. Front Hum Neurosci. 2021;15:186.
Nho W. Development and evaluation of an enhanced weighted frequency Fourier linear combiner algorithm using bandwidth information. Doctoral dissertation. University of Pittsburgh; 2006.
Ou J. Simulation study of tremor suppression and experiment of energy harvesting with piezoelectric materials. Master's thesis. University of North Texas; 2012.
Pahwa R, Dhall R, Ostrem J, Gwinn R, Lyons K, Ro S, et al. An acute randomized controlled trial of noninvasive peripheral nerve stimulation in essential tremor. Neuromodulation. 2019;22(5):537–45.
Pascual-Valdunciel A, Gonzalez-Sanchez M, Muceli S, Adan-Barrientos B, Escobar-Segura V, Perez-Sanchez JR, et al. Intramuscular stimulation of muscle afferents attains prolonged tremor reduction in essential tremor patients. IEEE Trans Biomed Eng. 2021;68(6):1768–76.
Pledgie S, Barner KE, Agrawal SK, Rahman T. Tremor suppression through impedance control. IEEE Trans Rehabil Eng. 2000;8(1):53–9.
Popović LZ, Šekara TB, Popović MB. Adaptive band-pass filter (ABPF) for tremor extraction from inertial sensor data. Comput Methods Prog Biomed. 2010;99(3):298–305.
Poulo SR. Adaptive filtering: algorithms and practical implementations. Int Ser Eng Comput Sci. 2008;694:23–50.
Priyandoko G, Mailah M, Jamaluddin H. Vehicle active suspension system using skyhook adaptive neuro active force control. Mech Syst Signal Process. 2009;23(3):855–68.
Prochazka A, Elek J, Javidan M. Attenuation of pathological tremors by functional electrical stimulation. I: method. Ann Biomed Eng. 1992;20(2):205–24.
Riley PO, Rosen MJ. Evaluating manual control devices for those with tremor disability. J Rehabil Res Dev. 1987;24(2):99–110.
Riviere CN, Rader RS, Thakor NV. Adaptive cancelling of physiological tremor for improved precision in microsurgery. IEEE Trans Biomed Eng. 1998;45(7):839–46.
Riviere CN, Thakral A, Iordachita II, Mitroi G, Stoianovici D. Predicting respiratory motion for active canceling during percutaneous needle insertion. In: Proceedings of the 23rd annual

international conference of the IEEE Engineering in Medicine and Biology Society; 2001 Oct 25–28. Istanbul, Turkey. p. 3477–80.

Rocon E, Pons JL. Upper limb exoskeleton for tremor suppression: validation. In: Exoskeletons in Rehabilitation Robotics. Berlin, Heidelberg: Springer; 2011. p. 99–111.

Rocon E, Ruiz AF, Pons JL. On the use of ultrasonic motors in orthotic rehabilitation of pathologic tremor. In: Proceedings of the ACTUATOR 2004 conference; 2004 June 14–16. Bremen, Germany. p. 387–90.

Rocon E, Ruiz AF, Pons JL. Biomechanical modelling of the upper limb for robotics-based orthotic tremor suppression. Appl Bionics Biomech. 2005a;2(2):81–5.

Rocon E, Ruiz AF, Pons JL, Belda-Lois JM, Sánchez-Lacuesta JJ. Rehabilitation robotics: a wearable exo-skeleton for tremor assessment and suppression. In: Proceedings of the 2005 IEEE international conference on robotics and automation; 2005b Apr 18–22. Barcelona, Spain. p. 2271–6.

Rocon E, Ruiz AF, Brunetti F, Pons JL, Belda-Lois JM, Sánchez-Lacuesta JJ. On the use of an active wearable exoskeleton for tremor suppression via biomechanical loading. In: Proceedings of the 2006 IEEE international conference on robotics and automation; 2006 May 15–19. Orlando, FL, USA. p. 3140–5.

Rocon E, Belda-Lois JM, Ruiz AF, Manto M, Moreno JC, Pons JL. Design and validation of a rehabilitation robotic exoskeleton for tremor assessment and suppression. IEEE Trans Neural Syst Rehabil Eng. 2007a;15(3):367–78.

Rocon E, Manto M, Pons J, Camut S, Belda JM. Mechanical suppression of essential tremor. Cerebellum. 2007b;6(1):73–8.

Rocon E, Gallego JA, Barrios L, Victoria AR, Ibánez J, Farina D, Negro F, Dideriksen JL, Conforto S, D'Alessio T, Severini G. Multimodal BCI-mediated FES suppression of pathological tremor. In: Proceedings of the 2010 annual international conference of the IEEE engineering in medicine and biology; 2010 Aug 31–Sept 4. Buenos Aires, Argentina. p. 3337–40.

Rocon E, Gallego JA, Belda-Lois JM, Pons JL. Assistive robotics as alternative treatment for tremor. In: Proceedings of the ROBOT2013: first Iberian robotics conference; 2014 Nov 28–29. Madrid, Spain. p. 173–9.

Rosen MJ, Arnold AS, Baiges IJ, Aisen ML, Eglowstein SR. Design of a controlled-energy-dissipation orthosis (CEDO) for functional suppression of intention tremors. J Rehabil Res Dev. 1995;32:1–16.

Seki M, Matsumoto Y, Ando T, Kobayashi Y, Fujie MG, Iijima H, Nagaoka M. Development of robotic upper limb orthosis with tremor suppressibility and elbow joint movability. In: Proceedings of the 2011 IEEE international conference on systems, man, and cybernetics; 2011a Oct 9–12. Anchorage, AK, USA. p. 729–35.

Seki M, Matsumoto Y, Ando T, Kobayashi Y, Iijima H, Nagaoka M, Fujie MG. The weight load inconsistency effect on voluntary movement recognition of essential tremor patient. In: Proceedings of the 2011 IEEE international conference on robotics and biomimetics; 2011b Dec 7–11. Phuket, Thailand. p. 901–7.

Shahtalebi S, Atashzar SF, Patel RV, Mohammadi A. HMFP-DBRNN: real-time hand motion filtering and prediction via deep bidirectional RNN. IEEE Robot Autom Lett. 2019a Jan;4(2):1061–8.

Shahtalebi S, Atashzar SF, Patel RV, Mohammadi A. Wake: wavelet decomposition coupled with adaptive kalman filtering for pathological tremor extraction. Biomed Signal Process Control. 2019b;48:179–88.

Shahtalebi S, Atashzar SF, Samotus O, Patel RV, Jog MS, Mohammadi A. Phtnet: characterization and deep mining of involuntary pathological hand tremor using recurrent neural network models. Sci Rep. 2020;10(1):1–9.

Shamroukh M, Kalimullah IQ, Chacko A, Barlingay SS, Kalaichelvi V, Chattopadhyay AB. Evaluation of control strategies in semi-active orthosis for suppression of upper limb pathological tremors. In: Proceedings of the international conference on innovations in electrical, electronics, instrumentation and media technology; 2017 Feb 3–4. Coimbatore, India. p. 75–80.

Skaramagkas V, Andrikopoulos G, Manesis S. An experimental investigation of essential hand tremor suppression via a soft exoskeletal glove. In: Proceedings of the 2020 European control conference; 2020 May 12–15. Saint Petersburg, Russia. p. 889–94.

Skaramagkas V, Andrikopoulos G, Manesis S. Towards essential hand tremor suppression via pneumatic artificial muscles. Actuators. 2021;10(9):206.

Stroeve S. Impedance characteristics of a neuromusculoskeletal model of the human arm I. Posture Control Biol Cybern. 1999;81(5):475–94.

Swallow L, Siores E. Tremor suppression using smart textile fibre systems. J Fiber Bioeng Inform. 2009;1(4):261–6.

Taheri B. Real-time pathological tremor identification and suppression in human arm via active orthotic devices. Doctoral dissertation. Southern Methodist University; 2013.

Taheri B, Case D, Richer E. Active tremor estimation and suppression in human elbow joint. In: Proceedings of the dynamic systems and control conference; 2011a Oct 31–Nov 2. Arlington, VA, USA. p. 115–20.

Taheri B, Case D, Richer E. Robust tremor attenuation for single DOF model of human elbow joint with parametric uncertainties. In: Proceedings of the ASME international mechanical engineering congress and exposition; 2011b Nov 11–17. Denver, Colorado, USA. p. 595–600.

Taheri B, Case D, Richer E. Theoretical development and experimental validation of an adaptive controller for tremor suppression at musculoskeletal level. In: Proceedings of the dynamic systems and control conference; 2013a Oct 21–23. Palo Alto, CA, USA. p. V002T22A005.

Taheri B, Case D, Richer E. Robust controller for tremor suppression at musculoskeletal level in human wrist. IEEE Trans Neural Syst Rehabil Eng. 2013b;22(2):379–88.

Taheri B, Case D, Richer E. Adaptive suppression of severe pathological tremor by torque estimation method. IEEE/ASME Trans Mechatron. 2014;20(2):717–27.

Vaz CA, Thakor NV. Adaptive Fourier estimation of time-varying evoked potentials. IEEE Trans Biomed Eng. 1989;36(4):448–55.

Vaz CA, Kong X, Thakor NV. An adaptive estimation of periodic signals using a Fourier linear combiner. IEEE Trans Signal Process. 1994;42(1):1–10.

Veluvolu KC, Ang WT. Estimation of physiological tremor from accelerometers for real-time applications. Sensors. 2011;11(3):3020–36.

Veluvolu KC, Tan UX, Latt WT, Shee CY, Ang WT. Bandlimited multiple Fourier linear combiner for real-time tremor compensation. In: Proceedings of the 29th annual international conference of the IEEE Engineering in Medicine and Biology Society; 2007 Aug 22–26. Lyon, France. p. 2847–2850.

Veluvolu KC, Latt WT, Ang WT. Double adaptive bandlimited multiple Fourier linear combiner for real-time estimation/filtering of physiological tremor. Biomed Signal Process Control. 2010;5(1):37–44.

Wang J, Barry OR. Multibody analysis and control of a full-wrist exoskeleton for tremor alleviation. J Biomech Eng. 2020;142(12):121008.

Wang S, Gao Y, Zhao J, Cai H. Adaptive sliding bandlimited multiple Fourier linear combiner for estimation of pathological tremor. Biomed Signal Process Control. 2014;10:260–74.

Wang Y, Tatinati S, Adhikari K, Huang L, Nazarpour K, Ang WT, Veluvolu KC. Multi-step prediction of physiological tremor with random quaternion neurons for surgical robotics applications. IEEE Access. 2018;6:42216–26.

Widjaja F, Shee CY, Zhang D, Ang WT, Poignet P, Bo A, Guiraud D. Current progress on pathological tremor modeling and active compensation using functional electrical stimulation. In: Proceedings of the 6th conference of the International Society for Gerontechnology; 2008 June 4–7. Pisa, Italy. p. 1–6.

Widjaja F, Shee CY, Ang WT, Au WL, Poignet P. Sensing of pathological tremor using surface electromyography and accelerometer for real-time attenuation. J Mech Med Biol. 2011;11(05):1347–71.

Xu FL, Hao MZ, Xu SQ, Hu ZX, Xiao Q, Lan N. Development of a closed-loop system for tremor suppression in patients with Parkinson's disease. In: Proceedings of the 38th annual

international conference of the IEEE Engineering in Medicine and Biology Society; 2016 Aug 16–20. Orlando, FL, USA. p. 1782–5.

Yi A, Zahedi A, Wang Y, Tan UX, Zhang D. A novel exoskeleton system based on magnetorheological fluid for tremor suppression of wrist joints. In: Proceedings of the IEEE 16th international conference on rehabilitation robotics; 2019 June 24–28. Toronto, ON, Canada. p. 1115–20.

Yu JY, Rajagopal A, Syrkin-Nikolau J, Shin S, Rosenbluth KH, Khosla D, et al. Transcutaneous afferent patterned stimulation therapy reduces hand tremor for one hour in essential tremor patients. Front Neurosci. 2020;14:1180.

Zahedi A, Wang Y, Martinez-Hernandez U, Zhang D. A wearable elbow exoskeleton for tremor suppression equipped with rotational semi-active actuator. Mech Syst Signal Process. 2021a;157:107674.

Zahedi A, Zhang B, Yi A, Zhang D. A soft exoskeleton for tremor suppression equipped with flexible semiactive actuator. Soft Rob. 2021b;8(4):432–47.

Zamanian AH, Richer E. Adaptive disturbance rejection controller for pathological tremor suppression with permanent magnet linear motor. In: Proceedings of the dynamic systems and control conference; 2017 Oct 11–13. Tysons, VA, USA. p. V001T37A003.

Zamanian AH, Richer E. Adaptive notch filter for pathological tremor suppression using permanent magnet linear motor. Mechatronics. 2019;63:102273.

Zhang D, Ang WT. Reciprocal EMG controlled FES for pathological tremor suppression of forearm. In: Proceedings of the 29th annual international conference of the IEEE Engineering in Medicine and Biology Society; 2007 Aug 22–26. Lyon, France. p. 4810–3.

Zhang JZ, Price BT, Adams RD, Burbank K, Knaga TJ. Detection of involuntary human hand motions using Empirical Mode Decomposition and Hilbert-Huang Transform. In: Proceedings of the 51st Midwest symposium on circuits and systems; 2008 Aug 10–13. Knoxville, TN, USA. p. 157–60.

Zhang D, Poignet P, Widjaja F, Ang WT. Neural oscillator-based control for pathological tremor suppression via functional electrical stimulation. Control Eng Pract. 2011;19(1):74–88.

Zhou Y, Jenkins ME, Naish MD, Trejos AL. Design and validation of a high-order weighted-frequency Fourier linear combiner-based Kalman filter for parkinsonian tremor estimation. In: Proceedings of the 38th annual international conference of the IEEE Engineering in Medicine and Biology Society; 2016 Aug 16–20. Orlando, FL, USA. p. 5893–6.

Zhou Y, Naish MD, Jenkins ME, Trejos AL. Design and validation of a novel mechatronic transmission system for a wearable tremor suppression device. Robot Auton Syst. 2017;91:38–48.

Zhou Y, Jenkins ME, Naish MD, Trejos AL. Impact of suppressed tremor: is suppression of proximal joints sufficient? In: Proceedings of the IEEE EMBS international conference on biomedical & health informatics; 2018a Mar 4–7. Las Vegas, NV, USA. p. 58–61.

Zhou Y, Jenkins ME, Naish MD, Trejos AL. Characterization of parkinsonian hand tremor and validation of a high-order tremor estimator. IEEE Trans Neural Syst Rehabil Eng. 2018b;26(9):1823–34.

Zhou Y, Jenkins ME, Naish MD, Trejos AL. Development of a wearable tremor suppression glove. In: Proceedings of the 7th IEEE international conference on biomedical robotics and biomechatronics; 2018c Aug 26–29. Enschede, The Netherlands. p. 640–5.

Zhou Y, Ibrahim A, Hardy KG, Jenkins ME, Naish MD, Trejos AL. Design and preliminary performance assessment of a wearable tremor suppression glove. IEEE Trans Biomed Eng. 2021;68(9):2846–57.

Chapter 23
Drug-Induced Tremors

Jessica McClard, Colin McLeod, and John C. Morgan

Abstract Drug-induced tremors are common in clinical practice, but often under-recognized or misdiagnosed. There are a myriad of drugs that can cause or exacerbate tremors, making the diagnosis difficult. Many tremorigenic drugs are frequently and widely prescribed, such as amiodarone, valproic acid, lithium, bronchodilators, antipsychotics, and antidepressants. Little is known regarding the mechanism by which these drugs cause tremor; however, it is important for clinicians to recognize potential tremorigenic drugs and develop management strategies for symptomatic patients.

Keywords Drug-induced tremor · Dopamine-blocking agents · Antiepileptics · Antidepressants · Bronchodilators · Immunosuppressants · Substances of abuse · Treatment of tremor

23.1 Introduction

Drug-induced movement disorders, including tremor, are frequently encountered in clinical practice (Factor et al. 2019). However, many factors make the diagnosis of drug-induced tremor difficult. Firstly, tremor is the most common movement disorder with multiple possible causes (van de Wardt et al. 2020). In addition, numerous drugs can induce tremors and new tremorigenic drugs are rapidly being identified (Factor et al. 2019; van de Wardt et al. 2020). Although postural and/or kinetic tremors are most often seen, iatrogenic tremors can have various presentations, depending on the specific drug involved (Table 23.1). Furthermore, some agents may result in a mixture of potential tremor types (Fig. 23.1) (Alty and Kempster 2011).

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Table 23.1 Drugs known to induce postural/kinetic tremors and rest tremor/Parkinsonism by drug class

Drug class	Postural/kinetic tremor	Rest tremor/Parkinsonism
Antiarrhythmics	Amiodarone Mexiletine Procainamide	Amiodarone (Rare) Mexiletine
Antidepressants and mood stabilizers	SSRIs/SNRIs (postural >>> kinetic) TCAs Lithium	SSRIs/SNRIs (Rare) Amoxapine Lithium (Rare)
Antiepileptics	Valproate Lamotrigine Topiramate (postural only)	Valproate
Antimicrobials	TMP/SMX Itraconazole Acyclovir	TMP/SMX Itraconazole Amphotericin B
Bronchodilators	Albuterol Salbutamol Salmeterol	
Dopamine receptor blockers and dopamine depleters	Typical antipsychotics Atypical antipsychotics	Typical antipsychotics Atypical antipsychotics VMAT2 inhibitors
Gastrointestinal agents	Metoclopramide Cimetidine Bismuth salts	Metoclopramide Promethazine Prochlorperazine
Immunosuppressants and chemotherapeutics	Tacrolimus Cyclosporine (postural only) Interferon alpha Cytarabine	
Substances of abuse/misuse	Alcohol Cocaine MDMA Nicotine/cigarettes	Alcohol Cocaine MDMA
Sympathomimetics, methylxanthines, and beta-adrenergic antagonists	Pseudoephedrine Caffeine Pindolol	
Hormones	Epinephrine Levothyroxine Corticosteroids	

MDMA 3,4-methylenedioxymethamphetamine, *SNRIs* serotonin norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants, *TMP/SMX* trimethoprim sulfamethoxazole, *VMAT2* vesicular monoamine transporter 2

Details regarding the clinical approach to diagnosing and classifying tremor are covered in another chapter. Similar to the methods employed to diagnose various types of tremors, drug-induced tremors require a careful review of the past medical history, investigation of previous and current drugs, and a detailed physical examination. Some features of the history that may heighten suspicion for a drug-induced etiology include a temporal relationship between onset of tremor

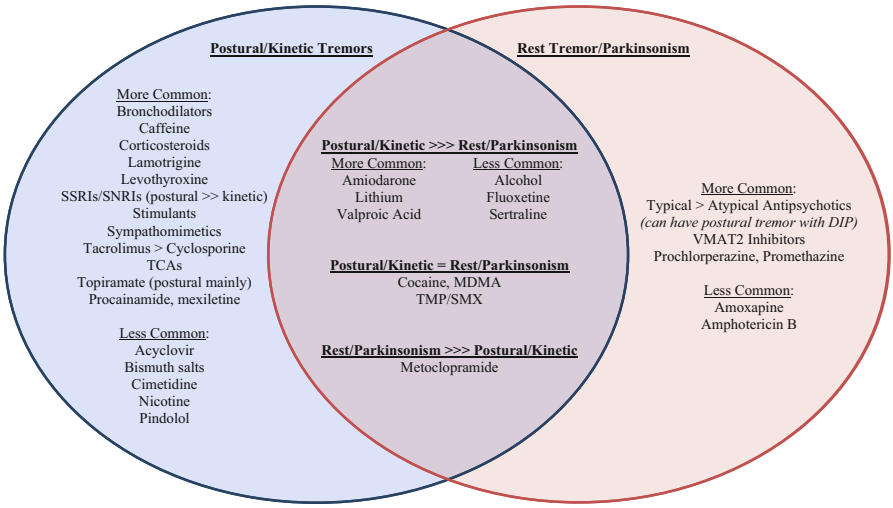

Fig. 23.1 Types of tremors induced by different drugs. DIP drug-induced parkinsonism, MDMA 3,4-methylenedioxymethamphetamine, SNRIs serotonin norepinephrine reuptake inhibitors, SSRIs selective serotonin reuptake inhibitors, TCAs tricyclic antidepressants, TMP/SMX trimethoprim sulfamethoxazole, VMAT2 vesicular monoamine transporter 2

and drug initiation or adjustment of a dose (van de Wardt et al. 2020). Some drugs are more likely than others to be associated with acute onset of tremor (Table 23.3). Other features of the history that are suggestive of a drug-induced etiology include polypharmacy, especially with combinations of tremorigenic drugs (Alty and Kempster 2011). Chronic symptoms may hint to exacerbation of an underlying tremor disorder or unmasking of undiagnosed parkinsonism. Risk factors that may increase the likelihood of a tremor being drug-induced include older age, comorbid medical conditions (i.e., hyperthyroidism or renal failure in combination with certain drugs), or agents administered in high doses (Factor et al. 2019). On exam, drug-induced tremors tend to be symmetric, except for some rest tremors with features of parkinsonism (Alty and Kempster 2011). The presence of multifocal resting myoclonus and negative myoclonus may suggest polypharmacy is ongoing. Isolated mirror movements or overflow movements on examination may steer suspicion away from drugs as the sole cause of tremor, as mirror movements in adult patients are usually pathologic (Cox et al. 2012). However, as previously stated, drugs can enhance underlying pathogenic tremor, such as essential tremor worsened by albuterol or rest tremor with Parkinson's disease exacerbated by amiodarone. Ultimately, the physical exam combined with a good history can be used to narrow down the most likely pharmacological culprit as signs of new-onset parkinsonism accompanied by rest tremor would not be expected to be drug-induced by classes of drugs known to cause postural or kinetic tremor (Fig. 23.1).

The mechanisms behind most drug-induced tremors are not fully understood, although multiple theories have been proposed (Table 23.2). In most cases, the

offending drug is thought to result in enhancement of physiological tremor (Morgan et al. 2017). As opposed to the limited knowledge regarding drug-induced tremor pathophysiology, more information is available regarding management (Table 23.2). Frequently, tremors are not bothersome to the patient or may improve with time (Table 23.3). Some cases may require careful discussion of the risks and benefits of discontinuing the drug, lowering the dose, or transitioning to a less tremorigenic alternative. Patients may also desire to start an additional drug to target the tremor symptoms, such as beta-adrenergic antagonists (Morgan and Sethi 2005).

The remainder of this chapter will focus on specific drugs that can induce tremor with emphasis on the type of tremor(s) encountered. It will also provide an overview of the risk factors, proposed mechanisms of tremor induction, and possible management strategies for particular drugs.

23.2 Antiarrhythmics

23.2.1 Amiodarone

Amiodarone, a class III antiarrhythmic indicated for management of ventricular and atrial arrhythmias, is known to have countless adverse effects, including neurotoxicity (Harris et al. 1983). The frequency of neurological side-effects has been as high as 70% in some studies (Greene et al. 1983). Tremor is one of the most common neurological side-effects (Charness et al. 1984). Others include ataxia, peripheral and demyelinating neuropathies, alterations in sleep or memory, myoclonus, dyskinesias, myopathy, and possibly vestibular dysfunction (Gürkov 2018; Orr and Ahlskog 2009). The typical tremor associated with amiodarone occurs at a frequency of 6–10 Hz. It is postural and/or kinetic. In some cases, the kinetic component may be asymmetric, but is not unilateral (Charness et al. 1984). Rest tremor and parkinsonism may rarely manifest in patients prescribed amiodarone (Werner and Olanow 1989; Ishida et al. 2010). Incidence of tremor with this drug ranges from 3% to 40% (Charness et al. 1984; Orr and Ahlskog 2009; Hyatt et al. 1988). More often, the tremor presents shortly after starting the drug (Charness et al. 1984). Risk of amiodarone-induced tremor is increased with higher doses and longer duration of treatment (Charness et al. 1984; Orr and Ahlskog 2009). To date, the mechanism of amiodarone neurotoxicity, including its implication in causing tremor, is not well understood. Thyroid dysfunction is a known complication with amiodarone therapy. Hyperthyroidism is one possible method by which the drug may induce tremor (Morgan et al. 2017). Exacerbation of underlying essential or parkinsonian tremors have also been reported (Charness et al. 1984; Orr and Ahlskog 2009). Recently, a case report found evidence of amiodarone deposition in the brain of a patient who developed tremor with parkinsonism but remained without evidence of another cause on autopsy (Ishida et al. 2010). Amiodarone-related side-effects involving other organ systems have been attributed to buildup of the drug and

Table 23.2 Possible mechanisms and management approach of tremor-inducing drugs

Drug or drug class	Proposed tremor mechanism(s)	Management strategies
Amiodarone	Likely enhanced physiologic tremor Possibly hyperthyroidism	Reduce dose to <200 mg daily Test for hyperthyroidism May respond to BB
SSRIs/SNRIs and TCAs	Likely enhanced physiologic tremor Enhanced central component (amitriptyline)	Monitor for improvement with time Reduce dose Switch to an SSRI/SNRI (TCAs) Add BB (may worsen depression)
Lithium	Increased activity of central oscillators	Reduce dose Switch to alternative agent Transition to long-acting formulation Start BB (may worsen depression) Start primidone
Valproate	Likely enhanced physiologic tremor Dopaminergic dysfunction	Reduce dose or switch to another AED Change to controlled-release formula Start BB or amantadine
Bronchodilators	Enhanced physiologic tremor Enhanced mechanical reflex component	Monitor for tolerance Reduce frequency Switch to long-acting formulation
Dopamine receptor blockers	Blockade of striatal dopamine receptors	Switch to atypical antipsychotic Discontinue the drug Add amantadine or an anticholinergic
VMAT2 inhibitors	Prevent presynaptic dopamine release	Discontinue the drug
Metoclopramide	Enhanced physiologic tremor Blockade of striatal dopamine receptors	Remove the drug Consider alternative motility agent (i.e., erythromycin)
Tacrolimus and cyclosporine	Enhanced physiologic tremor (likely)	Monitor if mild severity Reduce dose Switch to alternative drug
Interferon alpha	Decrease dopamine in the CNS (?)	Switch to alternative drug
Alcohol	Enhanced physiologic tremor (withdrawal) Cerebellar toxicity (alcoholism)	Reduce or discontinue use Add BB
Nicotine	Activation of nicotine acetylcholine receptors in the inferior olive (?)	Discontinue all nicotine use
Caffeine	Likely enhanced physiologic tremor	Reduce caffeine intake

AED antiepileptic agent, *BB* beta-blocker or beta-adrenergic antagonist, *CNS* central nervous system, *SNRIs* serotonin norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants, *VMAT2* vesicular monoamine transporter 2

Table 23.3 Typical timing of drug-induced tremor onset after starting and resolution after discontinuation organized by drug types

Drug or drug class	Timing of tremor onset	Timing of tremor resolution
Amiodarone	Within days to weeks	Within weeks (may be longer with parkinsonism/rest tremor
SSRIs and SNRIs	Within 1–2 weeks to 2 months	Within 1–2 months
TCAs	Not well studied (likely similar to SSRI/SNRIs)	Not well studied (likely similar to SSRI/SNRIs)
Lithium	Within 1 week	Improves quickly (exception: intention tremor after toxicity may be permanent)
Valproate	Postural/kinetic quicker than parkinsonism/rest tremor (onset may be progressive, over months)	Within weeks to several months
Bronchodilators	Hyperacute (within hours of use)	Quick offset; shortly after disuse or effects subside
Dopamine receptor blockers	Not well studied; more likely with longer duration of use	Parkinsonism/rest tremor may take up to 1 year or longer to improve
Alcohol	Within days (after withdrawal)	May persist for weeks; especially with 3-Hz leg tremor
Beta-blockers	Within days	Usually within 24–72 hours
Bismuth salts	Weeks to months	Not well studied

SNRIs serotonin norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

its active metabolite. Similar accumulation in the central nervous system, especially in pathways involving cells of the basal ganglia and cerebellum, could explain the drug's tremorigenic effect (Ishida et al. 2010; Bongard et al. 2006). When managing patients with amiodarone-induced tremor, reduction of the dose to 200 mg may be beneficial (Hilleman et al. 1998). Improvement or resolution has been demonstrated within a few weeks of discontinuing the drug (Charness et al. 1984), although, in rare cases of parkinsonism, it has been suggested that rate of recovery may depend on the length of amiodarone use (Werner and Olanow 1989). As previously stated, amiodarone may induce thyroid dysfunction. Similarly, tremor, especially the postural, can be seen with high doses of levothyroxine (Mandel et al. 1989). Therefore, it is important to exclude hyperthyroidism or even thyrotoxicosis as a possible cause for tremor (Morgan et al. 2017). In refractory cases, propranolol can produce a favorable outcome for symptomatic patients (Charness et al. 1984).

23.2.2 Others: Procainamide and Mexiletine

Tremors have been associated with the use of mexiletine and procainamide (Morgan and Sethi 2005; Rubinstein and Cabili 1986; Manolis et al. 1990). Procainamide

is a class IA antiarrhythmic that was noted to induce postural and kinetic tremors (Morgan and Sethi 2005; Rubinstein and Cabili 1986). Postural and kinetic tremors have also been documented with mexiletine (Morgan and Sethi 2005; Manolis et al. 1990). This class 1B antiarrhythmic was found to induce tremor in approximately 30% of patients in one case series compared to placebo (Impact Research Group 1984). Other neurological side-effects include ataxia and cognitive impairment; there have even been some cases of possible associated parkinsonism (Manolis et al. 1990; Impact Research Group 1984). The cause of tremor induction with these drugs is not known (Morgan and Sethi 2005).

23.3 Antidepressants and Mood Stabilizers

23.3.1 Selective Serotonin Reuptake Inhibitors (SSRIs) and Selective Norepinephrine Reuptake Inhibitors (SNRIs)

SSRIs and SNRIs are employed for treatment of anxiety and depression, along with other disorders. These drugs have been implicated in numerous movement disorders, including dystonia, akathisia, and myoclonus (Leonard and Faherty 1996). The frequency of tremor was noted to occur in 20% of patients treated with fluoxetine and 17% of patients treated with venlafaxine in one series (Diaz-Martinez et al. 1998). Characterization of the tremor seen with fluoxetine is most commonly postural with a frequency of 6–12 Hz. Kinetic tremors more often than rest tremor and parkinsonism are also seen with fluoxetine use (Serrano-Dueñas 2002). Other drugs in this class that are known to induce tremor include fluvoxamine, sertraline, citalopram, and paroxetine, of which the latter two were associated with jaw and chin tremors, respectively (Guelfi et al. 1983; Tarlaci 2004; John et al. 2013; Lambert et al. 1998). Most commonly, tremor is noted within 1–2 weeks and up to 2 months after starting these drugs (Diaz-Martinez et al. 1998; Tarlaci 2004; John et al. 2013). Etiology of tremor with these drugs is unclear. It has been theorized that SSRIs may result in over-excitation of serotonergic pathways involving the inferior olivary nucleus and red nucleus with ultimate effects on the thalamus and cortex leading to tremor (Diaz-Martinez et al. 1998). Citalopram was also shown to cause dose-dependent worsening of harmaline-induced tremor in rats along with decrease in serotonin turnover in the brainstem (Arshaduddin et al. 2004). In patients requiring management for drug-induced tremor, those attributed to SSRIs and SNRIs appear to improve with discontinuation of the drugs within 1–2 months (Diaz-Martinez et al. 1998; Tarlaci 2004; John et al. 2013).

23.3.2 Tricyclic Antidepressants (TCAs) and Tetracyclic Antidepressants

TCAs are often prescribed for various neurological and psychiatric conditions and are associated with tremors. Amitriptyline has been noted to induce severe postural tremors (Watanabe et al. 1978). These tremors occur in the 7–15 Hz range (Raethjen et al. 2001). Tremor has also been attributed as a side-effect of imipramine use (Guelfi et al. 1983). Amoxapine, a tetracyclic antidepressant, is known to cause parkinsonism (Ross 1990). The frequency of tremor induced by TCAs appears to be lower than those caused by SSRIs or SNRIs (Brambilla et al. 2005). Regarding the pathophysiology, a study evaluating drug-induced tremor using electromyography (EMG) found that amitriptyline heightened the central aspect of physiological tremor (Raethjen et al. 2001). The same study found that the tremor detected on EMG was not always evident clinically (Raethjen et al. 2001), although, if TCA-induced postural tremors are bothersome, there is evidence that tremor can lessen with time or may respond to dose reduction (Arbaizar et al. 2008). In addition, imipramine has been cited to improve with beta-adrenergic antagonists (Morgan and Sethi 2005). Careful discussion is required if beta-adrenergic antagonists are used, however, as these may worsen depression.

23.3.3 Withdrawal Syndromes and Serotonin Syndrome

Abrupt or rapid taper of antidepressants can lead to a withdrawal syndrome that consists of tremors, gastrointestinal symptoms, agitation, fatigue, and myalgias. It is most common within 1–3 days after discontinuation of the drug. Drugs with short half-lives, such as fluvoxamine, paroxetine, and even sertraline, are at higher risk (Arbaizar et al. 2008). In one systematic review, venlafaxine was found to be more commonly associated with withdrawal compared to other SNRIs, although withdrawal symptoms have also been seen with escitalopram (Fava et al. 2018).

Serotonin syndrome can occur with numerous drugs. These include, but are not limited to, tramadol and SSRIs/SNRIs (which inhibit serotonin reuptake), monoamine oxidase inhibitors (which inhibit serotonin catabolism), fentanyl (a serotonin receptor agonist), and lithium (which alters serotonin postsynaptic receptors) (Garel et al. 2021). Features of this condition are variable and can range from mild to life-threatening cases (Volpi-Abadie et al. 2013). Abnormal movements seen with this syndrome include myoclonus and tremor (Dunkley et al. 2003). Tremor is typically an early finding and more often affects the lower extremities (Morgan and Sethi 2005). Treatment of serotonin syndrome is outside the scope of this text.

23.3.4 Lithium

Lithium is frequently used in practice, despite multiple known adverse and toxic effects. It has efficacy in the treatment of mood disorders, including bipolar disorder and refractory cases of depression (Dennison et al. 2011). Tremor is one of the most frequently encountered side-effects seen. It is also one of the most common reasons for drug discontinuation and noncompliance (Burgess et al. 2001). As with other drugs, lithium-induced tremor can vary in presentation. The overall frequency has been cited between 4% and 65% of patients in different studies (Canning et al. 2012). The most commonly encountered type of tremor is an enhanced physiologic tremor. In these patients, the hands and upper extremities are typically involved with a frequency of 8–12 Hz (Baek et al. 2014). Tremor is often induced quickly and can occur within the first week of starting or increasing the drug. The tremor usually remains stable or improves with continued lithium use (Canning et al. 2012; Baek et al. 2014). Alternatively, parkinsonism and rest tremor occur rarely with lithium. Risk increases with age and is associated with longer exposure. Clinically, the rest tremor has a lower frequency in the 4–7 Hz range (Tyrer et al. 1981). Tremor may also be an early sign of lithium toxicity and occurred within 3 days in one retrospective study (Dennison et al. 2011). Tremor seen with toxicity is usually coarse and may involve multiple body parts (Speirs and Hirsch 1978). Other abnormalities such as altered mentation, hyperreflexia, ataxia, anorexia, emesis, or diarrhea should also heighten a clinical suspicion for lithium toxicity (Arbaizar et al. 2008; Speirs and Hirsch 1978). In severe cases of toxicity, irreversible damage may occur, in which intention tremors and other cerebellar symptoms may continue even after discontinuation of the drug (Speirs and Hirsch 1978). The risk of lithium-induced tremor is more common in the elderly, males, and patients with a family or personal history of essential tremor (Arbaizar et al. 2008). An additive effect on tremor can occur if lithium is combined with other drugs, including serotonergic agents (such as antidepressants) or drugs known to induce tremor (such as valproic acid) (Morgan and Sethi 2005). Lithium levels above 1–5 mEq/L or the addition/removal of agents known to alter lithium concentration increase the likelihood of tremor and possible toxicity (Baek et al. 2014; Speirs and Hirsch 1978). Of note, however, is the fact that tremor and features of toxicity have been reported in cases with serum levels within the therapeutic range (Speirs and Hirsch 1978). There is little evidence known as to the pathophysiology behind tremors induced by lithium. A possible effect on the central nervous system has been suggested, given levels of the drug in the brain correlate with tremor side-effects. There is also conflicting evidence that lithium may influence serotonergic pathways in the brainstem (Morgan et al. 2017). In one animal study, lithium led to reduced tau in the brain and elevated iron in the substantia nigra and cortex; it was proposed these changes may provide a model for parkinsonism associated with lithium treatment (Morgan et al. 2017; Lei et al. 2017). As most cases of lithium-induced tremor are not disabling, treatment is not always indicated (Morgan and Sethi 2005). If necessary, first steps for management include weighing the risks and

benefits of lowering the dose or switching to an alternative therapy (Morgan and Sethi 2005). A small, open-label study showed promising results when patients were switched to prolonged-release lithium preparation. In this study, there was tremor improvement within 1 week and sustained improvement at 12 weeks, compared to immediate-release formulation of lithium in bipolar patients (Pelacchi et al. 2022). Regarding medical therapy, propranolol and other beta-adrenergic agonists are used to treat lithium-induced tremor (Lapierre 1976; Dave and Langbart 1994). Other drugs typically indicated for essential tremor, such as primidone, have been applied successfully (Baek et al. 2014).

23.4 Antiepileptics

Antiepileptics have been associated with multiple movement disorders, including tremor. Postural and kinetic types are encountered in up to 45% of patients prescribed these agents. Parkinsonism and rest tremor are less common and occurred in 4.5% of the patients in one study (Zadikoff et al. 2007). Details regarding the incidence, risk factors, pathophysiology, and management of tremor induced by specific antiepileptic agents are discussed in the following section.

23.4.1 Valproic Acid

Valproic acid is commonly prescribed for treatment of various psychiatric conditions, migraine headaches, and epilepsy. Incidence of valproate-induced tremor has been cited at 14% in a study of pooled data. It is the antiepileptic most likely to be associated with tremor, with a 4.5-times higher risk compared to other anticonvulsants (Zhang et al. 2020). Postural and kinetic tremors involving the bilateral upper extremities are the most frequently encountered. Tremor is characterized as a low-amplitude and high-frequency (6–15 Hz) (Paparella et al. 2021). Isolated rest tremor and tremors involving different parts of the body can also be seen. Frequency of voice tremor and tremor involving the face, tongue, head, trunk, or lower extremities may vary by site involved (Paparella et al. 2021; Alonso-Juarez et al. 2017). Valproic acid is more likely to be associated with upper extremity rest tremor, head or voice tremor, and lower limb tremor compared to essential tremor (Paparella et al. 2021). Tremor is believed to be dose dependent, with one study citing increased likelihood of tremor in patients taking 1000–1500 mg per day of valproate, compared to lower doses (Zhang et al. 2020). Other risk factors may include female sex, family history of tremor, and longer treatment duration, but more studies are needed (Zhang et al. 2020; Lan et al. 2022). Valproate is also the most common antiepileptic agent to induce parkinsonism. Frequency of parkinsonism occurred in 10% of patients on valproate in a small study, compared to 2% of patients prescribed other anticonvulsants (Zadikoff et

al. 2007). Combined data from multiple studies found only 3% of subjects in a larger pool of patients displayed parkinsonism while on valproic acid (Baizabal-Carvallo and Alonso-Juarez 2021). Patients may present with rest tremor, which can be asymmetric, and have other clinical features similar to idiopathic Parkinson's disease. Typically, onset of tremor and parkinsonism is slowly progressive over months (Silver and Factor 2013). The mechanism behind valproate-induced tremor is not fully understood (Morgan et al. 2017). It has been hypothesized that alterations in pathways involving the neurotransmitter GABA (gamma-aminobutyric acid) may be implied in the pathophysiology of essential tremor (Gironell 2014). Similarly, one of the mechanisms of action of valproic acid is to increase GABA, which may contribute to drug-induced tremor (Ghodke-Puranik et al. 2013). In an animal model, valproate was associated with possible toxic effects on dopaminergic areas of the brain (Morgan et al. 2017). A decrease in serum dopamine and norepinephrine levels was also demonstrated in patients with tremor on valproic acid (Hamed and Abdellah 2017). However, further studies are needed to determine the link between these alterations in neurotransmitters and the pathogenesis of tremor with valproate. When symptomatic, tremors and parkinsonism may respond to lowering the dose or switching to an alternative anticonvulsant within several weeks to months (Morgan and Sethi 2005; Silver and Factor 2013). Studies have also shown that transition to controlled-released preparations can result in tremor improvement (Rinnerthaler et al. 2005). Some patients with valproate-induced parkinsonism may improve with levodopa (Silver and Factor 2013). In refractory cases or if the drug cannot be changed, benefit may be found with the use of propranolol or amantadine (Karas et al. 1983).

23.4.2 Other Antiepileptics

Tremor was found to occur in 4% of patients treated with adjunctive lamotrigine compared to 1% with placebo (Morgan and Sethi 2005). In a more recent study, postural and intention tremors were diagnosed clinically in 10% of patients prescribed lamotrigine for epilepsy. This was compared to diagnosis by objective accelerometry through which 25% of patients were found to have pathological tremor. Given the large proportion of kinetic tremor in this study, it was proposed that lamotrigine-induced tremor may occur via cerebellar pathways (Kovács et al. 2019). Management by switching to another antiepileptic resulted in resolution of lamotrigine-induced tremor in one case report (Yang et al. 2010). Numerous additional anticonvulsants have been implicated in drug-induced tremors (Zhang et al. 2020). Topiramate has been noted to cause postural tremors (Alonso-Navarro and Jiménez-Jiménez 2006). When used as an adjunctive treatment, gabapentin-induced tremor was more common (6.8%) compared to placebo (3.2%) (Morgan and Sethi 2005). Additional anticonvulsants associated with tremors include carbamazepine, oxcarbazepine, tiagabine, phenytoin, and vigabatrin (Morgan and Sethi 2005; Alonso-Navarro and Jiménez-Jiménez 2006). Pathophysiology leading to tremor

with these drugs is not known and management approach is similar to that of most drug-induced tremors.

23.5 Antimicrobials

Although antibiotics, antifungals, antiparasitic agents, and antivirals are commonly used, tremor induced by these drugs are rarely documented and limited mostly to case reports.

23.5.1 Antibiotics

Trimethoprim sulfamethoxazole (TMP/SMX) is a frequently encountered antibiotic in clinical practice and is rarely associated with neurological side-effects (Aboulafia 1996). Infrequently, tremor can be seen and is most often cited in immunocompromised individuals being treated for *Pneumocystis carinii* pneumonia (Aboulafia 1996; Van Gerpen 1997; Patterson and Couchenour 1999). Debilitating, symmetric, postural, and action tremors have been described. This tremor pattern can involve the upper or lower limbs and, in one case, involved the head (Van Gerpen 1997; Patterson and Couchenour 1999). A low-amplitude rest tremor has also been described (Aboulafia 1996). TMP/SMX-associated tremor presents shortly after initiation, resolves quickly after discontinuation, and may reoccur with rechallenge (Aboulafia 1996; Van Gerpen 1997; Patterson and Couchenour 1999). The pathophysiology by which TMP/SMX causes tremor is not known (Patterson and Couchenour 1999).

Ertapenem is an antibiotic belonging to the carbapenem family. Although tremor rarely occurs with this drug, 3.3–5.1% of patients develop neurological side-effects (Köse and Temoçin 2018). Risk appears to be higher in those with acute or chronic kidney disease and tremor can affect the hand or voice (Köse and Temoçin 2018; Hanna et al. 2018). Tremor appears and resolves within days to weeks of exposure or discontinuation (Köse and Temoçin 2018; Hanna et al. 2018).

Tremor may present alongside other signs of neurotoxicity in some cases. One patient requiring admission to a hospital for renal insufficiency and infection developed cefuroxime-induced tremor along with myoclonus and encephalopathy (van Dam et al. 2017). Another report documented a man with hallucinations and upper and lower limb postural and action tremors who was administered erythromycin and methylprednisolone. Tremors affected handwriting and were also present in the head and face. Symptoms resolved within 3 days of drug discontinuation (Gallerani and Boari 2008).

23.5.2 Antifungals

Amphotericin B induced parkinsonism with rest tremor and encephalopathy in three children with bone marrow transplants (Mott et al. 1995). Five patients with prolonged use of itraconazole for treatment of aspergillosis were found to have drug-induced upper limb tremor. Two of the five patients developed upper limb rest and postural tremors (with or without action tremor) that were low amplitude and in the 4–6 Hz range. Three of the five patients developed symmetric fine, resting hand tremors that resolved after drug discontinuation (Lestner and Denning 2010). Tremor has also occurred in one patient prescribed fluconazole after bone marrow transplantation and resolved shortly after the drug was discontinued (Quabeck et al. 1992).

23.5.3 Antivirals

Acyclovir is frequently used in the treatment of infections related to varicella zoster and herpes simplex (Mahad et al. 2005). Acyclovir-induced tremor is encountered in 40–58% of treated patients (Mahad et al. 2005). In a small study of bone marrow transplantation recipients, five out of six patients developed acyclovir-induced tremors. Tremor occurred in the hands or worsened with action in some cases (Wade and Meyers 1983). Tremor may be related to higher acyclovir doses or longer duration of use and resolves after cessation (Wade and Meyers 1983). Regarding other antivirals, mild tremor of the hand was noted in a patient administered famciclovir following renal transplantation that developed lamivudine resistance to hepatitis B viral infection; symptoms resolved after the drug was discontinued (Tang et al. 2002). A woman enrolled in a trial of tenofovir and emtricitabine for use as antiretroviral pre-exposure prophylaxis developed a fine hand tremor at rest and with action with associated peripheral neuropathy. Symptoms resolved gradually after drugs were stopped (Owino et al. 2013). Although its use has been replaced in recent years by more effective and less toxic antivirals, vidarabine has been known to induce tremor as well as encephalopathy (Wang et al. 2021; Cullis and Cushing 1984).

23.5.4 Antiparasitic Agents

Ivermectin is most commonly used in the treatment of the intestinal strongyloidiasis. Tremor is an adverse effect of this drug, along with other signs of central nervous system toxicity (Turner et al. 2005).

23.6 Bronchodilators

Tremor is a common adverse event noted in patients prescribed beta-adrenergic agonists for respiratory diseases. Albuterol was demonstrated to induce postural tremor significantly more often in children compared to placebo (Mazer et al. 1990). The frequency of tremor related to salbutamol has ranged from 7% to 20% (Morgan and Sethi 2005). Postural tremor caused by salbutamol used in asthma and chronic obstructive pulmonary disease (COPD) is dose dependent (Nizet et al. 2004). Similarly, a dose-dependent tremor response was found for patients treated with rac-formoterol (Whale et al. 2008). The pathophysiology behind bronchodilator-induced tremor is most likely through their effect on muscle. In a 1960s' experiment, ischemic-inducing measures in the arm were taken to prevent administration of epinephrine and resulted in prevention of tremor induction (Morgan et al. 2017). Evidence of a peripheral mechanism of beta-adrenergic agonists has been further supported by the presence of β2-adrenergic receptors on muscle spindles and extrafusal fibers and the activation of these fibers enhances physiologic tremor (Abila et al. 1985). In a study evaluating the effects of salbutamol and propranolol on tremor, salbutamol worsened tremor but did not affect the corticomuscular coherence, indicating there may be an additional central mechanism to tremor generation with these drugs (Baker and Baker 2012). Intervention may not always be necessary in bronchodilator-induced tremor. In a study of children treated with inhaled albuterol, tremor had no clear effect on fine motor function. Furthermore, patients may develop tolerance with extended use of these drugs (Mazer et al. 1990). As-needed formoterol compared to scheduled doses of the drug resulted in decreased frequency of tremor in some patients (Richter et al. 2007). If indicated, tremor may also improve with the use of long-acting formulations (Morgan and Sethi 2005). Of note, corticosteroids, such as prednisone or methylprednisolone, are also used frequently in the treatment of respiratory conditions such as asthma. These drugs are well-known to worsen underlying physiologic or essential tremor and have also been attributed to induction of postural tremors.

23.7 Dopamine Receptor Antagonists and Dopamine Depleting Agents

23.7.1 Dopamine Receptor Antagonists

Dopamine-blocking agents are frequently prescribed in the treatment of various psychiatric and other conditions. Drug-induced parkinsonism (DIP) is the clinical presentation most often encountered with these drugs. Frequency ranges from 20% to 35% for typical and atypical neuroleptics combined (Ward and Citrome 2018). However, DIP occurs in up to 60% of patients taking typical antipsychotics (Morgan and Sethi 2005). Dopamine-blocking agents also induce rest and postural tremors,

but usually accompany the DIP presentation (Morgan and Sethi 2005; Sethi 2001). This type of tremor is difficult to separate from idiopathic Parkinson's disease on clinical examination. Antipsychotic-induced tremor usually begins in the arms and can be asymmetric (Sethi and Zamrini 1990). The association of DIP and tremor with neuroleptic use may be more likely in females, older patients, and those with familial predisposition or AIDS (Morgan and Sethi 2005; Sethi 2001). Risk may also vary based on individual susceptibility and the specific agent or dose that is prescribed (Morgan and Sethi 2005; Sethi 2001). All neuroleptics have the potential to cause DIP (Shin and Chung 2012). Among atypical antipsychotics, tremor is seen more often with thioridazine and fluphenazine than chlorpromazine (Sethi and Zamrini 1990). Lower incidence of DIP is seen with atypical antipsychotics, such as clozapine, risperidone, olanzapine, ziprasidone, and quetiapine. Clozapine and quetiapine are believed to be the least likely to cause DIP (Shin and Chung 2012). The pathophysiology behind antipsychotic-induced tremor and parkinsonism stems from the effect of dopamine D2-receptor blockade and the subsequent alterations to the nigrostriatal pathways (Ward and Citrome 2018). Compared to the loss of presynaptic dopamine transporters seen in idiopathic Parkinson's disease, normal I-123-ioflupane single photon emission computed tomography imaging signifies dysfunction of the postsynaptic dopaminergic neurons in patients with DIP due to neuroleptics (Jennings et al. 2004; Booij et al. 2001). Management of these patients typically consists of switching from a typical to an atypical neuroleptic or discontinuing neuroleptics altogether. Symptoms may resolve after removal of the offending agent but can take up to 1 year or longer (Lim et al. 2013). DIP may present in some patients by unmasking a pre-existing dopamine loss in the substantia nigra, in which case parkinsonism would not be reversible (Morgan and Sethi 2005). If alternative drugs or discontinuation of the antipsychotics are not an option, treatment with amantadine or anticholinergics may be beneficial (Ward and Citrome 2018).

23.7.2 Tardive Tremor

Tardive tremor is rare and mainly presents with a postural component but may have rest and/or kinetic features (Tarsy and Indorf 2002; Stacy and Jankovic 1992). The upper and lower extremities are typically involved; tremor may also be evident in the head or lips. It has been characterized as coarse with a frequency of 3–5 Hz (Stacy and Jankovic 1992). Tardive tremor presents after extended use of neuroleptic agents, with length from exposure ranging from 2 to 20 years (Tarsy and Indorf 2002; Martino et al. 2016). As opposed to drug-induced parkinsonism, tardive tremor will persist after discontinuation of the antipsychotic. Treatment with dopamine depleting agents, such as tetrabenazine, or re-exposure to neuroleptics improves the tremor (Tarsy and Indorf 2002).

23.7.3 Dopamine Depleting Agents

Vesicular monoamine transporter 2 (VMAT2) inhibitors are used for management of Huntington's disease and tardive dyskinesia. Drugs in this class include tetrabenazine, deutetrabenazine, and valbenazine. As VMAT2 inhibitors cause depletion of dopamine by decreasing the amount released into synapses, they can induce parkinsonism and rest tremor (Ward and Citrome 2018). Specifically, valbenazine has been cited to cause rest tremor in cases of drug-induced parkinsonism and in a patient where the drug unmasked underlying Parkinson's disease (Vasireddy and Guduru 2020; Vasireddy et al. 2020). Similar to antipsychotics, symptoms may improve with discontinuation of the drug (Ward and Citrome 2018).

23.8 Gastrointestinal Agents

23.8.1 Metoclopramide

Metoclopramide is commonly used for nausea/vomiting and gastric motility disorders (Shprecher 2012). A well-known side-effect includes drug-induced parkinsonism with rest tremor. Alternatively, presentations resembling essential tremor have been reported that may even improve with alcohol (Ahronheim 1982). Metoclopramide is also associated with tardive syndromes. Case reports have noted resting and postural tardive tremors in elderly patients in the setting of previous metoclopramide use (Tarsy and Indorf 2002; Stacy and Jankovic 1992). The proposed mechanism of action of this drug-induced tremor is thought to be via antagonist effect on dopamine receptors (Shprecher 2012).

23.8.2 Other Antiemetics: Promethazine and Prochlorperazine

Promethazine and prochlorperazine are commonly prescribed as antiemetics. Both have been associated with drug-induced parkinsonism with resting tremors (Wright et al. 1998; Thanvi and Treadwell 2009). Risk is higher with prolonged use and in the case of prochlorperazine, more commonly in the elderly (Thanvi and Treadwell 2009). Interestingly, in studies comparing promethazine to another antihistamine, loratadine, promethazine led to decreased physiologic tremor while loratadine increased it (Naicker et al. 2013; Baumann-Birkbeck et al. 2014).

23.8.3 Misoprostol

Misoprostol is a prostaglandin E1 analog indicated for gastric ulcer prevention in setting of nonsteroidal anti-inflammatory drug use. Toxicity with this drug has been associated with tremor and was documented in a woman who ingested approximately 15 times the maximum recommended dose (Graber and Meier 1991).

23.8.4 Cimetidine

Cimetidine, a histamine H2-receptor-blocking agent, is prescribed to treat gastroesophageal reflux and peptic ulcers. Postural and action tremors in three patients were determined to be cimetidine-induced. In all cases, tremor improved with removal, appeared again with re-exposure, and improved or resolved with propranolol. Mechanism by which this tremor is induced is unclear but may be related to effects on histamine signaling (Bateman et al. 1981).

23.8.5 Bismuth Salts

Bismuth salts, such as bismuth subsalicylate, can result in a rare, subacute encephalopathy syndrome with marked psychosis, delirium, ataxia, myoclonus, and seizures (Gordon et al. 1995). Postural and kinetic tremors of the upper limbs have been reported as part of this syndrome (Gordon et al. 1995). Recovery after discontinuation may take weeks to months (Gordon et al. 1995; Borbinha et al. 2019). The pathophysiology behind bismuth-related encephalopathy is not fully understood. However, concentration of bismuth in the gray matter, especially the thalamus and cerebellum, of patients who died from this drug-induced encephalopathy was approximately double that of the white matter (Lambert 1991).

23.9 Immunosuppressants and Chemotherapeutics

23.9.1 Calcineurin and Non-Calcineurin Inhibitors

Immunosuppressants and immunomodulators are frequently used in treatment of patients with autoimmune diseases and following solid organ transplantation. The calcineurin inhibitors tacrolimus and cyclosporine have disabling neurological side-effects, of which tremor is the most common (Erro et al. 2018). Combined, the frequency of tremor with these drugs can be as high as 70% (Erro et al. 2018). The etiology of calcineurin inhibitor-induced tremor is attributed to enhancement of

physiologic tremor (Paul et al. 2004). Tacrolimus has been attributed to tremor in up to approximately 54% of kidney transplant patients and may be more likely to induce tremor compared to cyclosporine (Erro et al. 2018). Tremor occurred in 36% of pediatric liver transplant recipients in one study (Uemoto et al. 1993). In another study, 23% developed severe tremors of the hands after liver transplantation that affected writing and worsened with action. Most cases, but not all, were alleviated by dose reduction (Wijdicks et al. 1994). Data from an open-label trial of kidney transplant patients showed improvement in tremor amplitude, tremor ratings, and quality of life after transition to an extended-released preparation of tacrolimus. Switching to this formulation may be a viable management option (Langone et al. 2015). Cyclosporine-induced tremor is seen in up to 40% of patients (Gijtenbeek et al. 1999). Generalized postural and, less often, kinetic tremors are typically observed (Gijtenbeek et al. 1999). Higher blood levels increase the risk, but tremors are typically mild and still encountered with normal serum measurements, therefore dose reduction is not always needed (Gijtenbeek et al. 1999). Tremor has also been noted with sirolimus, a non-calcineurin inhibitor, in a series of kidney transplanted patients; however, occurrence was less common than patients receiving calcineurin inhibitors (Erro et al. 2018).

23.9.2 Interferons

Interferons are used as a chemotherapeutic agent and for immunomodulation. Action and rest tremors can occur with interferon alpha (Nishihori et al. 2005). In one study, 22% of patients treated for melanoma had worsening of action tremors (Caraceni et al. 1998). One woman developed a facial tremor during prolonged use of the drug for treatment of chronic myeloid leukemia (CML) (Tan et al. 2003). Parkinsonism was discovered in another patient on this chemotherapy for CML, possibly due to interferon alpha's ability to decrease dopamine in the central nervous system (Sarasombath et al. 2002).

23.9.3 Antineoplastic Agents

Generally, chemotherapeutic agents rarely induce tremor and evidence in the literature is limited to case reports. Thalidomide is approved for treatment of multiple myeloma and erythema nodosum leprosum. Mild tremors occur in approximately 35% of patients treated with this drug (Ghobrial and Rajkumar 2003), although severe tremors have been reported with thalidomide (Chiruka and Chapman 2005). As opposed to irreversible thalidomide-induced neuropathy, tremors typically resolve after discontinuation of the drug. If alternative agents are not an option, it is recommended to resume the drug at a 50% reduced dose (Ghobrial and Rajkumar 2003). Vincristine that was administered with doxorubicin resulted

in parkinsonism with head and limb tremor in an infant treated for leukemia (Ross 1990). A woman, also being treated for leukemia, developed a coarse tremor following administration of the vincristine intraventricularly in setting of metastasis to the meninges (Morgan and Sethi 2005). Platinum analogs, namely cisplatin, can induce tremors along with other neurological symptoms (Amptoulach and Tsavaris 2011). There is a case report of a patient who developed action tremor during treatment with 5-flurouracil; symptoms resolved with drug discontinuation and returned with re-exposure (Ross 1990). Additional iatrogenic causes of tremor with chemotherapeutic agents include paclitaxel, cytosine arabinoside, ifosfamide, methotrexate, tamoxifen, and cytarabine (Bhatia et al. 2018).

23.9.4 Immune Checkpoint Inhibitors

Ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab are monoclonal antibodies used individually or in conjunction to treat cancer (Vogrig et al. 2020). Recently, side-effects of parkinsonism and postural tremor have been reported (Vogrig et al. 2020; Maetani et al. 2019; Xing et al. 2022; Carl et al. 2015). All cases occurred in setting of autoimmune encephalitis, including those with anti-thyroid antibodies, along with other neurological derangements. As such, tremor and parkinsonism in these cases may be drug- induced; however, cases may also be attributed to thyroid dysfunction or sequela of the underlying autoimmune process (Vogrig et al. 2020; Maetani et al. 2019; Xing et al. 2022; Carl et al. 2015).

23.10 Substances of Abuse or Misuse

23.10.1 Alcohol

Various forms of tremor have been attributed to alcohol use and abuse. A postural tremor is common and most often affects the upper limbs (Neiman et al. 1990; Koller et al. 1985). Amplitude with this tremor may be erratic and large; the frequency can range from 6 to 11 Hz (Neiman et al. 1990). Tremor is more commonly seen early in withdrawal states (Neiman et al. 1990). Postural tremor was found to occur in 47% of abstinent alcoholics in one series, compared to 3% in healthy controls, but was mild in most cases (Koller et al. 1985). A second type of tremor, the "metabolic tremor," occurs in the setting of alcoholic liver disease and is a separate entity from asterixis seen with hepatic dysfunction (Neiman et al. 1990). Lastly, a 3-Hz leg tremor has been described in the setting of cerebellar damage along with parkinsonism and rest tremors of the upper extremities (Neiman et al. 1990). Increased catecholamine release during alcohol withdrawal states may be a possible mechanism by which alcohol can induce tremor via direct effect on peripheral adrenergic receptors (Neiman et al. 1990). After alcohol discontinuation,

tremor may lessen but can remain for weeks, especially in the case of a 3-Hz leg tremor (Neiman et al. 1990). Parkinsonism may also occur shortly after and last for weeks following alcohol disuse but does not typically persist (Brust 2010). In severe cases, patients may respond to propranolol and benzodiazepines are useful in the setting of alcohol withdrawal (Neiman et al. 1990; Koller et al. 1985).

23.10.2 Stimulants

A multitude of movement disorders, including tremor, have been attributed to the use of psychostimulants. Tremor-inducing drugs in this category include amphetamine-like substances (i.e., cocaine, methamphetamine, dextroamphetamine, methylphenidate, and cathinone) and related compounds, like 3,4-methylenedioxymethamphetamine (MDMA) (Brust 2010; Asser and Taba 2015). MDMA has been associated with postural and kinetic tremors. Postural tremor lasted up to 10 days after use in one patient (Flavel et al. 2012). Rest tremor and parkinsonism have also been attributed to cocaine and MDMA use (Daras et al. 1994; O'Suilleabhain and Giller 2003). In one MDMA-induced patient, symptoms improved with levodopa (O'Suilleabhain and Giller 2003).

23.10.3 Nicotine

Cigarette use has been associated with postural and kinetic tremors (Louis 2007). Tremor amplitude has been found to be at least two times higher in smokers (Lippold et al. 1980). Although one study found increased risk of kinetic tremor in females who smoked, other studies have not seen a correlation between tobacco use and sex, age, or anxiety levels (Louis 2007; Shiffman et al. 1983). Chewing gum produces the same degree of tremor as smoking an equivalent dose of nicotine, suggesting nicotine plays a role in the pathophysiology of this drug-induced tremor (Shiffman et al. 1983). In an animal model, nicotine administration was noted to induce kinetic tremor and it was suggested the mechanism may be through activation of nicotinic acetylcholine receptors in the inferior olive (Kunisawa et al. 2016).

23.11 Sympathomimetics, Methylxanthines, and Beta-Adrenergic Antagonists

23.11.1 Sympathomimetics

Epinephrine is a sympathomimetic amine that can cause tremor. It is most commonly used in the treatment of anaphylaxis. The tremorigenic effect has been

attributed to enhancement of physiological tremor at the level of the muscle (Morgan and Sethi 2005). While restrictions are now in place in the United States regarding distribution of ephedrine and phenylpropanolamine containing compounds, these sympathomimetic drugs are known to induce tremors (Dietz Jr. 1981; Supiyaphun et al. 2002). Pseudoephedrine, however, is still used in decongestants and allergy drugs. Tremor was found to occur in 39% of patients in a study of pseudoephedrine use in combination with loratadine for allergic rhinitis (Supiyaphun et al. 2002). Fortunately, symptoms typically resolve after this drug is discontinued.

23.11.2 Methylxanthines

Methylxanthines, such as theophylline, aminophylline, and caffeine, have tremorigenic effects via tremor induction or enhancement. Aminophylline was shown to cause worsening of tremor amplitude in essential tremor patients (Buss et al. 1997). However, theophylline, an adenosine A2A antagonist also indicated for COPD treatment, resulted in improvement in essential tremor to the same extent but in twice the amount of time required for propranolol (Mally and Stone 1995). More robust data are available in the literature for the tremor-inducing effects of caffeine, although data are mixed. Six percent of patients with Parkinson's disease, 8% of those with essential tremor, and 2% of controls reported subjective worsening of tremor after coffee intake. However, there was no significant objective evidence with accelerometry of worsening tremor after administration of 325 mg oral caffeine (Koller et al. 1987a).

23.11.3 Beta-Adrenergic Antagonists

Pindolol, a beta-adrenergic antagonist used to treat numerous cardiac conditions, is a documented source of drug-induced tremors (Hod et al. 1980). As opposed to other beta-adrenergic antagonists used in the treatment of tremor, pindolol can induce new or exacerbate known postural and kinetic tremors (Al-Shorafat et al. 2021; Koller et al. 1987b). In case reports, tremor involves the upper limbs at a frequency of approximately 7 Hz (Al-Shorafat et al. 2021; Koller et al. 1987b). A trial comparing propranolol and pindolol for treatment of essential tremor resulted in worsening tremor amplitude in the pindolol-treated group (Teravainen et al. 1977). The mechanism behind beta-adrenergic antagonists that induced tremor is suspected to be secondary to partial activation of beta-adrenergic receptors (Al-Shorafat et al. 2021). These tremors typically develop within days of therapy initiation and disappear after 24–72 hours of termination (Hod et al. 1980), although, in one patient with exacerbation of an underlying tremor, improvement did not occur until after 1 month of withdrawal (Al-Shorafat et al. 2021). Regarding other beta-adrenergic antagonists, metoprolol administered for hypertension was implicated in

development of new postural and kinetic tremors with a resting component in one patient. In this case, resolution of tremor occurred after switching to carvedilol (Al-Shorafat et al. 2021).

23.12 Conclusion

Many patients develop tremors, including those caused by drugs. Most drugs cause postural or kinetic tremors, but rest tremor with parkinsonism and other types of tremors may occur. If possible, it is important for clinicians to recognize factors that place patients at risk for iatrogenic tremor prior to initiation of a tremorigenic drug. When diagnosing drug-induced or drug-enhanced tremor, a careful history is needed, especially regarding a temporal relationship with initiation of the drug. Tremorigenic drugs are prescribed by physicians from every discipline of medicine. While some drugs are commonly known to induce tremor, others are not. Awareness of these drugs is vital as the list of tremor-causing agents continues to grow. In addition, future research is needed to determine the mechanism by which these drugs cause tremor. While most patients improve with time or discontinuation of tremor-inducing drugs, additional studies are also needed to determine the best management approach.

References

Abila B, Wilson JF, Marshall RW, Richens A. The tremorolytic action of beta-adrenoceptor blockers in essential, physiological and isoprenaline-induced tremor is mediated by beta-adrenoceptors located in a deep peripheral compartment. Br J Clin Pharmacol. 1985;20(4):369–76.

Aboulafia DM. Tremors associated with trimethoprim-sulfamethoxazole therapy in a patient with AIDS: case report and review. Clin Infect Dis. 1996;22(3):598–600.

Ahronheim JC. Metoclopramide and tremor. Ann Intern Med. 1982 Oct;97(4):621.

Alonso-Juarez M, Torres-Russotto D, Crespo-Morfin P, Baizabal-Carvallo JF. The clinical features and functional impact of valproate-induced tremor. Parkinsonism Relat Disord. 2017;44:147–50.

Alonso-Navarro H, Jiménez-Jiménez FJ. Reversible tremor, myoclonus, and fasciculations associated with topiramate use for migraine. Clin Neuropharmacol. 2006;29(3):157–9.

Al-Shorafat DM, Bhowmick S, Espay AJ, Fasano A. β-blocker-induced tremor. Mov Disord Clin Pract. 2021;8(3):449–52.

Alty JE, Kempster PA. A practical guide to the differential diagnosis of tremor. Postgrad Med J. 2011;87(1031):623–9.

Amptoulach S, Tsavaris N. Neurotoxicity caused by the treatment with platinum analogues. Chemother Res Pract. 2011;2011:843019.

Arbaizar B, Gómez-Acebo I, Llorca J. Postural induced-tremor in psychiatry. Psychiatry Clin Neurosci. 2008;62(6):638–45.

Arshaduddin M, Al Kadasah S, Biary N, Al Deeb S, Al Moutaery K, Tariq M. Citalopram, a selective serotonin reuptake inhibitor augments harmaline-induced tremor in rats. Behav Brain Res. 2004;153(1):15–20.

Asser A, Taba P. Psychostimulants and movement disorders. Front Neurol. 2015;6:75.
Baek JH, Kinrys G, Nierenberg AA. Lithium tremor revisited: pathophysiology and treatment. Acta Psychiatr Scand. 2014;129(1):17–23.
Baizabal-Carvallo JF, Alonso-Juarez M. Valproate-induced rest tremor and parkinsonism. Acta Neurol Belg. 2021;121(2):515–9.
Baker MR, Baker SN. Beta-adrenergic modulation of tremor and corticomuscular coherence in humans. PLoS One. 2012;7(11):e49088.
Bateman DN, Bevan P, Longley BP, Mastaglia F, Wandless I. Cimetidine induced postural and action tremor. J Neurol Neurosurg Psychiatry. 1981;44(1):94.
Baumann-Birkbeck L, Grant GD, Anoopkumar-Dukie S, Kavanagh JJ. Drowsiness and motor responses to consecutive daily doses of promethazine and loratadine. Clin Neurophysiol. 2014;125(12):2390–6.
Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM, Deuschl G, Tremor Task Force of the International Parkinson and Movement Disorder Society. Consensus Statement on the classification of tremors. From the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33(1):75–87.
Bongard V, Marc D, Philippe V, Jean-Louis M, Maryse LM. Incidence rate of adverse drug reactions during long-term follow-up of patients newly treated with amiodarone. Am J Ther. 2006;13(4):315–9.
Booij J, Speelman JD, Horstink MW, Wolters EC. The clinical benefit of imaging striatal dopamine transporters with [123I]FP-CIT SPET in differentiating patients with presynaptic parkinsonism from those with other forms of parkinsonism. Eur J Nucl Med. 2001;28(3):266–72.
Borbinha C, Serrazina F, Salavisa M, Viana-Baptista M. Bismuth encephalopathy- a rare complication of long-standing use of bismuth subsalicylate. BMC Neurol. 2019;19(1):212. Published 2019 Aug 29.
Brambilla P, Cipriani A, Hotopf M, Barbui C. Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. Pharmacopsychiatry. 2005;38(2):69–77.
Brust JC. Substance abuse and movement disorders. Mov Disord. 2010;25(13):2010–20.
Burgess S, Geddes J, Hawton K, Townsend E, Jamison K, Goodwin G. Lithium for maintenance treatment of mood disorders. Cochrane Database Syst Rev. 2001;(3):CD003013.
Buss DC, Marshall RW, Milligan N, McQueen I, Compston DA, Routledge PA. The effect of intravenous aminophylline on essential tremor. Br J Clin Pharmacol. 1997;43(1):119–21.
Canning JE, Burton S, Hall B. Lithium and valproate-induced tremors. Ment Health Clin. 2012;1(7):174–6.
Caraceni A, Gangeri L, Martini C, Belli F, Brunelli C, Baldini M, Mascheroni L, Lenisa L, Cascinelli N. Neurotoxicity of interferon-alpha in melanoma therapy: results from a randomized controlled trial. Cancer. 1998;83(3):482–9.
Carl D, Grüllich C, Hering S, Schabet M. Steroid responsive encephalopathy associated with autoimmune thyroiditis following ipilimumab therapy: a case report. BMC Res Notes. 2015;8:316.
Charness ME, Morady F, Scheinman MM. Frequent neurologic toxicity associated with amiodarone therapy. Neurology. 1984;34(5):669–71.
Chiruka S, Chapman CS. Severe tremors associated with use of thalidomide. Am J Hematol. 2005;78(1):81–2.
Cox BC, Cincotta M, Espay AJ. Mirror movements in movement disorders: a review. Tremor Other Hyperkinet Mov (N Y). 2012;2:tre-02-59-398-1.
Cullis PA, Cushing R. Vidarabine encephalopathy. J Neurol Neurosurg Psychiatry. 1984;47(12):1351–4.
Daras M, Koppel BS, Atos-Radzion E. Cocaine-induced choreoathetoid movements ('crack dancing'). Neurology. 1994;44(4):751–2.
Dave M, Langbart MM. Nadolol for lithium tremor in the presence of liver damage. Ann Clin Psychiatry. 1994;6(1):51–2.

Dennison U, Clarkson M, O'Mullane J, Cassidy EM. The incidence and clinical correlates of lithium toxicity: a retrospective review. Ir J Med Sci. 2011;180(3):661–5.
Diaz-Martinez A, Benassinni O, Ontiveros A, Gonzalez S, Salin R, Basquedano G, Martinez RA. A randomized, open-label comparison of venlafaxine and fluoxetine in depressed outpatients. Clin Ther. 1998;20(3):467–76.
Dietz AJ Jr. Amphetamine-like reactions to phenylpropanolamine. JAMA. 1981;245(6):601–2.
Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM. 2003;96(9):635–42.
Erro R, Bacchin R, Magrinelli F, Tomei P, Geroin C, Squintani G, Lupo A, Zaza G, Tinazzi M. Tremor induced by Calcineurin inhibitor immunosuppression: a single-centre observational study in kidney transplanted patients. J Neurol. 2018;265(7):1676–83.
Factor SA, Burkhard PR, Caroff S, Friedman JH, Marras C, Tinazzi M, Comella CL. Recent developments in drug-induced movement disorders: a mixed picture. Lancet Neurol. 2019;18(9):880–90.
Fava GA, Benasi G, Lucente M, Offidani E, Cosci F, Guidi J. Withdrawal symptoms after serotonin-noradrenaline reuptake inhibitor discontinuation: systematic review. Psychother Psychosom. 2018;87(4):195–203.
Flavel SC, Koch JD, White JM, Todd G. Illicit stimulant use in humans is associated with a long-term increase in tremor. PLoS One. 2012;7(12):e52025.
Gallerani M, Boari B. Hallucinations and tremors due to oral therapeutic doses of erythromycin and methylprednisolone. Intern Emerg Med. 2008;3(3):283–5.
Garel N, Greenway KT, Tabbane K, Joober R. Serotonin syndrome: SSRIs are not the only culprit. J Psychiatry Neurosci. 2021;46(3):E369–70.
Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. J Support Oncol. 2003;1(3):194–205.
Ghodke-Puranik Y, Thorn CF, Lamba JK, Leeder JS, Song W, Birnbaum AK, Altman RB, Klein TE. Valproic acid pathway: pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics. 2013;23(4):236–41.
Gijtenbeek JM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. J Neurol. 1999;246(5):339–46.
Gironell A. The GABA hypothesis in essential tremor: lights and shadows. Tremor Other Hyperkinet Mov (N Y). 2014;4:254.
Gordon MF, Abrams RI, Rubin DB, Barr WB, Correa DD. Bismuth subsalicylate toxicity as a cause of prolonged encephalopathy with myoclonus. Mov Disord 1995;10(2):220–2.
Graber DJ, Meier KH. Acute misoprostol toxicity. Ann Emerg Med. 1991;20(5):549–51.
Greene HL, Graham EL, Werner JA, Sears GK, Gross BW, Gorham JP, Kudenchuk PJ, Trobaugh GB. Toxic and therapeutic effects of amiodarone in the treatment of cardiac arrhythmias. J Am Coll Cardiol. 1983;2(6):1114–28.
Guelfi JD, Dreyfus JF, Pichot P. A double-blind controlled clinical trial comparing fluvoxamine with imipramine. Br J Clin Pharmacol. 1983;15(Suppl 3):411S–7S.
Gürkov R. Amiodarone: a newly discovered association with bilateral vestibulopathy. Front Neurol. 2018;9:119.
Hamed SA, Abdellah MM. The relationship between valproate induced tremors and circulating neurotransmitters: a preliminary study. Int J Neurosci. 2017;127(3):236–42.
Hanna RM, Sun SF, Gaynor P. A case of ertapenem neurotoxicity resulting in vocal tremor and altered mentation in a dialysis dependent liver transplant patient. Antibiotics (Basel). 2018;8(1):1.
Harris L, McKenna WJ, Rowland E, Holt DW, Storey GC, Krikler DM. Side effects of long-term amiodarone therapy. Circulation. 1983;67(1):45–51.
Hilleman D, Miller MA, Parker R, Doering P, Pieper JA. Optimal management of amiodarone therapy: efficacy and side effects. Pharmacotherapy. 1998;18(6 Pt 2):138S–45S.
Hod H, Har-Zahav J, Kaplinsky N, Frankl O. Pindolol-induced tremor. Postgrad Med J. 1980;56(655):346–7.

Hyatt RH, Sinha B, Vallon A, Bailey RJ, Martin A. Noncardiac side-effects of long-term oral amiodarone in the elderly. Age Ageing. 1988;17(2):116–22.
Ishida S, Sugino M, Hosokawa T, Sato T, Furutama D, Fukuda A, Kimura F, Kuwabara H, Shibayama Y, Hanafusa T. Amiodarone-induced liver cirrhosis and parkinsonism: a case report. Clin Neuropathol. 2010;29(2):84–8.
International mexiletine and placebo antiarrhythmic coronary trial: I. Report on arrhythmia and other findings. Impact Research Group. J Am Coll Cardiol. 1984;4(6):1148–63.
Jennings DL, Seibyl JP, Oakes D, Eberly S, Murphy J, Marek K. (123I) beta-CIT and single-photon emission computed tomographic imaging vs clinical evaluation in Parkinsonian syndrome: unmasking an early diagnosis. Arch Neurol. 2004;61(8):1224–9.
John P, McConnell K, Saif MW. Chin tremors associated with paroxetine in a patient with pancreatic adenocarcinoma. JOP. 2013;14(6):661–3.
Karas BJ, Wilder BJ, Hammond EJ, Bauman AW. Treatment of valproate tremors. Neurology. 1983;33(10):1380–2.
Koller W, O'Hara R, Dorus W, Bauer J. Tremor in chronic alcoholism. Neurology. 1985;35(11):1660–2.
Koller W, Cone S, Herbster G. Caffeine and tremor. Neurology. 1987a;37(1):169–72.
Koller W, Orebaugh C, Lawson L, Potempa K. Pindolol-induced tremor. Clin Neuropharmacol. 1987b;10(5):449–52.
Köse H, Temoçin F. Delerium and tremor associated with ertapenem treatment. Edge J Med. 2018;57(1):60–3.
Kovács A, Farkas Z, Kelemen A, Juhos V, Szűcs A, Kamondi A. Lamotrigine induces tremor among epilepsy patients probably via cerebellar pathways. Tohoku J Exp Med. 2019;248(4):273–84.
Kunisawa N, Iha HA, Shimizu S, Tokudome K, Mukai T, Kinboshi M, Serikawa T, Ohno Y. Nicotine evokes kinetic tremor by activating the inferior olive via α7 nicotinic acetylcholine receptors. Behav Brain Res. 2016;314:173–80.
Lambert JR. Pharmacology of bismuth-containing compounds. Rev Infect Dis. 1991;13(Suppl 8):S691–5.
Lambert MT, Trutia C, Petty F. Extrapyramidal adverse effects associated with sertraline. Prog Neuro-Psychopharmacol Biol Psychiatry. 1998;22(5):741–8.
Lan L, Zhao X, Jian S, Li C, Wang M, Zhou Q, Huang S, Zhu S, Kang H, Kirsch HE. Investigation of the risk of valproic acid-induced tremor: clinical, neuroimaging, and genetic factors. Psychopharmacology. 2022;239(1):173–84.
Langone A, Steinberg SM, Gedaly R, Chan LK, Shah T, Sethi KD, Nigro V, Morgan JC, Investigators STRATO. Switching STudy of Kidney TRansplant PAtients with Tremor to LCP-TacrO (STRATO): an open-label, multicenter, prospective phase 3b study. Clin Transpl. 2015;29(9):796–805.
Lapierre YD. Control of lithium tremor with propranolol. Can Med Assoc J. 1976;114(7):619–20, 24.
Lei P, Ayton S, Appukuttan AT, Moon S, Duce JA, Volitakis I, Cherny R, Wood SJ, Greenough M, Berger G, Pantelis C, McGorry P, Yung A, Finkelstein DI, Bush AI. Lithium suppression of tau induces brain iron accumulation and neurodegeneration. Mol Psychiatry. 2017;22(3):396–406.
Leonard BE, Faherty C. SSRIs and movement disorders: is serotonin the culprit? Hum Psychopharmacol Clin Exp. 1996;11:S75–82.
Lestner JM, Denning DW. Tremor: a newly described adverse event with long-term itraconazole therapy. J Neurol Neurosurg Psychiatry. 2010;81(3):327–9.
Lim TT, Ahmed A, Itin I, Gostkowski M, Rudolph J, Cooper S, Fernandez HH. Is 6 months of neuroleptic withdrawal sufficient to distinguish drug-induced parkinsonism from Parkinson's disease? Int J Neurosci. 2013;123(3):170–4.
Lippold OC, Williams EJ, Wilson CG. Finger tremor and cigarette smoking. Br J Clin Pharmacol. 1980;10(1):83–6.
Louis ED. Kinetic tremor: differences between smokers and non-smokers. Neurotoxicology. 2007;28(3):569–75.

Maetani Y, Nezu T, Ueno H, Aoki S, Hosomi N, Maruyama H. Steroid-responsive nivolumab-induced involuntary movement with anti-thyroid antibodies. Intern Med. 2019;58(24):3577–81.
Mahad DJ, Helldén A, Jarvis J, Mitra D, Gholkar A, Chinnery PF. Aciclovir induced posterior leucoencephalopathy. J Neurol Neurosurg Psychiatry. 2005;76(9):1308–9.
Mally J, Stone TW. Efficacy of an adenosine antagonist, theophylline, in essential tremor: comparison with placebo and propranolol. J Neurol Sci. 1995;132(2):129–32.
Mandel SH, Magnusson AR, Burton BT, Swanson JR, LaFranchi SH. Massive levothyroxine ingestion. Conservative management. Clin Pediatr (Phila). 1989;28(8):374–6.
Manolis AS, Deering TF, Cameron J, Estes NA 3rd. Mexiletine: pharmacology and therapeutic use. Clin Cardiol. 1990;13(5):349–59.
Martino D, Espay AJ, Fasano A, Morgante F. Disorders of movement a guide to diagnosis and treatment. 1st ed. Berlin Heidelberg: Springer; 2016.
Mazer B, Figueroa-Rosario W, Bender B. The effect of albuterol aerosol on fine-motor performance in children with chronic asthma. J Allergy Clin Immunol. 1990;86(2):243–8.
Morgan JC, Sethi KD. Drug-induced tremors. Lancet Neurol. 2005;4(12):866–76.
Morgan JC, Kurek JA, Davis JL, Sethi KD. Insights into pathophysiology from medication-induced tremor. Tremor Other Hyperkinet Mov (N Y). 2017;7:442.
Mott SH, Packer RJ, Vezina LG, Kapur S, Dinndorf PA, Conry JA, Pranzatelli MR, Quinones RR. Encephalopathy with parkinsonian features in children following bone marrow transplantations and high-dose amphotericin B. Ann Neurol. 1995;37(6):810–4.
Naicker P, Anoopkumar-Dukie S, Grant GD, Kavanagh JJ. The effects of antihistamines with varying anticholinergic properties on voluntary and involuntary movement. Clin Neurophysiol. 2013;124(9):1840–5.
Neiman J, Lang AE, Fornazzari L, Carlen PL. Movement disorders in alcoholism: a review. Neurology. 1990;40(5):741–6.
Nishihori T, Abdo-Matkiwsky M, Fleishman SB, Blum RH. Severe action tremor related to interferon-alpha 2b therapy for malignant melanoma. Am J Clin Oncol. 2005;28(5):526.
Nizet TA, Broeders ME, Folgering HT. Tremor side effects of salbutamol, quantified by a laser pointer technique. Respir Med. 2004;98(9):844–50.
Orr CF, Ahlskog JE. Frequency, characteristics, and risk factors for amiodarone neurotoxicity. Arch Neurol. 2009;66(7):865–9.
O'Suilleabhain P, Giller C. Rapidly progressive Parkinsonism in a self-reported user of ecstasy and other drugs. Mov Disord. 2003;18(11):1378–81.
Owino F, Mandala J, Ambia J, Agot K, Van Damme L. Neurological syndrome in an HIV-prevention trial participant randomized to daily tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) in Bondo. Kenya Int Med Case Rep J. 2013;6:91–3.
Paparella G, Angelini L, De Biase A, Cannavacciuolo A, Colella D, Di Bonaventura C, Giallonardo AT, Berardelli A, Bologna M. Clinical and kinematic features of valproate-induced tremor and differences with essential tremor. Cerebellum. 2021;20(3):374–83.
Patterson RG, Couchenour RL. Trimethoprim-sulfamethoxazole-induced tremor in an immunocompetent patients. Pharmacotherapy. 1999;19(12):1456–8.
Paul F, Müller J, Christe W, Steinmüller T, Poewe W, Wissel J. Postural hand tremor before and following liver transplantation and immunosuppression with cyclosporine or tacrolimus in patients without clinical signs of hepatic encephalopathy. Clin Transpl. 2004;18(4):429–33.
Pelacchi F, Dell'Osso L, Bondi E, Amore M, Fagiolini A, Iazzetta P, Pierucci D, Gorini M, Quarchioni E, Comandini A, Salvatori E, Cattaneo A, Pompili M, SALT Study Group. Clinical evaluation of switching from immediate-release to prolonged-release lithium in bipolar patients, poorly tolerant to lithium immediate-release treatment: a randomized clinical trial. Brain Behav. 2022;12(3):e2485.
Quabeck K, Müller KD, Beelen DW, Dermoumi H, Kölbel M, Kraft J, Ansorg R, Schaefer UW. Prophylaxis and treatment of fungal infections with fluconazole in bone marrow transplant patients. Mycoses. 1992;35(9–10):221–4.

Raethjen J, Lemke MR, Lindemann M, Wenzelburger R, Krack P, Deuschl G. Amitriptyline enhances the central component of physiological tremor. J Neurol Neurosurg Psychiatry. 2001;70(1):78–82.
Richter K, Hartmann U, Metzenauer P, Magnussen H. Randomised trial comparing as-needed versus regular treatment with formoterol in patients with persistent asthma. Respir Med. 2007;101(3):467–75.
Rinnerthaler M, Luef G, Mueller J, Seppi K, Wissel J, Trinka E, Bauer G, Poewe W. Computerized tremor analysis of valproate-induced tremor: a comparative study of controlled-release versus conventional valproate. Epilepsia. 2005;46(2):320–3.
Ross RT. Drug-induced parkinsonism and other movement disorders. Can J Neurol Sci. 1990;17(2):155–62.
Rubinstein A, Cabili S. Tremor induced by procainamide. Am J Cardiol. 1986;57(4):340–1.
Sarasombath P, Sumida K, Kaku DA. Parkinsonism associated with interferon alpha therapy for chronic myelogenous leukemia. Hawaii Med J. 2002;61(3):48–57.
Serrano-Dueñas M. Fluoxetine-induced tremor: clinical features in 21 patients. Parkinsonism Relat Disord. 2002;8(5):325–7.
Sethi KD. Movement disorders induced by dopamine blocking agents. Semin Neurol. 2001;21(1):59–68.
Sethi KD, Zamrini EY. Asymmetry in clinical features of drug-induced parkinsonism. J Neuropsychiatry Clin Neurosci. 1990;2(1):64–6.
Shiffman SM, Gritz ER, Maltese J, Lee MA, Schneider NG, Jarvik ME. Effects of cigarette smoking and oral nicotine on hand tremor. Clin Pharmacol Ther. 1983;33(6):800–5.
Shin HW, Chung SJ. Drug-induced parkinsonism. J Clin Neurol. 2012;8(1):15–21.
Shprecher D. Sensory trick with metoclopramide-associated tardive tremor. BMJ Case Rep. 2012;2012:bcr1120115156.
Silver M, Factor SA. Valproic acid-induced parkinsonism: levodopa responsiveness with dyskinesia. Parkinsonism Relat Disord. 2013;19(8):758–60.
Speirs J, Hirsch SR. Severe lithium toxicity with “normal” serum concentrations. Br Med J. 1978;1(6116):815–6.
Stacy M, Jankovic J. Tardive tremor. Mov Disord. 1992;7(1):53–7.
Supiyaphun P, Chochaipanichnon L, Kerekhanjanarong V, Saengpanich S. A comparative study of the side effects between pseudoephedrine in Loratadine plus Pseudoephedrine Sulfate Repetabs Tables and loratadine + pseudoephedrine tablet in treatment of allergic rhinitis in Thai patients. J Med Assoc Thail. 2002;85(6):722–7.
Tan EK, Chan LL, Lo YL. “Myorhythmia” slow facial tremor from chronic interferon alpha-2a usage. Neurology. 2003;61(9):1302–3.
Tang S, Ho SK, Moniri K, Lai KN, Chan TM. Efficacy of famciclovir in the treatment of lamivudine resistance related to an atypical hepatitis B virus mutant. Transplantation. 2002;73(1):148–51.
Tarlaci S. Citalopram-induced jaw tremor. Clin Neurol Neurosurg. 2004;107(1):73–5.
Tarsy D, Indorf G. Tardive tremor due to metoclopramide. Mov Disord. 2002;17(3):620–1.
Teravainen H, Larsen A, Fogelholm R. Comparison between the effects of pindolol and propranolol on essential tremor. Neurology. 1977;27(5):439–42.
Thanvi B, Treadwell S. Drug induced parkinsonism: a common cause of parkinsonism in older people. Postgrad Med J. 2009;85(1004):322–6.
Turner SA, Maclean JD, Fleckenstein L, Greenaway C. Parenteral administration of ivermectin in a patient with disseminated strongyloidiasis. Am J Trop Med Hyg. 2005;73(5):911–4.
Tyrer P, Lee I, Trotter C. Physiological characteristics of tremor after chronic lithium therapy. Br J Psychiatry. 1981;139:59–61.
Uemoto S, Tanaka K, Honda K, Tokunaga Y, Sano K, Katoh H, Yamamoto E, Takada Y, Ozawa K. Experience with FK506 in living-related liver transplantation. Transplantation. 1993;55(2):288–92.

van Dam DG, Burgers DM, Foudraine N, Janssen PK, Neef C, le Noble JL. Treatment of cefuroxime-induced neurotoxicity with continuous venovenous haemofiltration. Neth J Med. 2017;75(1):32–4.

van de Wardt J, van der Stouwe AMM, Dirkx M, Elting JWJ, Post B, Tijssen MA, Helmich RC. Systematic clinical approach for diagnosing upper limb tremor. J Neurol Neurosurg Psychiatry. 2020;91(8):822–30.

Van Gerpen JA. Tremor caused by trimethoprim-sulfamethoxazole in a patient with AIDS. Neurology. 1997;48(2):537–8.

Vasireddy RP, Guduru Z. Parkinsonism secondary to use of valbenazine and reversal with the addition of levodopa: a case report (1183). Neurology. 2020;94(15 Supplement):1183.

Vasireddy RP, Sokola B, Guduru Z. New generation VMAT2 inhibitors induced parkinsonism. Clin Park Relat Disord. 2020;3:100078.

Vogrig A, Muñiz-Castrillo S, Joubert B, Picard G, Rogemond V, Marchal C, Chiappa AM, Chanson E, Skowron F, Leblanc A, Ducray F, Honnorat J. Central nervous system complications associated with immune checkpoint inhibitors. J Neurol Neurosurg Psychiatry. 2020;91(7):772–8.

Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. Ochsner J. 2013;13(4):533–40.

Wade JC, Meyers JD. Neurologic symptoms associated with parenteral acyclovir treatment after marrow transplantation. Ann Intern Med. 1983;98(6):921–5.

Wang Z, Zang R, Niu Z, Wang W, Wang X, Tang Y. Synthesis and antiviral effect of phosphamide modified vidarabine for treating HSV 1 infections. Bioorg Med Chem Lett. 2021;52:128405.

Ward KM, Citrome L. Antipsychotic-related movement disorders: drug-induced parkinsonism vs. tardive dyskinesia-key differences in pathophysiology and clinical management. Neurol Ther. 2018;7(2):233–48.

Watanabe S, Yokoyama S, Kubo S, Iwai H, Kuyama C. A double-blind controlled study of clinical efficacy of maprotiline and amitriptyline in depression. Folia Psychiatr Neurol Jpn. 1978;32(1):1–31.

Werner EG, Olanow CW. Parkinsonism and amiodarone therapy. Ann Neurol. 1989;25(6):630–2.

Whale CI, Sovani MP, Mortimer KJ, Harrison TW, Tattersfield AE. Systemic and bronchodilator effects of inhaled rac-formoterol in subjects with chronic obstructive pulmonary disease: a dose-response study. Br J Clin Pharmacol. 2008;65(6):841–7.

Wijdicks EF, Wiesner RH, Dahlke LJ, Krom RA. FK506-induced neurotoxicity in liver transplantation. Ann Neurol. 1994;35(4):498–501.

Wright CD, Jilka J, Gentry WB. Efficacy of promethazine suppositories dispensed to outpatient surgical patients. Yale J Biol Med. 1998;71(5):391–5.

Xing F, Marsili L, Truong DD. Parkinsonism in viral, paraneoplastic, and autoimmune diseases. J Neurol Sci. 2022;433:120014.

Yang JH, Chung SW, Kim JS. Action tremor associated with lamotrigine monotherapy. J Mov Disord. 2010;3(1):18–9.

Zadikoff C, Munhoz RP, Asante AN, Politzer N, Wennberg R, Carlen P, Lang A. Movement disorders in patients taking anticonvulsants. J Neurol Neurosurg Psychiatry. 2007;78(2):147–51.

Zhang CQ, He BM, Hu ML, Sun HB. Risk of valproic acid-related tremor: a systematic review and meta-analysis. Front Neurol. 2020;11:576579.

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