TREMOR SYNDROMES: CURRENT CONCEPTS AND FUTURE PERSPECTIVES

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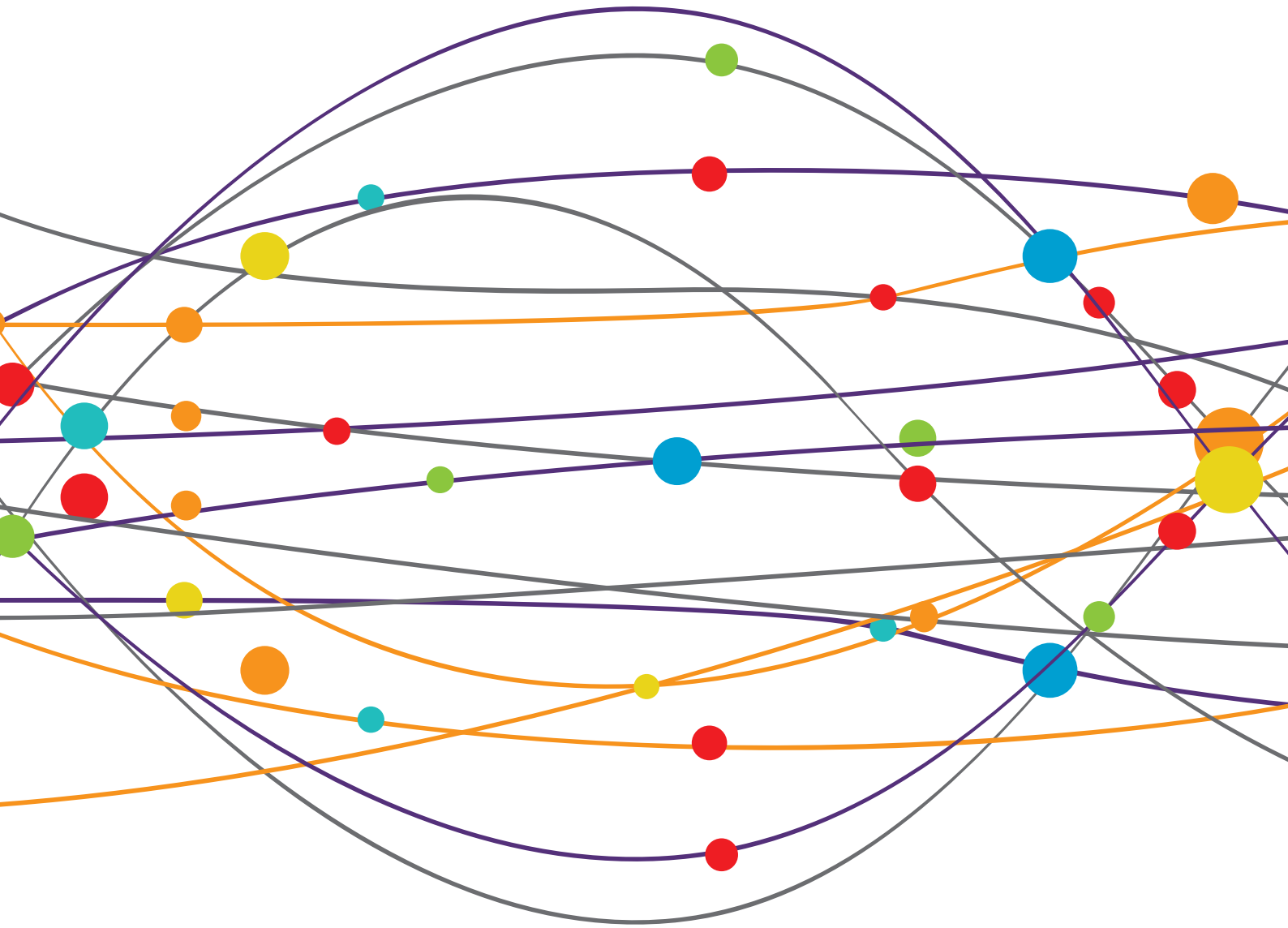

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TREMOR SYNDROMES: CURRENT CONCEPTS AND FUTURE PERSPECTIVES

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EDITORIAL
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Editorial: Tremor Syndromes: Current Concepts and Future Perspectives

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Editorial on the Research Topic

Tremor Syndromes: Current Concepts and Future Perspectives

A tremor is a rhythmic, oscillatory movement of a body part produced by alternating or synchronous contractions of antagonist muscles (1). It is the most common movement disorder and can be classified according to its phenomenology, distribution, frequency, or etiology. Phenomenologically there are two major categories of tremors: rest tremors and action tremors. Action tremors can be subdivided into postural, kinetic, isometric, and task- or position-specific tremors. In the last decade, there have been many advancements in the field of tremors including neurophysiology, neuroimaging, and genetics (2). The Frontiers Research Topic *"Tremor Syndromes: Current Concepts and Future Perspectives"* has been published to highlight the current knowledge and literature in the field of tremor research. We have been fortunate that some of the leading researchers and working groups have made outstanding contributions. In this regard, open access publication has clear advantages to spread the knowledge and update the field on the recent advances. This special issue has systematic reviews and original articles covering a wide range of subjects related to tremor research. In a review article, Lenka and Jankovic have discussed different types of tremor syndromes including the recent tremor classification. The first attempt to classify tremors was done in 1998 when consensus criteria were published by the Movement Disorders Society (3). This classification was based on the distinction between rest, postural, kinetic, and intention tremors with additional data from medical history and neurologic examination. However, subsequent advances highlighted the limitations of these criteria. To overcome these, a new consensus criterion for classifying tremors were published recently (2018), and it was based on axis I (clinical characteristics, including historical features, tremor characteristics, associated signs, and laboratory tests) and axis II [etiology (acquired, genetic, or idiopathic)] (4). This tremor classification has many new additions, including a syndrome-based approach, an updated definition of "Essential tremor," a new terminology "Essential tremor plus (ET plus)," and a new category "Indeterminate tremor." The new classification is certainly an important advancement adding more clarification and a clinic-based approach. However, there are some controversies mainly focusing on the new terminology "Essential tremor plus" (5). The definition of ET plus is based on the identification of soft signs including questionable dystonia. In another review article Louis, the author has provided excellent evidence based on clinical, etiological, and pathophysiological studies explaining the heterogeneity across ET patients. In the past decade, there has been great advancement in the understanding of the pathophysiology of ET. Buijink et al. have published an explorative study hypothesizing that inhibitory gamma-aminobutyric acid (GABA) and excitatory Glx (glutamate + glutamine) levels in the dentate nuclei of the

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cerebellum could be differentially altered in ET patients responsive to either β-adrenergic blockers or anticonvulsants. They compared ET patients using either propranolol, or anticonvulsants and healthy controls by measuring GABA, glutamate, and N-acetyl-L-aspartate (NAA) levels in the deep cerebellar nuclei using ^{1}H-magnetic resonance spectroscopy and observed no group differences and no correlation with tremor severity. These data could provide imaging evidence of the heterogeneity of ET. In a systematic review, Holtbernd and Shah have summarized structural, functional, and metabolic neuroimaging studies. They have concluded that there is robust evidence indicating that the cerebellum plays a key role within a multiple tremor oscillator network in ET. However, the dopaminergic and iron imaging do not suggest any substantial overlap of ET and PD pathophysiology. In another study, Becktepe et al. have found evidence for a direct association between white matter hyperintensities volume and tremor severity in an MRI study on 47 elderly ET patients. Lesions in the Guillain- Mollaret triangle frequently cause various types of tremors, but their pathophysiology is poorly understood. In a systematic review, Kakei et al. have proposed that tremor results from errors in predictions carried out by the cerebellar circuitry. Deep brain stimulation (DBS) of the ventralis intermedius (VIM) nucleus of the thalamus and the posterior subthalamic area (PSA) is effective in ET treatment (6). In a research article, Kim et al. have compared the stimulation-induced side effects of DBS targeting VIM and PSA areas. They hypothesized that changing active DBS contacts to simultaneous targeting of VIM and PSA may help ameliorate stimulation-induced side-effects. In another review article, Peters and Tisch have summarized the prevalence, risk factors, and long-term outcomes of habituation after DBS in tremor syndromes. The authors have provided some evidence that dystonic tremor and ET may be more susceptible to habituation than Parkinsonian tremor. Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that has been used for a better understanding of tremor pathophysiology. In a review article, Frey et al. have provided some evidence that repetitive TMS (rTMS) pulses can modulate brain functions through plasticity effects and may provide some therapeutic benefits. Wearable devices have been used for the assessment of tremors. In a review article, Vescio et al. have highlighted the use of wearable technologies for differential diagnosis of tremors. They have also considered possible future use based on inertial sensing for measuring tremors. In another review article, Lorra-Millan et al. have demonstrated the feasibility of managing upper limb tremors through wearable technologies that suppress tremors by modifying limb biomechanics.

Several important themes have emerged from these important research papers and review articles. First, we have a better understanding of the tremor phenomenology and phenotypes. Second, there is growing evidence of the involvement of newer networks in the pathogenesis of tremors. Also, the neuropathologic changes observed in ET patients have helped us to identify pathologic endophenotypes that may allow for the recognition of distinct genetic or clinical variants. Third, interest has grown in the use of novel technologies in tremor treatment and finding new targets and treatment strategies. These findings will be helpful in collaborative and coordinated research on a multinational level. That will also help in standard data collection using common data elements for clinical, neurophysiological, genetic, and pathological studies. Future prospective studies recruiting a large cohort of patients may be planned to collect bio-samples, characterize the natural history of tremor syndrome, identify the pathophysiological mechanism and investigate potential etiologies of various phenotypes (2, 5).

Finally, an inclusive acknowledgment is due to the authors and reviewers who have contributed to this Research Topic. Their honest efforts and commitment have been truly admirable.

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SP, JB-L, and S-HK have contributed to manuscript writing, editing, and critique. All authors contributed to the article and approved the submitted version.

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REVIEW
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The Essential Tremors: Evolving Concepts of a Family of Diseases

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The past 10 years has seen a remarkable advance in our understanding of the disease traditionally referred to as "essential tremor" (ET). First, the clinical phenotype of ET has been expanded from that of a bland, unidimensional, and monosymptomatic entity to one with a host of heterogeneous features. These features include a broader and more nuanced collection of tremors, non-tremor motor features (e.g., gait abnormalities) and a range of non-motor features, including cognitive, psychiatric, sleep, and other abnormalities. The natural history of these features, as well as their relationships with one another and with disease duration and severity, are better appreciated than they were previously. Studies of disease etiology have identified a number of candidate genes as well as explored several environmental determinants of disease. In addition, the decade has seen the beginnings and expansion of rigorous postmortem studies that have identified and described the postmortem changes in the brains of patients with ET. This emerging science has given rise to a new notion that the disease, in many cases, is one of cerebellar system degeneration. Across all of these studies (clinical, etiological, and pathophysiological) is the observation that there is heterogeneity across patients and that "essential tremor" is likely not a single disease but, rather, a family of diseases. The time has come to use the more appropriate terminology, "the essential tremors," to fully describe and encapsulate what is now apparent. In this paper, the author will review the clinical, etiological, and pathophysiological findings, referred to above, and make the argument that the terminology should evolve to reflect advances in science and that "the essential tremors" is a more scientifically appropriate term.

Keywords: essential tremor, the essential tremors, terminology, classification, heterogeneity, disease

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INTRODUCTION

During the last decade or two, we have witnessed notable advances in our understanding of the neurological disease that traditionally has been referred to as "essential tremor" (ET). Advances have spanned several key areas, from clinical features to natural history and from etiology to disease pathogenesis. This evolution is largely driven by new data and, along with these new data, a growing appreciation of the broader diversity and assortment of clinical features, etiological factors, and pathophysiological mechanisms. In this paper, we review the clinical, etiological, and pathophysiological heterogeneity in ET and put forth the argument that the terminology should adapt to reflect advances in science and that "the essential tremors" is a more scientifically appropriate term.

EXPANSION OF THE CLINICAL PHENOTYPE OF ET

Introduction

The clinical phenotype of ET has expanded from that of a bland, unidimensional, monosymptomatic entity to one with a diverse array of features. These may include both a broader and a more nuanced assemblage of tremors, the appearance of motor features aside from tremors (e.g., gait abnormalities), and a range of non-motor features, including cognitive, psychiatric, and sleep abnormalities, among others. Here, we review the details.

Tremors

A myriad of tremors may be seen in patients with ET. The primary clinical feature of ET is kinetic tremor (1–4). This may be observed during a range of activities of daily living, from writing to drinking to eating, and may be elicited on neurological examination during a variety of maneuvers (e.g., finger-nose-finger maneuver, spiral drawing, pouring water between two cups) (1, 5). In ∼50% of ET patients, the tremor has an intentional component (6), with observed worsening of tremor as the patient approaches the target (i.e., either the finger or the nose) during the finger-nose-finger maneuver. Intention tremor in ET is not limited to the arms; 10% of ET patients exhibit intention tremor in their neck when their head approaches a target (7). This may be observed, for example, when the patient lowers their head to meet the cup or spoon as it approaches their face during the tasks of drinking or using a spoon (1). Intention tremor is observed during toe-to-target movements in 27.3% of ET patients (8).

In addition to kinetic and intention tremors, patients with ET often have postural tremor of the arms, which can range in severity, although the amplitude of this tremor is generally lower than that of the kinetic tremor (3, 9).

Tremor at rest, without the other cardinal features of Parkinsonism such as bradykinesia or rigidity, occurs in ∼1–35% of patients with ET, depending on the method of case ascertainment (10, 11). In contrast to that seen in patients with Parkinson's disease, it is a late-disease feature, and it has only been observed in the arm (i.e., it has not been observed in the leg) (1, 2, 10, 11).

Over time, there is a tendency for the tremor in ET to involve other body regions aside from the upper limbs, and patients may develop cranial tremors, involving the neck, voice, or jaw (1, 12, 13). Hence, there is heterogeneity not only with respect to the activation condition during which tremor is observed (e.g., kinetic, postural, intention, and rest) but with respect to the somatotopic distribution of tremor. Cranial tremors, and especially neck tremor, is particularly prevalent in women with ET, among whom the prevalence of neck tremor is several times higher than that of neck tremor in men with ET (14, 15). This neck tremor often begins as a uni-directional tremor, either "no–no" (i.e., horizontal) or "yes–yes" (i.e., vertical); with time this can evolve into a more complex, multi-directional tremor (1, 16).

Other Motor Features

The motor features of ET are not limited to tremors. Another motor feature of ET is gait ataxia (17–19), which may be elicited on neurological examination by asking patients to perform tandem gait. The number of tandem gait missteps in ET is in excess of that seen in control subjects of similar age (17, 19). In most ET patients, this ataxia is mild, although in some ET patients it may reach moderate severity (20). This ataxia has been shown to result in a reduction in patients' confidence in balance and a mild but significant increase in the number of near-falls and falls in ET patients compared to age-matched controls (21). There are several studies that suggest that certain phenotypic features (e.g., midline tremor) track with greater gait difficulty (22, 23). Subclinical eye movement abnormalities (24–26) as well as other motor abnormalities (e.g., eye-hand incoordination, greater temporal variability in repetitive movements, and abnormalities in motor learning) point to what is likely to be a more pervasive underlying abnormality of cerebellar function in ET (27–31).

There are other motor features as well. Several studies have also reported the presence of movement slowness in finger tapping and other tasks in ET cases compared to controls, with a heterogeneous range of values across ET cases (32–34).

The above discussion would be incomplete without a discussion of dystonia. There is growing recognition and acceptance that some degree of dystonia may be present during the examination of patients with ET (35–38). It is apparent that the presence vs. absence, distribution, severity, and natural history of that dystonia is not uniformly distributed across patients, although further work needs to be done to define the full spectrum of dystonic postures in patients with ET. Such work will have obvious implications for the conceptualization and framing of the entity now referred to as "dystonic tremor." The ensuing discussion should recognize that different underlying disease entities may have overlapping clinical features; in this case, both tremor and dystonia might be referable to a disordered cerebellum (39–41).

Non-motor Features

As with many neurodegenerative movement disorders (e.g., Parkinson's disease, Huntington's disease), the clinical features in ET extend beyond the motor system. These non-motor features may be divided into those that are cognitive, psychiatric, sensory, and other (e.g., sleep). These have been reviewed in detail elsewhere (42–47).

Beginning with studies published nearly two decades ago, investigators observed mild cognitive deficits in patients with ET when compared with controls, and the number of such studies is considerable (42, 48, 49). These deficits involve a number of cognitive domains, particularly executive function and memory (50). Studies have documented that the rate of cognitive decline in older ET patients is greater than that observed in age-matched controls (51). Epidemiological studies in Spain and New York have demonstrated that, beyond the presence of mild cognitive deficits, ET is associated with both an increased odds of prevalent dementia (52, 53) and an increased risk of incident dementia (53, 54). Conversion rate in ET from mild cognitive impairment to dementia seems to be in excess of that seen in control groups (55).

The basis for the cognitive changes and dementia in ET is likely to be multi-factorial, and further studies are needed (42, 56, 57).

Many neurodegenerative diseases are indeed neuropsychiatric disorders. In ET, the presence of specific personality traits has been demonstrated in several studies (58–60), as well as a range of psychiatric features (anxiety, social phobia, and depression) (61–63), and there is evidence that some of these (e.g., depression) could be primary rather than a response to the disabling features of tremor (64).

Olfactory deficits have been variably reported in some although not all ET cohorts (65, 66), and hearing deficits have more consistently been reported in other cohorts (67–69). Sleep abnormalities have consistently been demonstrated in patients with ET (70–72).

Additional Clinical Features

The age of onset in ET is not uniform. That is, there is considerable heterogeneity. Whether an individual who develops the disease at age 40 years has the same underlying disease as someone who develops the disease at a more advanced age (e.g., 75 years) is an interesting question. To date, no compelling data have been presented to suggest that there is an age cutoff for developing ET. In a similar sense, there is no age cutoff for Parkinson's disease or Alzheimer's disease.

Electrophysiological Features

Electrophysiological studies also point to heterogeneity in ET. For example, there is evidence from kinematic recordings that ET cases with head tremor differ from those without head tremor with respect to the severity of their limb tremor (73). Other electrophysiological studies, using electromyography and testing of long-latency reflexes, suggest that ET cases are dividable into distinct groups based on the mode of activation of antagonist muscles or reflex pattern (74, 75). Different responses to cerebellar transcranial magnetic stimulation, observed across studies, could also be the result of heterogeneity across patient groups (76, 77).

Neuroimaging Features

A variety of neuroimaging studies in ET have attempted to identify subdivisions of patients who differ with respect to neuroimaging features. There is some evidence that patients with head tremor differ from those without head tremor in resting-state fMRI studies (78) and that in tractography studies, ET patients with vs. without resting tremor differ from one another with respect to structural connectivity (79).

Pharmacological and Surgical Response Phenotype

Additional evidence of heterogeneity in ET comes from the observed variable response to medications across patients. It is a common observation in clinical trials that responsiveness to medication is not uniform across patients and that there tend to be responders and non-responders and that the proportion of the latter is sizable (80). Several studies have shown that patients with specific phenotypic, electrophysiologic, or neuroimaging features respond more favorably to propranolol (74, 81).

There is also some evidence in the literature that surgical responsiveness may differ across ET patients with, for example, thalamotomy used as a salvage solution in patients who do not respond to deep brain stimulation surgery (82). However, one study that examined clinical correlates of deep brain stimulation surgical outcome across ET patients did not identify any clinical characteristics that correlated with response (83).

Summary

The past decade or two has seen an expansion of the ET phenotype. This is broadly recognized in the field. How to deal with this heterogeneity is not clear. There have been some initial attempts to develop new nomenclature to acknowledge that ET might not comprise a single entity (e.g., ET vs. "ET-plus") (38), although the proposed terminology has been criticized, and further work is needed (37, 84–87). More specifically, it is important to recognize clinical heterogeneity within ET; however, it is then important to take additional steps to determine whether that clinical heterogeneity is a marker of distinct, separable underlying etiological, pathophysiological, and/or mechanistic entities. If the clinical differences are not linkable to such meaningful differences, then they are superficial ones, and they should not be used as the basis for decisions about disease classification and disease nomenclature.

GREATER UNDERSTANDING OF THE NATURAL HISTORY OF ET AND RECOGNITION OF HETEROGENEITY ACROSS PATIENTS

Over the past decade or two, we have developed a greater understanding of the natural history of ET. In most individuals with ET, tremor amplitude increases with time (88, 89). The pattern of progression is not the same in all individuals. Several patterns of progression have been described, the two most common of which are (1) late life onset (i.e., after age 60) with progression and (2) early life onset (i.e., before age 40) with mild, stable tremor for many years followed in the 60s and onwards with progression (1). The least common pattern is that of early life (e.g., childhood) onset with marked worsening over the ensuing decade (1).

Aside from the above-described heterogeneity in *pattern* of progression, we also know that patients are not homogeneous with respect to *rate* of progression. There are faster progressors and slower progressors (90, 91), and in ET families, there is a fourfold difference in rate of progression, with some families being markedly faster progressors than others (92). A number of factors have been identified that seem to track with or predict differences in rate of progression, including older age of onset (90), family membership (slower vs. faster progressing family) (92), and asymmetrical tremor (91).

A feature of progression in ET is the layering on of additional tremors with time [e.g., intention tremor (6), rest tremor (11), and head tremor (15)], with the number of such features increasing over time (93). Yet these features do not

monotonously each appear in all ET patients—patients differ with respect to their development of these features.

In this discussion, we have focused on motor features of ET and specifically tremor. Yet there is evidence that non-motor features, and particularly cognitive deficits, occur in ET. Some patients go on to develop mild cognitive impairment or dementia; however, the development of these more severe forms of cognitive impairment are not uniform; some patients dement and others do not (55).

From the above discussion, one may see that on multiple planes, there is heterogeneity across patients with respect to natural history, with differences in pattern of progression, rate of progression, and features of progression.

ADVANCES IN KNOWLEDGE REGARDING DISEASE ETIOLOGY AND RECOGNITION OF ETIOLOGICAL HETEROGENEITY

A number of genes have been associated with familial ET, with these genes either present in a single family or a small number of families (94, 95). Genome-wide association studies have found associations between ET and single nucleotide polymorphisms (SNPs) in the region of LINGO1, and other such studies have identified SNPs in other genes (STK32B, PPARGC1A, and CTNNA3) (95). What is apparent is that a host of genetic factors is likely to be linked with ET and that there is genetic heterogeneity (96, 97). Stated another way, there is more than one genetic cause for ET. Furthermore, there are environmental determinants of disease as well (98, 99), indicating additional etiological heterogeneity.

GREATER UNDERSTANDING OF UNDERLYING DISEASE PATHOPHYSIOLOGY AND RECOGNITION OF PATHOPHYSIOLOGICAL HETEROGENEITY IN ET

The decade has seen the beginnings and expansion of rigorous and controlled postmortem studies of ET brains, and these have identified and systematically cataloged the postmortem changes in the brains of patients with ET. This new science has given rise to a new notion that the disease, in many cases, is one of cerebellar system degeneration (100–104). This being said, there is evidence of heterogeneity. While the majority of ET cases evidence a host of related degenerative features in the cerebellar cortex (105), a sizable minority of cases has Lewy body pathology (105), and an even smaller number has intranuclear inclusions (106, 107). These data indicate that the postmortem findings, and hence the pathomechanisms, are not uniform across all ET cases. Even within ET cases with cerebellar pathology, there is a range of severity of such pathology (102, 105).

HETEROGENEITY ACROSS A CONTINUUM—WHAT IS A FAMILY OF DISEASES?

The modern concept of disease is that etiological factors (i.e., genetic or environmental) are the proximate causes of disease, and these set a series of pathophysiological processes in motion, which then result in clinical features. Hence, in terms of timed events, etiology leads to pathophysiology, and this in turn leads to clinical features. As such, a "disease" is defined by its features along a time continuum, spanning from etiology to pathophysiology to clinical.

We observed from the above discussions that all along this continuum, there is evidence of multi-dimensionality, variety, and diverseness, that is, heterogeneity. It is likely that specific elements in the proximate cause of ET (etiology) will eventually be linkable to particular elements in pathophysiology and in clinical features—in other words, that certain causes will be linked with certain pathophysiologies and this, in turn, with a specific constellation of clinical features.

This is not revolutionary thinking. In the same way, during the second half of the 20th century, it became apparent that not all of the Parkinsonisms were the same—that progressive supranuclear palsy, for example, was distinguishable on each of these planes (different genes, different postmortem findings, and overlapping but differing clinical features) from idiopathic Parkinson's disease. Similarly, "motor neuron disease" encapsulates a discrete set of diseases within this broad disease family. Parkinsonisms, motor neuron disease—these are *families of diseases*. In ET, current knowledge of genetic causes and pathophysiology are quite rudimentary, making it difficult at this juncture to define etiological-pathophysiological-clinical entities (i.e., "diseases") that exist within "the essential tremors," but it is only a matter of time before such links are observed. Preliminary work suggest that certain anatomic features of ET are linkable to pharmacological response phenotype, for example (81), and that certain clinical features (i.e., older onset) are associated with more degenerative pathology in ET (90).

A CALL FOR MORE APPROPRIATE TERMINOLOGY THAT MATCHES OUR UNDERSTANDING

In science, one may reach the point when the existing terminology is lagging behind the state of knowledge. While some degree of disconnect is not problematic, when it reaches a point when the terminology is incorrectly framing and falsely characterizing the entity it is meant to apply to and when it interferes with clear thinking about the entity, it is time for a change. "Essential tremor" is in fact a term that was coined in the second half of the 19th century (108); this was a different time. Based on the arguments put forth in this paper, it is now time to recognize that we are dealing with a family of diseases, more appropriately referred to as "the essential tremors." While it may seem premature to start to use this terminology in the absence of a clear knowledge of

the different diseases, there is enough evidence of heterogeneity that the terminology should change in advance, as the science is certainly heading in this direction. Indeed, in this paper, data are presented from more than 100 peer-reviewed studies, which support the thesis that ET is not one entity and is therefore more than one entity—the ETs. The term "ET-plus" was coined in acknowledgment of this heterogeneity, although differentiation solely on clinical features is overly simplistic, and this terminology should not stick. Conceptually, however, that attempt to acknowledge heterogeneity and to modify and broaden terminology is an acknowledgment that ET is a family of diseases.

One may ask whether it might not be better to preserve the term "ET" for those cases with a limited and classical set of clinical features and separate out other cases who have additional features. This is a problematic approach. We know from genetic studies and postmortem studies that ET cases with different etiologies and different pathophysiologies can share the same clinical phenotype; hence, there is etiological and pathophysiological heterogeneity (i.e., different disease entities) even under the umbrella of the same clinical phenotype. Classification systems and nomenclature should reflect not only superficial clinical differences but more meaningful underlying drivers of those differences.

CONCLUSIONS

In this paper, we review the clinical, etiological, and pathophysiological heterogeneity in ET, and we put forth the argument that our terminology should evolve to reflect and keep pace with advances in science and that "the essential tremors" is a more scientifically appropriate term.

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GABA, Glutamate, and NAA Levels in the Deep Cerebellar Nuclei of Essential Tremor Patients

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Buijink AWG, Prent N, Puts NA, Schrantee A, Potters WV and van Rootselaar A-F (2021) GABA, Glutamate, and NAA Levels in the Deep Cerebellar Nuclei of Essential Tremor Patients. Front. Neurol. 12:664735. doi: 10.3389/fneur.2021.664735

Background: Essential tremor is among the commonly observed movement disorders in clinical practice, however the exact pathophysiological mechanisms underlying tremor are unknown. It has been suggested that Purkinje cell alterations play a causal factor in tremorgenesis. Altered levels of inhibitory (GABA) and excitatory (glutamate+glutamine, Glx) neurotransmitters could be markers for Purkinje cell alterations. We hypothesize that GABA and Glx levels in the dentate nuclei could be differentially altered in patients responsive to either anticonvulsants or β-adrenergic blockers.

Methods: In this explorative study in patients with essential tremor, we measured gamma-aminobutyric acid (GABA) and glutamate+glutamine (Glx) levels in the dentate nucleus region using ^{1}H-magnetic resonance spectroscopy (MRS) in seven patients using propranolol, five patients using anticonvulsants, and eight healthy controls.

Results: There were no group differences with respect to GABA+/Cr, Glx/Cr, NAA/Cr, and GABA+/Glx ratios. There was no correlation with tremor severity.

Discussion: Our results are in line with previously published studies; however, additional studies on a larger number of patients are warranted to confirm these findings. Furthermore medication-subgroups did not exhibit differences with respect to GABA+/Cr, Glx/Cr, NAA/Cr, and GABA+/Glx ratios. A recent study, of similar size, found an inverse association between tremor severity and the GABA+/Glx ratio in the cerebellum of essential tremor patients. We were unable to replicate these findings. The field of tremor research is plagued by heterogeneous results, and we would caution against drawing firm conclusions based on pilot studies.

Keywords: tremor, gamma-aminobutyric acid, ^{1}H-magnetic resonance spectroscopy, essential tremor, cerebellum

INTRODUCTION

A prevalent hypothesis on the pathophysiology of essential tremor (ET) suggests Purkinje cell pathology as a causal factor in tremorgenesis. Purkinje cells form the sole output from the cerebellar cortex, and lead to the deep cerebellar nuclei, including the dentate nucleus. Several previous studies showed Purkinje cell alterations, decreased cerebellar cortical N-acetyl-L-aspartate (NAA) levels supporting neurodegenerative processes, and decreased numbers of gamma-aminobutyric acid (GABA) receptors in the dentate nucleus in patients with ET (1–4). The hypothesis that altered levels of inhibitory (GABA) and excitatory (glutamate+glutamine, Glx) neurotransmitters could be a marker for Purkinje cell loss could not be confirmed in previous ^{1}H-magnetic resonance spectroscopy (MRS) studies, which showed no differences between ET and control subjects (5, 6). These studies suggest that the lack of observed differences could be due to compensatory terminal sprouting of Purkinje cells (6). A recent study, however, did show an inverse association between tremor severity and cerebellar GABA+/Glx ratio (5). The relevance of this observation is debatable, since GABA+/Cr and Glx/Cr ratios did not show group differences in this study.

Several treatments for ET currently exist, of which propranolol, primidone, topiramate, and gabapentin have a level A or B recommendation, based on small studies (7). The mechanism of action of β-adrenergic blockers like propranolol is unknown. Anticonvulsants might act through ion channel and gamma-aminobutyric-acid (GABA) receptor modulation (8). Interestingly, response to primidone is not a predictor for response to propranolol (9). A consensus paper on ET research suggested characterizing ET subtypes based on medication response (10). We hypothesize that GABA and Glx levels in the dentate nuclei could be differentially altered in ET patients responsive to either anticonvulsants or β-adrenergic blockers. In this explorative study, our aim was to assess whether subtyping ET based on medication use might provide differences in GABA and Glx levels in the dentate nucleus region in specific subgroups. We will compare ET patients using either propranolol or anticonvulsants, and healthy controls.

MATERIALS AND METHODS

Participants

Patients were either recruited through a website of our research group, referred by neurologists from other hospitals or through our research database. Patients were selected based on criteria for ET defined by the Consensus Statement on the Classification of Tremors (11), and the use of anticonvulsant medication (GABA group) or propranolol (PROP group). Patients with characteristics of ET plus were excluded. Other exclusion criteria were a score <26 on the Mini-Mental State Examination, neurological disorders (for patients: other than essential tremor), age < 18 years, the use of medication affecting the CNS and magnetic resonance-related contra-indications. Patients tapered their anti-tremor medication following a personalized scheme to allow for proper washout based on the half-life of the specific preparations. Measurements took place after four half-lives had elapsed, ensuring a subtherapeutic remaining fraction of 1/16. Patients were videoed following a strict protocol based on The Essential Tremor Rating Assessment Scale (TETRAS) (12). Reviewing these videos, blinded to treatment group, tremor severity was assessed OFF medication by an experienced rater (A.W.G.B.) using TETRAS parts A and B (12). For practical reasons, tremor severity could not be assessed while on medication. Healthy controls, also fulfilling the criteria above, were matched for age, gender and handedness. Data was anonymized. The study was carried out in accordance with the Declaration of World Medical Association (13) and was approved by the Medical Ethical Committee of the Academic Medical Center, Amsterdam.

Data Acquisition

All participants underwent a magnetic resonance spectroscopy (MRS) scan session, in which GABA levels were assessed in a single voxel in the right deep cerebellar nuclei region. Data were acquired using a 3.0 T Philips MR Scanner (Philips Medical Systems, Best, The Netherlands), using a 32-channel receive-only head coil and body coil transmission. The anatomical T1-weighted image was obtained with the following scan parameters: TR/TE = 9.0/3.7ms, flip angle 8°, FOV = 256 mm × 256 mm × 170 mm, voxel size = 1.0 mm × 1.0 mm × 1.0 mm. The T2*–weighted image was obtained with the following scan parameters: TR/TE = 25.7/21.8 ms, flip angle 17°, FOV = 213 mm × 216 mm × 130 mm, voxel size = 1.0 mm × 1.0 mm × 1.1 mm. J-difference edited MRS spectra were acquired using a MEGA-PRESS sequence from a 2.5 cm × 2.5 cm × 2.5 cm voxel in the right deep cerebellar nuclei region (as seen on the T2* image) with the following parameters: TR/TE = 2,000/68 ms, dynamic scans = 320 (2 × 160 ON and OFF), 14 ms editing pulses placed at 1.9 ppm (ON) and 7.46 ppm (OFF) with 1,024 data points and 2 kHz spectral width, for an ∼10 min acquisition. The voxel was placed manually and centered on the characteristic hypointensity in the deep cerebellar nuclei region as seen on T2* images, and angled to contain as little CSF as possible (**Figure 1A**).

Image Analysis

Edited MRS spectra were analyzed using the Gannet GABA analysis toolbox ([version 3.0 (14)], **Figure 1B**). Phasing, apodization, and frequency correction were performed automatically in this toolbox. GABA+ and Glx levels were calculated according to standard procedures, as described in detail elsewhere. In short, the time-domain data is processed into a frequency-domain GABA+ and Glx-edited spectrum. Using a nonlinear, least-squares fitting, the GABA+ and Glx level at respectively 3 and 3.75 ppm are estimated. The assessment of GABA+ using MEGA-PRESS however results in co-editing of macro-molecules such as proteins (because the editing pulse at 1.9 ppm is known to co-edit macromolecule signals at 1.7 ppm), which contribute to the edited GABA peak at 3.0 ppm and are therefore referred to as GABA+ levels. GABA levels are quantified against the creatine signal. GABA+ fit errors were calculated with the Gannet GABA analysis toolbox to assess the data quality of the spectra.

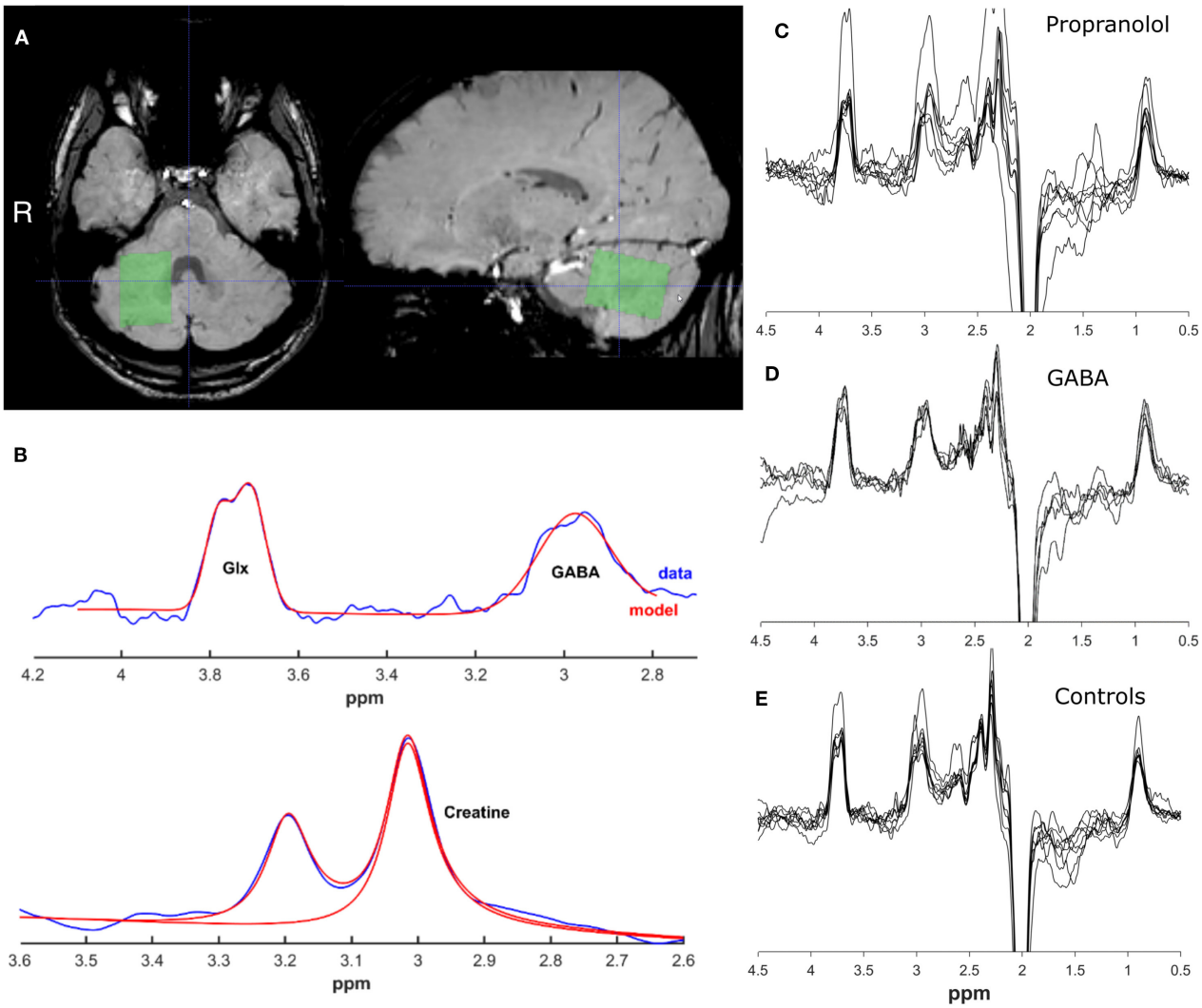

FIGURE 1 | Representative voxel placement and spectra. **(A)** Location of MRS voxel on a T2*–weighted image. **(B)** Example spectra and fitted model for creatine, GABA+ and Glx peak range. Images were created using GANNET toolbox v3.0. **(C)** All spectra for propranolol group **(D)**. All spectra for GABA group **(E)**. All spectra for control group.

The SPM12 toolbox (version 3) was used in MATLAB (The Mathworks, Natick, MA) to co-register the T1-weighted scan to the MRS scan in the Gannet toolbox. Using the segment function of SPM12, the T1-weighted image was segmented to determine the tissue fractions (gray matter, white matter, and CSF) for the voxel. The Gannet toolbox estimates the CSF-corrected GABA+ values based on these tissue fractions (14). Exclusion criteria for bad data quality were based on visual inspection of the GABA+ edited difference spectrum, frequency drifts of the residual water spectrum, the creatine signal before and after frequency and phase correction, and the fit of the GABA+, the water and creatine signal, in addition to quantitative measurements of the provided fit error and expected full-width/half-maximum of the signal peaks, and on visual inspection of the voxel position.

Statistical Analysis

MATLAB was used for all statistical analyses. Considering the small sample size, non-parametric tests were chosen. Wilcoxon rank-sum tests were performed to compare GABA+/Cr-levels, Glx/Cr-levels, GABA/Glx levels and NAA/Cr levels between medication subgroups of ET (GABA and PROP), and to compare each patient group to healthy controls. Spearman's rank correlation coefficients were calculated between MRS output measures and TETRAS-scores OFF-medication. $P < 0.05$ were considered statistically significant. Because the probability of type I error cannot be decreased without increasing the probability of type II error, such that real differences may not be detected, no correction for multiple comparisons was applied for this pilot study. There are no available formal sample size criteria for MRS studies. Considering the recent study by Tapper and colleagues

TABLE 1 | Demographical data of total included subjects ($n = 20$) and subject groups.

	Total	GABA	PROP	HC
n	20	5	7	8
Males (%)	14 (70%)	4 (80%)	4 (67%)	6 (75%)
Age in years (SD)	62.2 (12.2)	69.8 (3.3)	55.9 (11.6)	63.0 (14.1)
Age at onset (SD)	37.5 (21.2)	36.6 (29.1)	38.14 (16.00)	N/A
Disease duration (SD)	24.2 (19.6)	33.2 (26.3)	17.71 (11.32)	N/A
Familial tremor (%)	10 (83%)	4 (80%)	6 (86%)	N/A
Alcohol sensitivity (%)	7 (60%)	2 (40%)	5 (71%)	N/A
TETRAS (SD)	17.7 (8.9)	24.70 (8.68)	12.64 (4.93)	N/A
Head tremor (%)	5 (42%)	3 (60%)	2 (29%)	N/A
Tremor medication	N/A	Primidone ($n = 3$)	Propranolol ($n = 7$)	N/A
		Gabapentin ($n = 2$)		

Data are mean (SD) or n (%). Subject groups: GABAergic medication (GABA), propranolol medication (PROP), healthy controls (HC). N/A, not applicable. TETRAS, The Essential Tremor Rating Assessment Scale. For full characteristics per patient including specific medication use and previously tried tremor-medication see ***Supplementary Table 1****.*

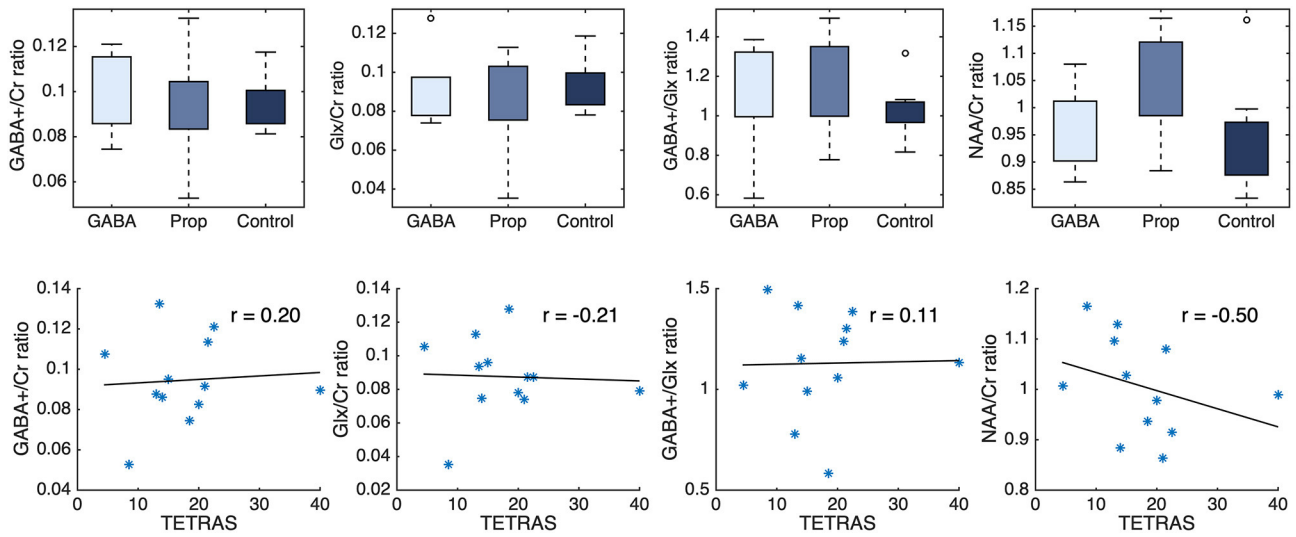

FIGURE 2 | (Upper) GABA+/Cr, Glx/Cr, GABA+/Glx, and NAA/Cr ratios show no difference between ET patients using GABAergic-medication (GABA) or propranolol medication (Prop), and healthy controls (Control). **(Lower)** TETRAS-scores (OFF-medication) of ET patients are not correlated with GABA+s/Cr, Glx/Cr, GABA+/Glx, and NAA/Cr ratios. *represent individual ET patients. Cr, creatine; ET, Essential Tremor; Glx, glutamate plus glutamine.

(5), and the exploratory nature of this study, a similar sample size was chosen.

RESULTS

Demographical and Clinical Characteristics

After screening, 26 participants were eligible for inclusion. In retrospect two patients did not meet the inclusion criteria of the Consensus Statement on the Classification of Tremor based on the video recordings. Four cases were excluded because of poor data quality. Five ET patients responsive to anticonvulsants, seven ET patients responsive to propranolol medication and 8 healthy controls were included in the final analysis. See **Figures 1C–E** for all MRS spectra. Demographical and clinical characteristics are presented in **Table 1**. For characteristics per patient including specific medication use and previously tried tremor-medication see **Supplementary Table 1**.

MRS Results

There was no significant difference between healthy controls ($n = 8$), patients responsive to propranolol ($n = 7$, PROP) and patients responsive to anticonvulsants ($n = 5$, GABA) regarding GABA+/Cr, Glx/Cr, GABA+/Glx, and NAA/Cr ratios (**Figure 2**). For GABA+/Cr ratio: PROP vs. controls [W] = 54, $p = 0.87$, GABA vs. controls [W] = 38, $p = 0.72$, PROP vs. GABA [W] = 36, $p = 0.64$. For Glx/Cr ratio: PROP vs. controls [W] = 53, $p = 0.78$, GABA vs. controls [W] = 34, $p = 0.94$, PROP vs. GABA [W] = 32, $p = 1.00$. For GABA+/Glx ratio: PROP vs. controls [W] = 72, $p = 0.07$, GABA vs. controls [W] = 44, $p = 0.22$, PROP vs. GABA [W] = 34, $p = 0.88$. For NAA/Cr ratio: PROP vs. controls [W] = 63, $p = 0.46$,

GABA vs. controls [W] = 39, $p = 0.62$, PROP vs. GABA [W] = 23, $p = 0.15$. For details of all measurements, frequency drift, signal-to-noise-ratios, and full width at half maximum please see **Supplementary Table 2**. TETRAS-scores (OFF-medication) were not correlated with GABA+/Cr ($r = 0.20$, $p = 0.53$), Glx/Cr ($r = -0.20$, $p = 0.51$), GABA+/Glx ($r = 0.10$, $p = 0.75$), and NAA/Cr ratios ($r = -0.50$, $p = 0.10$) in ET (combined groups, $n = 12$).

DISCUSSION

This explorative study suggests that GABA+, Glx, and NAA levels within the dentate nucleus region are not different in ET compared to healthy controls. Additionally, medication-subgroups did not exhibit differences in metabolites of interest. As mentioned previously, two earlier studies provided similar results, where no differences in GABA+ and Glx levels were detected (5, 6). An additional study compared GABA+ levels between ET patients using primidone or no primidone during MRS measurements, and found no effect of concurrent primidone use on GABA concentrations (15). The more recent study by Tapper et al. did observe a small but statistically significant inverse association between GABA+/Glx ratios and tremor severity. In this study, 10 ET cases and 6 healthy controls were included. Voxel size was similar to our study (25 mm × 25 mm × 25 mm vs. 35 mm × 25 mm × 25 mm), however, we have only included MRS spectra of the right deep cerebellar nuclei region due to limited available scanning time, in contrast with inclusion of both right and left side in the study by Tapper et al. Tremor rating scales were different between studies, and are not directly comparable. GABA+ as measured using MRS is an indirect marker of neurotransmitter levels, reflecting cellular pools of GABA, but is also composed of macromolecules and homocarnosine (16). Glx is the combined signal of glutamate and glutamine, which cannot be separated using this technique. In addition to its role as a neurotransmitter, glutamate plays an extremely important role in energy metabolism, and glutamine is predominantly metabolic (16). Thus, GABA+ and Glx do not merely reflect "inhibition" or "excitation." Moreover, these signals are noisy, and the GABA+/Glx ratio is therefore even more noisy, which makes the interpretation of this ratio complicated. It is debatable whether conclusions about pathophysiological mechanisms can be based on this ratio, especially when the GABA+/Cr and Glx/Cr ratios do not show group differences. Further research in this area is needed.

A major limitation of this study is its small sample size. Small group sizes and selection based on current medication use might have caused a type II error. However, the overlapping distributions per subgroup indicate that differences, if any, would be small. As already mentioned, the study by Tapper et al. did observe a statistically significant difference in GABA+/Glx ratios between ET patients and controls. It is worth mentioning that low power also increases the risk of type I error, reducing the likelihood that a statistically significant result reflects a true effect (17). The fact that results regarding GABA+ and Glx levels are in accordance with both previous MRS studies supports our results. Another limitation is the difference in mean age between the PROP and GABA group. Exact matching of subjects based on age was not feasible in the current setting. Although essential tremor is a common disorder, many patients have some (minor) additional symptoms (ET plus). We have used very strict inclusion criteria with respect to the disorder, co-morbidity, medication use and ability to undergo an MR-scan. A previous study did not find an age effect when looking at GABA levels corrected for voxel composition (18). We have used the same method of correction for voxel composition in our study.

In this explorative study, we confirm a previously identified lack of differences in GABA+ and Glx levels in the dentate nucleus region of essential tremor patients quantified with MRS (5, 6). Medication-subgroups did not exhibit differences in this respect. Furthermore, we could not replicate a previously observed association between GABA+/Glx ratios and tremor severity. MRS is a valuable technique in assessing metabolite changes within the tremor network. However, replication studies are needed before further conclusions can be drawn on the pathophysiological basis of these changes. The field of tremor research is plagued by heterogeneous results, and we would caution against drawing firm conclusions based on pilot studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethical Committee of the Academic Medical Center, Amsterdam. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB and A-FR set up the study. AB performed data collection, interpreted the data, and wrote the initial manuscript. NP and WP performed data collection and analyzed the data. NAP and AS provided technical assistance and interpreted the data. All authors contributed in writing the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.664735/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Stimulation-Induced Side Effects of Deep Brain Stimulation in the Ventralis Intermedius and Posterior Subthalamic Area for Essential Tremor

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Deep brain stimulation (DBS) targeting the ventralis intermedius (VIM) nucleus of the thalamus and the posterior subthalamic area (PSA) has been shown to be an effective treatment for essential tremor (ET). The aim of this study was to compare the stimulation-induced side effects of DBS targeting the VIM and PSA using a single electrode. Patients with medication-refractory ET who underwent DBS electrode implantation between July 2011 and October 2020 using a surgical technique that simultaneously targets the VIM and PSA with a single electrode were enrolled in this study. A total of 93 patients with ET who had 115 implanted DBS electrodes (71 unilateral and 22 bilateral) were enrolled. The Clinical Rating Scale for Tremor (CRST) subscores improved from 20.0 preoperatively to 4.3 (78.5% reduction) at 6 months, 6.3 (68.5% reduction) at 1 year, and 6.5 (67.5% reduction) at 2 years postoperation. The best clinical effect was achieved in the PSA at significantly lower stimulation amplitudes. Gait disturbance and clumsiness in the leg was found in 13 patients (14.0%) upon stimulation of the PSA and in significantly few patients upon stimulation of the VIM ($p = 0.0002$). Fourteen patients (15.1%) experienced dysarthria when the VIM was stimulated; this number was significantly more than that with PSA stimulation ($p = 0.0233$). Transient paresthesia occurred in 13 patients (14.0%) after PSA stimulation and in six patients (6.5%) after VIM stimulation. Gait disturbance and dysarthria were significantly more prevalent in patients undergoing bilateral DBS than in those undergoing unilateral DBS ($p = 0.00112$ and $p = 0.0011$, respectively). Paresthesia resolved either after reducing the amplitude or switching to bipolar stimulation. However, to control gait disturbance and dysarthria, some loss of optimal tremor control was necessary at that particular electrode contact. In the present study, the most common

stimulation-induced side effect associated with VIM DBS was dysarthria, while that associated with PSA DBS was gait disturbance. Significantly, more side effects were associated with bilateral DBS than with unilateral DBS. Therefore, changing active DBS contacts to simultaneous targeting of the VIM and PSA may be especially helpful for ameliorating stimulation-induced side effects.

Keywords: deep brain stimulation, dysarthria, essential tremor, paresthesia, posterior subthalamic area, stimulation-induced side effect, ventralis intermedius

INTRODUCTION

Deep brain stimulation (DBS) is a safe and effective treatment for medically refractory essential tremor (ET) (1). The nucleus ventralis intermedius (VIM) of the thalamus has been used as a primary target for DBS (2). However, proximal postural tremors and distal intention tremors are often refractory to VIM DBS. Several studies exploring potential targets for DBS have reported promising results for the posterior subthalamic area (PSA) with respect to tremor suppression (3–10), particularly for tremors that are difficult to control with VIM DBS (5, 6). The PSA, including the zona incerta, prelemniscal radiation, and cerebellothalamic tract (containing the dentatorubrothalamic tract) (11, 12), has been suggested as a potentially effective target for DBS to treat ET. With the advancement of surgical techniques, targeting the PSA by advancing the electrode deeper along the appropriate trajectory from the VIM is now possible (5, 13–15). Since the VIM and PSA are located at different contacts along the same electrode, this approach allows for a comparison of the two targets in terms of tremor reduction and stimulation-induced side effects. The investigation of stimulation-induced side effects is necessary, particularly with respect to the PSA, as the destruction of the PSA by lesioning has been associated with significant adverse events (16–18). Therefore, in the present study, we analyzed and compared stimulation-induced side effects and tremor reduction associated with DBS targeting the VIM and PSA *via* a single electrode based on individual active contacts.

MATERIALS AND METHODS

Patients

In the present study, patients with medically refractory ET who were implanted with a single DBS electrode simultaneously targeting the VIM and PSA at our hospital between July 2011 and October 2020 were retrospectively reviewed. Patients who were followed up for <6 months and those diagnosed with tremors other than ET (such as dystonia tremor or multiple sclerosis tremor) were excluded. This study received ethical approval from the institutional review board of our institution.

Surgical Procedure

The surgical technique used in this study has been described previously (13). The operation involved frame-based stereotactic implantation of a DBS electrode that simultaneously targeted the VIM and PSA. Stereotactic 1.5 T magnetic resonance imaging (MRI) was performed preoperatively, and the data were transferred to the Leksell SurgiPlan (Elekta, Stockholm, Sweden). Standard stereotactic coordinates for VIM localization were as follows: 13–15 mm lateral to the midline and 25–28.5% of the length of the anterior commissure-posterior commissure line anterior to the posterior commissure in the intercommissural plane. PSA localization was verified using MRI and the Schaltenbrand atlas. After localizing the targets, the angle of the trajectory necessary to advance the electrode to the PSA between the subthalamic nucleus and the red nucleus was determined using T2-weighted MRI. Trajectory planning was performed using the VIM as the primary target. The coronal and sagittal angles were adjusted as needed to create a trajectory that hit the PSA target, and procedures to evaluate the effect of stimulation on tremors and possible side effects were performed under local anesthesia. During surgery, the ventral thalamic border was identified using microelectrode recordings. The electrode was then advanced to a location that was 5–6 mm below the ventral thalamic border, and a test stimulation was initiated to evaluate tremor reduction and identify any side effects. Previously, microelectrode recordings have been used to indirectly locate the PSA based on the verification of the motor-evoked firing of VIM neurons and tremor cells inside the VIM nucleus of the thalamus. For permanent stimulation, DBS electrodes (model 3387, Medtronic, Minneapolis, MN, USA) were used. Based on the microelectrode recording results, contacts 0 and 1 were located in the PSA, and contacts 2 and 3 were located in the VIM. After the electrodes were implanted, postoperative computed tomography (CT) was performed before the frame was removed, and the scans were merged with preoperative MR images to determine the positions of the electrodes. Lastly, an implantable pulse generator (Soletra, Activa SC, Activa PC, or Activa RC, Medtronic) was implanted subcutaneously in the infraclavicular region under general anesthesia during the same session.

DBS Contacts and Parameters

During the first programming session, contact 0 or 1 (PSA) was activated, followed by contact 2 or 3 (VIM) for either single or double monopolar stimulation. In the case of bilateral electrodes, two electrodes were simultaneously activated in the same way. The effect of stimulation on each contact was evaluated to determine stimulation-induced side effects. Lastly, dual activation of contact 0 or 1 and contact 2 or 3 (VIM + PSA) was performed in all patients. The active contacts with the best clinical effects (tremor reduction in the contralateral hand) and the fewest side effects were analyzed. The contacts displaying the best effect were chosen

for chronic stimulation. The effect of each electrode on the tremors in the contralateral hand was evaluated separately. The amplitude, frequency, and pulse width were modulated using the optimal therapeutic window to improve the tremor. More complex stimulation paradigms, such as interleave or bipolar settings, were chosen if needed. Based on the stimulation parameters required for tremor suppression in each patient, group comparisons were performed. Importantly, even if a surgeon plans a trajectory that hits the PSA and VIM, the final location of the electrode could be altered due to surgical errors, intraoperative adjustments according to micro- or macrostimulation, and/or trajectory modifications to avoid vessels. The final location of the active contacts that were chosen for chronic stimulation were verified using the postoperative CT scan merged with the preoperative MRI image and the Schaltenbrand atlas using the Leksell SurgiPlan (**Figure 1**). For further analysis, stereotactic surgical planning was performed using Stealth Station S8 (Medtronic) according to previous target coordinates for each electrode. The planning data were uploaded into SureTune 3 (Medtronic) and merged with the postoperative CT data. Anatomical structures (e.g., VIM, zona incerta, subthalamic nucleus, substantia nigra pars reticulata, and red nucleus) were identified to reveal the relationship between stimulation-induced side effects and the location of the electrodes.

Tremor Outcomes

Patients were evaluated according to the Clinical Rating Scale for Tremor (CRST) preoperatively and at 6 months, 1, and 2 years after DBS electrode implantation. As 22 patients received bilateral DBS, the effect of each electrode was evaluated separately. The CRST subscores for the treated upper extremity were calculated by adding the scores of all single items pertaining to that extremity from parts A and B of the CRST (19). The "writing" item was only included for the dominant hand, leading to maximum possible scores of 32 or 28 points per extremity. This evaluation using the CRST was performed according to the methodology presented by Stacy et al. (20).

Statistical Analysis

Changes in CRST subscores were evaluated using a linear mixed model in the MIXED procedure of SAS (version 9.4, SAS INC., Cary, NC, USA). The analysis used repeated measures data obtained from each patient with no input for missing data because the follow-up period varied for each patient. To determine whether a statistical difference in CRST scores existed between the groups over time, the interaction between group and time was evaluated. In addition, to visualize changes in CRST scores over time, least-square means and standard errors for each time point were obtained to show the mean profile plot. The analysis of variance and Kruskal-Wallis tests were used to compare variables. The Fisher's exact test was used to compare the stimulation-induced side effects of each contact. All p-values were two-tailed, and statistical significance was set at $p < 0.05$.

RESULTS

Baseline Characteristics

A total of 97 patients underwent DBS for ET control between July 2011 and October 2020. Four patients with follow-up periods of <6 months, two patients who did not undergo follow-up clinical evaluation after DBS, and one patient who was diagnosed with multiple sclerosis were excluded from this study. Finally, the present study included 93 patients with 115 implanted DBS electrodes (71 unilateral and 22 bilateral). Patient demographics are shown in **Table 1**. With regard to stimulation parameters, the median amplitude, pulse width, and frequency were 2.4 V, 80 μs, and 160 Hz, respectively.

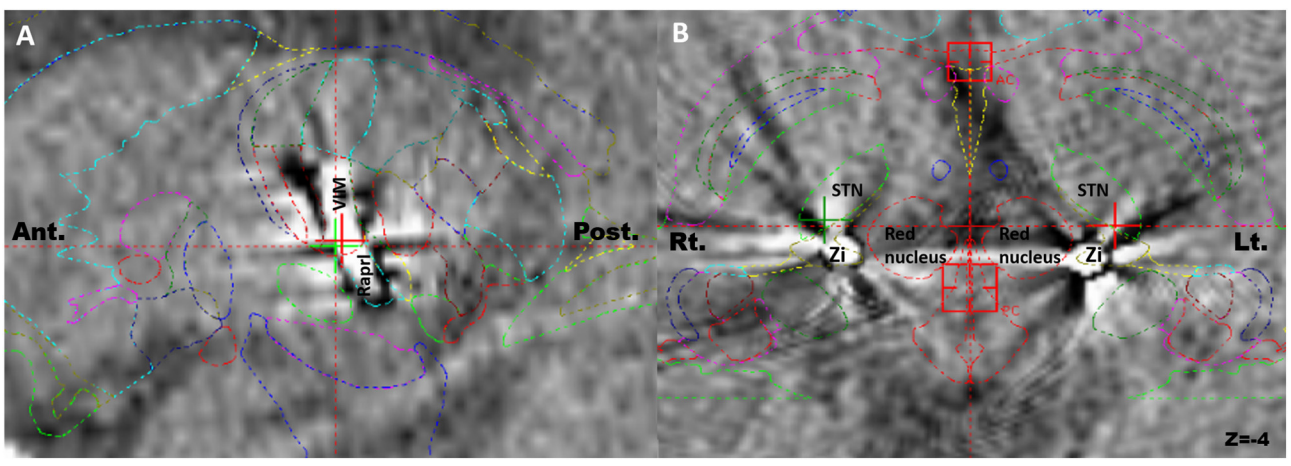

FIGURE 1 | Postoperative computed tomography scans merged with preoperative magnetic resonance images for identification of the actual electrodes and active contacts using Schaltenbrand atlas. **(A)** The electrode hit the ventralis intermedius and the prelemniscal radiation simultaneously in the sagittal plane. **(B)** The tips of bilateral electrodes were located in the zona incerta in the axial plane. Ant, anterior; Post, posterior; Rt, right; Lt, left.

Location of Active Contacts for Chronic Stimulation

Among the 115 electrodes, 210 active contacts were identified; in 37.8, 29.4, 25.9, and 6.9% of the patients, the contacts 1, 0, 2, and 3 were chosen for chronic stimulation, respectively (**Table 2**). Based on the lead analysis, the most stimulated structure was the zona incerta (43.8%), followed by the VIM (27.6%) and the prelemniscal radiation (24.2%). Notably, our analysis revealed that the surgical procedure had good accuracy in terms of positioning the intended targets to hit the VIM and PSA simultaneously.

TABLE 1 | Patient demographics and stimulation parameters.

Age*	62.9 ± 7.8
Follow-up duration** (months)	38 [16,65]
Sex* **	
Male	76 (78.4%)
Female	21 (21.6%)
Uni/Bilateral* **	
Unilateral	71 (73.2%)
Bilateral	22 (22.7%)
Baseline CRST subscore	19.0
Amplitude**	2.4 [1.9, 2.8]
Pulse width**	80 [60, 90]
Frequency**	160 [130, 160]

Values are presented as mean ± SD.
***Values are presented as median [Q1, Q3].*
****Values are presented as percentage.*
CRST, Clinical Rating Scale for Tremor.

TABLE 2 | Locations of active contacts for chronic stimulation.

Electrode	115
PSA (contact 0 or 1)	55 (47.8%)
VIM (contact 2 or 3)	9 (7.8%)
PSA + VIM (contact 0 or 1 and contact 2 or 3)	51 (44.4%)
Active contacts	210
0	62 (29.4%)
1	79 (37.8%)
2	54 (25.9%)
3	15 (6.9%)
Location	
Zi	92 (43.8%)
VIM	58 (27.6%)
Raprl	51 (24.2%)
Vop	6 (2.9%)
STN	2 (1.0%)
Voa	1 (0.5%)

PSA, posterior subthalamic area; Raprl, preleminiscal radiation; STN, subthalamic nucleus; VIM, ventral intermediate nucleus of the thalamus; Voa, ventrooralis anterior nucleus of the thalamus; Vop, ventrooralis posterior nucleus of the thalamus; Zi, zona incerta.

Tremor Reduction and Stimulation Parameters for Chronic Stimulation

The overall CRST subscore decreased from 20.0 at baseline ($N = 115$) to 4.3 (78.5% decrease), 6.3 (68.5% decrease), and 6.5 (67.5% decrease) at the 6 month ($N = 115$), 1 year ($N = 93$), and 2 year ($N = 65$) follow-ups, respectively (**Table 3**). A significant difference was observed in CRST subscores over time ($p < 0.001$). The least-square means of the CRST subscores were significantly different among the groups at baseline, with a score of 17.6 in the PSA, 20.7 in the VIM, and 21.7 in the VIM + PSA (**Table 3**). The CRST subscore decreased from 17.6 to 4.0 (77.3% decrease) in the PSA, from 20.7 to 3.9 (81.2% decrease) in the VIM, and from 21.7 to 5.0 (77.0% decrease) in the VIM + PSA at the 6 month follow-up. However, the CRST subscore increased slightly after 6 months in all three groups. Although the CRST subscores among the three groups were not statistically significant over time, chronic stimulation 2 years after DBS of the PSA (5.3, 70.0% decrease from baseline) resulted in slightly better tremor control than that after DBS of the VIM (6.8, 67.1% decrease from baseline) and the VIM + PSA (7.7, 64.5% decrease from baseline). **Figure 2** shows the mean profile plot of the changes in CRST subscores over time among the three groups. The mean amplitude, pulse width, and frequency for chronic stimulation were 2.1 V, 79.7 μs, and 149.6 Hz, respectively, in the PSA; 3.1 V, 81.7 μs, and 153.3 Hz, respectively, in the VIM; and 2.7 V, 87.6 μs, and 161.3 Hz, respectively, in the VIM + PSA (**Table 4**). The best clinical effect was achieved with the PSA at significantly lower stimulation amplitudes and frequencies ($p = 0.002$ and $p = 0.016$, respectively).

Stimulation-Induced Side Effects

Table 5 shows the stimulation-induced side effects of each contact in the 93 included patients. A total of 13 patients (14.0%) reported gait disturbance and reduced leg control when either contact 0 or 1 below the intercommissural line (ICL) was stimulated (**Figure 3A**); this number was significantly higher than that when contact 2 or 3 above the ICL was stimulated ($p = 0.0002$). Dysarthria occurred in 14 patients (15.1%) when contact 2 or 3 was stimulated (**Figure 3B**); this number was significantly higher than that when contact 0 or 1 was stimulated ($p = 0.0233$). Transient paresthesia occurred in 13 patients (14.0%) after stimulation below the ICL and in six cases (6.5%) after stimulation above the ICL. Gait disturbance and dysarthria occurred significantly more frequently in those undergoing bilateral DBS than in those undergoing unilateral DBS (31.8% vs. 8.5%, $p = 0.00112$ and 45.5% vs. 11.3%, $p = 0.0011$, respectively). Paresthesia resolved either after a reduction in amplitude or change to bipolar stimulation without any loss of optimal tremor control. To reduce the side effect of gait disturbance due to stimulation below the ICL and dysarthria due to stimulation above the ICL, some sacrifice of optimal tremor control was required at that particular electrode contact. These side effects were reversible when changing the active contact to dual VIM + PSA stimulation (**Figure 3C**) or to bipolar stimulation (**Figure 3D**).

TABLE 3 | Clinical Rating Scale for Tremor (CRST) subscores over evaluation visits.

Follow-up	Total ($N = 115$)		*p*-value (time)	PSA (contact 0 or 1)		VIM (contact 2 or 3)		PSA + VIM (contact 0 or 1 and 2 or 3)		*p*-value (group and time)
	CRST estimate	SE		CRST estimate	SE	CRST estimate	SE	CRST estimate	SE	
Baseline	19.9815	0.6426	–	17.6306	0.8913	20.7267	2.1853	21.6665	0.9577	**0.0095**
6 months	4.2570	0.4380	**<0.001**	4.0150	0.6342	3.8712	1.4714	4.9715	0.7353	0.5914
1 year	6.3256	0.5629	**<0.001**	5.3927	0.7832	6.1902	1.7618	7.4118	0.9446	0.2662
2 years	6.5970	0.5799	**<0.001**	5.3210	0.8351	6.8074	1.5768	7.6784	1.0359	0.3105

CRST, Clinical Rating Scale for Tremor; PSA, posterior subthalamic area; SE, standard error; VIM, ventral intermediate nucleus of the thalamus. Boldface type indicated statistical significance ($p < 0.05$). The change in CRST subscores was evaluated using a linear mixed model.

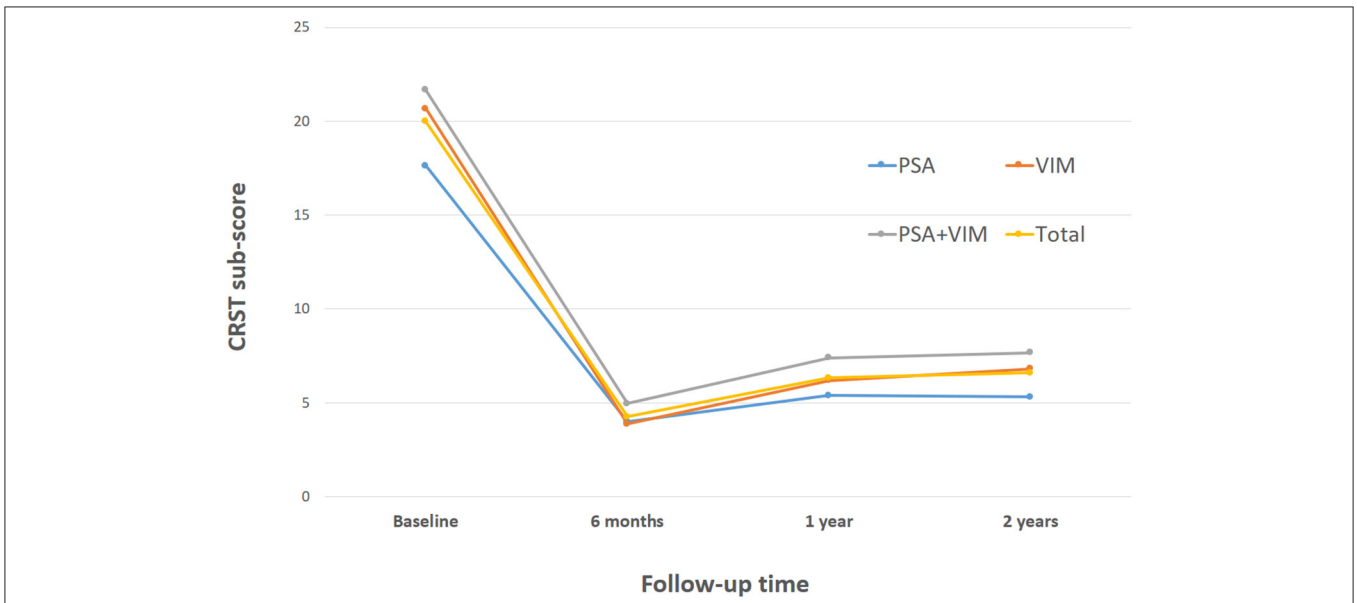

FIGURE 2 | Changes of Clinical Rating Scale for Tremor (CRST) subscores over time. CRST subscores at evaluation visits. The graphs represent LSmeans and SE of the CRST subscores at different evaluation visits. PSA, posterior subthalamic area; VIM, ventral intermediate nucleus of the thalamus.

TABLE 4 | Chronic stimulation parameters.

Parameters	PSA ($N = 55$)	VIM ($N = 9$)	PSA+VIM ($N = 51$)	*p*-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Voltage	2.1 ± 0.8	3.1 ± 1.8	2.7 ± 0.7	**0.024**
Pulse width	79.7 ± 20.1	81.7 ± 23.2	87.6 ± 28.8	0.391
Frequency	149.6 ± 16.2	153.3 ± 19.7	161.3 ± 16.9	**0.016**

PSA, posterior subthalamic area; VIM, ventral intermediate nucleus of the thalamus. Boldface type indicated statistical significance ($p < 0.05$).

DISCUSSION

In the present study, we investigated tremor outcomes and stimulation-induced side effects of DBS targeting the VIM and PSA *via* a single electrode. The strengths of our study are the large number of patients (115 implanted DBS electrodes in 93 patients with ET) and evaluation of long-term outcomes. In the present study, dysarthria, gait disturbance, and paresthesia were the most common stimulation-induced side effects, consistent with previous reports (21–23). We identified that single electrode DBS targeting both the PSA and VIM can be used when stimulation-induced side effects occur.

Clinical Outcomes

PSA (contact 0 or 1) was most often chosen for chronic stimulation followed by VIM + PSA and VIM (**Table 2**). Tremor improved from baseline at all time points (**Table 3**). Additionally, favorable outcomes in terms of overall improvement in CRST subscores for the treated side were observed in this study, and among the three groups, there was no significant difference in tremor suppression with respect to each patient's individual active contacts (**Table 3**). The VIM required a significantly lower stimulation amplitude (**Table 4**). Additionally, although tremor was less effectively controlled over time with VIM + PSA stimulation (**Table 3**), the least-square means of CRST subscores were significantly higher at baseline with VIM + PSA

TABLE 5 | Stimulation-induced side effects on each contact.

Stimulation-induced side effect	PSA (contact 0 or 1) *N* (%)	VIM (contact 2 or 3) *N* (%)	*p*-value	Unilateral DBS (total 71) *N* (%)	Bilateral DBS (total 22) *N* (%)	*p*-value
Gait disturbance	13 (14.0%)	0 (0%)	**0.0002**	6 (8.5%)	7 (31.8%)	**0.0112**
Dysarthria	4 (4.3%)	14 (15.1%)	**0.0233**	8 (11.3%)	10 (45.5%)	**0.0011**
Paresthesia	13 (14.0%)	6 (6.5%)	0.1448	15 (21.1%)	4 (18.2%)	1.00

Boldface type indicated statistical significance ($p < 0.05$).
DBS, deep brain stimulation; ICL, intercommissural line; PSA, posterior subthalamic area; VIM, ventral intermediate nucleus of the thalamus.

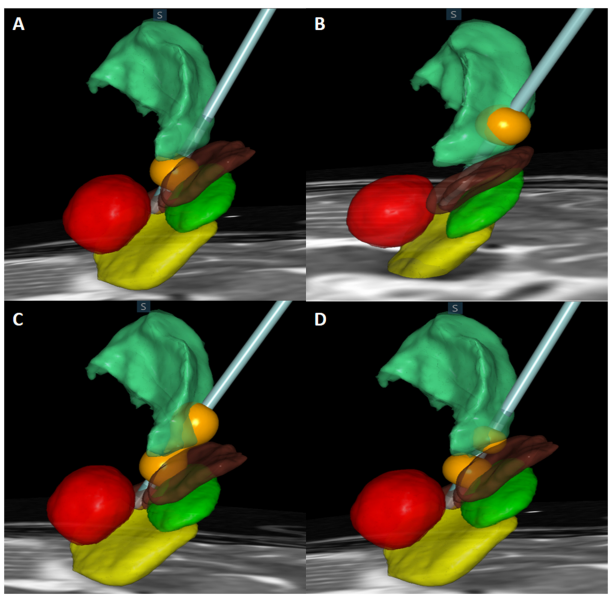

FIGURE 3 | Actual electrode and contact of stimulation in relation to the subthalamic nucleus (STN) (green), substantia nigra (SNr) (yellow), red nucleus (red), zona incerta (Zi) (brown), and ventralis intermedius (VIM) (light green) are shown. **(A)** Monopolar stimulation of contact 1 located in the Zi. **(B)** Monopolar stimulation of contact 3 located in the VIM. **(C)** Dual stimulation of contact 1 in the Zi and contact 3 in the VIM. **(D)** Bipolar stimulation of contacts 1 and 2.

stimulation. These findings suggest that the VIM and PSA should be chosen as the active contacts for patients with severe tremors.

Dysarthria

The most common stimulation-induced side effect associated with VIM DBS was dysarthria (**Table 5**). A meta-analysis reported that the most commonly reported speech disorder following thalamic DBS was dysarthria (24.2%) (24). Dysarthria has been frequently observed after VIM DBS (18, 25, 26), most likely due to its effects on the corticobulbar fibers of the internal capsule (27–31). The unintended lateral spread of current can also activate the corticospinal tract and subsequently lead to involuntary muscle contraction of the arms and/or legs as well as lead to dysarthria (32, 33). With VIM DBS, this is often considered a consequence of excessively lateral electrode placement, affecting the internal capsule (18, 34). Notably, in the present study, stimulation-induced dysarthria was ameliorated by changing active DBS contacts to either VIM + PSA or bipolar stimulation.

Paresthesia

Gait disturbance and paresthesia were more commonly associated with stimulation of the PSA (**Table 5**), and paresthesia was usually transient. However, when paresthesia persisted, it could be eliminated by adjusting DBS parameters, such as a reduction in amplitude or bipolar stimulation. Paresthesia is the most common side effect of stimulation of the medial lemniscus, posterior in the subthalamic area (31, 33), and the spread of electric current to the ventral caudal thalamic nucleus, which is posterior to the VIM (25, 30, 32). Paresthesia exacerbated by the spread of electric current away from the VIM can be ameliorated by a more anterior placement of the electrode within the VIM (35, 36). Sensory side effects are often considered susceptible to habituation over time and less prone to impede the treatment results (37). Paresthesia can be overcome with programming adjustments (38). Paresthesia can be diminished by decreasing the amplitude of stimulation since it is voltage dependent. Our findings suggest that a slow, gradual increase in amplitude and the use of bipolar stimulation to minimize the spread of current to the nearby medial lemniscus are effective in ameliorating stimulation-induced paresthesia.

Gait Disturbance

In 10 patients, stimulation *via* active contacts in the PSA (0 and 1) was changed to VIM + PSA stimulation due to stimulation-induced gait disturbance and reduced leg control despite the loss of optimal tremor control. Previous studies have also observed side effects of PSA stimulation, which mainly included stimulation-induced gait ataxia and clumsiness of the contralateral lower limb (18, 39). Stimulation of the cerebellothalamic tract has also been shown to cause postural instability and gait ataxia. These symptoms can be attributed to chronic VIM/PSA stimulation leading to maladaptive plasticity of different fiber tracts (vestibulocerebellar-thalamic afferents and cerebello-rubrospinal tracts) (26, 40–42). More posterior and medial stimulation could activate the cerebellothalamic tracts, leading to gait disturbance or ataxia (16, 32). Cerebellar symptoms, including hypotonia, dysmetria, and gait disturbance or imbalance, were often reported after ablation of the subthalamic dorsal area (18, 43–45). Although the destruction of the PSA by lesioning has been reported to be associated with significant adverse events (43, 45), in the present study, no severe adverse events were observed during the evaluation of PSA DBS. This may be because while PSA DBS overrides tremor oscillations, it does not interrupt patterns of information related to proprioceptive sensations (46). Previous studies have suggested that large pulse width stimulation might account for

DBS-induced cerebellar side effects and have recommended short pulse width settings for DBS (47–49). Another important issue is that patients with ET often have concomitant cerebellar ataxia, a phenomenon recently classified as ET plus syndrome (32, 50). Baseline ataxia may become more apparent after a successful reduction in tremor through DBS.

Unilateral vs. Bilateral

Gait disturbance and dysarthria were significantly more frequent in those undergoing bilateral DBS than in those undergoing unilateral DBS (**Table 5**). Previous studies have also reported that stimulation-induced side effects are more frequently observed after bilateral procedures than after unilateral procedures (18, 51–55), with a 2- to 3-fold higher risk of dysarthria and ataxia associated with bilateral procedures (24, 32, 36, 52, 56). However, bilateral stimulation is more effective than unilateral stimulation for treating severe bilateral tremors and tremors combined with midline axial tremors (e.g., head tremors) and voice tremors (57). When treating axial tremors that require bilateral DBS, careful evaluation of long-term benefits and risks that may affect the patient's quality of life is essential, and staged operations should be considered at times. Since we activated bilateral electrodes simultaneously for severe bilateral tremors and axial tremors in this study, it was not possible to determine the effect of each electrode individually. Furthermore, it was difficult to determine each electrode's effect on dysarthria and gait disturbance. Therefore, since numerous stimulation-induced side effects associated with bilateral stimulation have been reported, our center recently changed our protocol so that the electrode on the contralateral side with respect to severe tremors is activated first and the other electrode is activated in a delayed manner.

Limitations

The current study has several limitations. A major limitation is that it was a retrospective review of a single institution's clinical practice. Randomized controlled trials comparing the VIM and PSA directly through "on-off" stimulation of each contact are necessary to confirm our conclusions. Second, the follow-up period varied for each patient. The CRST score was evaluated preoperatively ($N = 115$ electrodes) and again at 6 months ($N = 115$), 1 year ($N = 93$), and 2 years ($N = 65$) postoperation. To compensate for this weakness, we adopted a linear mixed model. Further investigations with continuous follow-up are necessary to confirm the long-term effects of VIM and PSA DBS on tremor reduction, as well as to assess tolerance. Third, only parts A and B of the CRST, which were objective measurements rated by an experienced examiner, were evaluated. Part C of the CRST, which includes a patient-reported measurement of functional disability due to the tremor, and the Essential Tremor Questionnaire, assessing quality of life in relation to the tremor, were not included since these were subjective measurements. Further studies are needed to determine functional disability and quality of life in patients with ET undergoing DBS. Lastly, while we identified that more adverse side effects were associated with bilateral stimulation than with unilateral stimulation, we failed to confirm the effect of either electrode individually or according to target as both electrodes were activated simultaneously. Therefore, prospectively designed studies are needed to confirm our conclusions.

CONCLUSION

In the present study, we analyzed tremor outcomes and stimulation-induced side effects in a large sample of patients (115 DBS electrodes in 93 patients with ET) who underwent DBS targeting both the VIM and PSA using a single electrode. Favorable results in terms of overall tremor improvement, stimulation-induced side effects, and surgical accuracy for the intended targets were observed. Knowing the different stimulation-induced side effects associated with the PSA and VIM and their effects on the results of the treatment is essential. The most common stimulation-induced side effects associated with VIM DBS and PSA DBS were dysarthria and gait disturbance, respectively. These side effects were significantly more common in those undergoing bilateral DBS than in those undergoing unilateral DBS. Additionally, in this study, we found that changing active DBS contacts to simultaneous targeting of the VIM + PSA may be especially helpful for ameliorating stimulation-induced side effects.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Severance Hospital Clinical Trial Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JC: conceptualization, writing (review and editing), and resources. MK: visualization and roles/writing (original draft). KC: data curation and formal analysis. SP: methodology and software. WC: project administration investigation. HJ: supervision and validation. All authors contributed to the article and approved the submitted version.

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Wearable Devices for Assessment of Tremor

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Tremor is an impairing symptom associated with several neurological diseases. Some of such diseases are neurodegenerative, and tremor characterization may be of help in differential diagnosis. To date, electromyography (EMG) is the gold standard for the analysis and diagnosis of tremors. In the last decade, however, several studies have been conducted for the validation of different techniques and new, non-invasive, portable, or even wearable devices have been recently proposed as complementary tools to EMG for a better characterization of tremors. Such devices have proven to be useful for monitoring the efficacy of therapies or even aiding in differential diagnosis. The aim of this review is to present systematically such new solutions, trying to highlight their potentialities and limitations, with a hint to future developments.

Keywords: tremor, wearable devices, Parkinson's disease, essential tremor, monitoring, diagnosis

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INTRODUCTION

Tremor is generally defined as an involuntary, rhythmic, oscillatory movement of a body part (1). Limbs and head, when unsupported, may exhibit slight tremor, referred to as physiological tremor. Such tremor is generally not visible or symptomatic unless it is enhanced by fatigue or anxiety. Pathological tremor, on the other hand, is usually visible and persistent and can severely compromise the execution of normal life tasks, like eating, dressing, writing.

Tremor symptoms may affect one body region (focal tremor), two or more adjacent parts (segmental tremor), one side (hemitremor), or the whole body (generalized tremor). According to activation conditions, two kinds of tremors are generally considered: *rest tremor*, when the affected part is relaxed, and *action tremor* (kinetic, postural, or isometric), when the subject performs voluntary movements or voluntarily maintains a certain position against gravity. Tremor features include frequency (usually in the range of 4–8 Hz) and amplitude. When two or more antagonist muscles are involved in tremor, activation patterns are defined according to the relative timing of tremor electromyography (EMG) bursts: synchronous pattern, when muscle bursts are in phase, and alternating pattern, when bursts are phase-shifted (2), as shown in **Figures 1A–D**.

Surface EMG is the gold standard technique for the diagnosis, characterization, and monitoring of tremor (3). Unfortunately, it suffers from uncertainty and errors due to bad positioning of electrodes, changes in skin conductance, and cross-talking from other muscles. To avoid such inconveniences, needle EMG (4) is the most reliable technique for a precise characterization of tremor features, but it is invasive and costly.

Generally, EMG is unsuitable for continuous monitoring or frequent assessment of tremor characteristics.

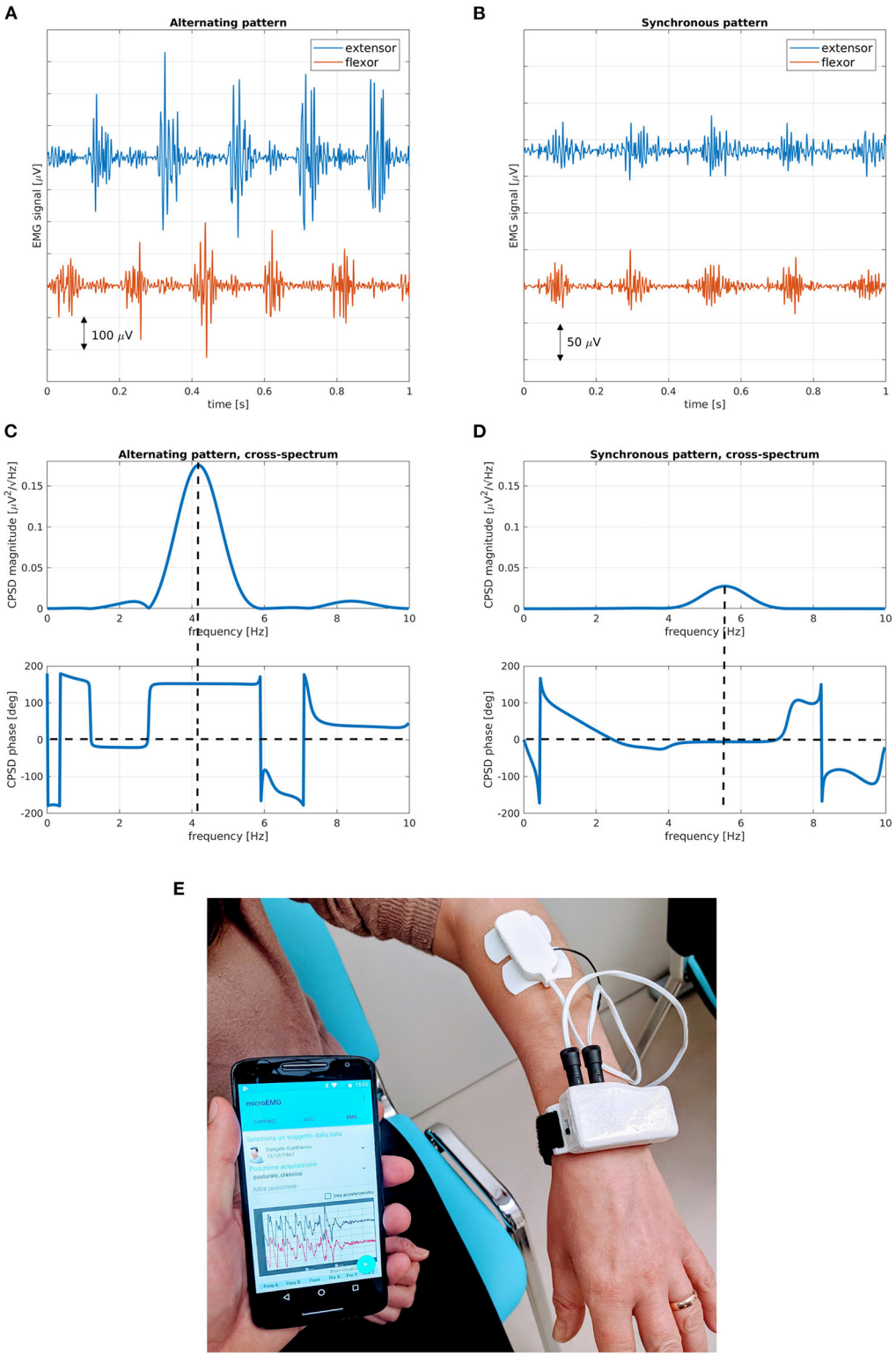

FIGURE 1 | Electrophysiological and spectral characteristics of tremor patterns. Muscle bursts for **(A)** alternating and **(B)** synchronous tremor patterns; magnitude and phase cross-spectral diagrams for **(C)** alternating and **(D)** synchronous tremor patterns. **(E)** Wrist-worn device, with EMG plates and mobile app for the characterization of tremor patterns. Alternating bursts of antagonist muscles show a marked phase difference at peak tremor frequency, while synchronous bursts have a small phase difference at peak tremor frequency. In alternating tremors, peak amplitude is usually higher and average frequency is lower than in synchronous tremors. EMG, electromyography; CPSD, cross power spectral density.

In the last decade, the large diffusion of mobile devices has fostered the development of several portable and wearable solutions for health monitoring or even for disease diagnosis. Most of such devices are based on inertial sensors (accelerometers and gyroscopes), while others use a combination of inertial and electrophysiological information. Many of them can be interfaced with smartphones or tablets through wireless communication protocols (Bluetooth, Wi-Fi, etc.). Smartphones, smartwatches, and tablets have sufficient computing resources for performing complex calculations, such as digital signal processing and artificial intelligence (AI).

Mobile devices, together with the advent of the Internet of Things (IoT), have dramatically changed people's lifestyles and have found newer and newer areas of application, allowing for continuous monitoring of disease symptoms and vital signs. However, signal processing techniques and sensing technologies need to be properly selected in order to provide data in agreement with the clinical-functional assessment of tremor (5).

In this brief review, we mainly focus on novel wearable solutions for the automated acquisition and analysis of tremor data. For this purpose, three main classes of wearable devices are identified: (1) devices for assessing tremor features, (2) devices for monitoring tremor and efficacy of therapies, and (3) devices for differential diagnosis between tremulous disorders. **Table 1** reports a synthetic view and classification of the examined literature.

METHODS

For the purposes of this review, PubMed and Google Scholar search engines were queried using combinations of the following keywords: tremor, wearable, device, assessment, monitoring, and diagnosis. The words "tremor" and "wearable" were used as fixed keys in all searching queries. Only articles published in the last decade were selected.

DEVICES FOR THE ASSESSMENT AND CHARACTERIZATION OF TREMOR

Inertial sensors have proven to be of great help in clinical practice (43), especially in the assessment, diagnosis, and treatment of tremor in Parkinson's disease (PD) (44–46).

The large diffusion of smartphones, tablets, and smartwatches has fostered the development of specialized software applications that make use of on-board sensors for inertial measurements of tremor and other movement alterations (20–23). LeMoyne et al. (20) used a common smartphone for estimating tremor frequency in PD subjects. The authors used the same equipment for assessing tremor in essential tremor (ET) subjects (21), discriminating between *on* and *off* state during deep brain stimulation (DBS). Araújo et al. (22) found a good agreement between EMG measurements and accelerometer estimations made by three different mobile apps. A similar approach was used by Bhatti et al. (23) for the evaluation of orthostatic tremor. However, these solutions can reliably estimate frequency only.

Along with the introduction of smartphone apps, several dedicated devices and methods have been proposed for tremor measurement. A summary of characteristics and specifications required for motion sensing transducers and analysis methods for assessing tremor severity in terms of amplitude and occurrence is reported by Elble and McNames (6).

Heldman et al. (7) evaluated a commercial motion-sensing device, worn on the hand or fingers of the most affected side, in ET subjects while performing motion tasks. The results of this study opened a way toward continuous rating of tremor severity during routine or spontaneous activities of daily living. Other hand- or wrist-wearable devices were introduced later for evaluating rest and action (postural and isometric) tremor in PD subjects using an inertial measurement unit (IMU), made of a triaxial accelerometer and a triaxial gyroscope, both on the same silicon chip (8), or a set of four triaxial accelerometers (9). An IMU was also used by Hssayeni et al. (10) to assess tremor severity in PD and by Mahadevan et al. (11) and Dai et al. (12) in order to discriminate between bradykinesia and tremor. Sanchez-Perez et al. (13) devised a novel algorithm based on fuzzy logic for the evaluation of rest tremor severity. These authors achieved a good level of agreement with Unified Parkinson Disease Rating Scale (UPDRS) part III (10–13), thus showing the equivalence between clinical scales and tremor assessment by wearable sensors.

A wrist-worn device with and external IMU placed on a finger was proposed by Jeon et al. (14), together with various AI techniques for the automatic scoring of rest tremor in PD. Other studies (24–27) have focused on the use of commercial smartwatches, which have become easily available in the last years. López-Blanco et al. were able to correlate the root mean square of angular velocity acquired from the triaxial gyroscope of an Android-based smartwatch to the Fahn–Tolosa–Marin (FTM) tremor rating scale (TRS) scores of ET subjects (24) and to UPDRS-III scores of PD subjects (26). Varghese et al. (25) used a smartwatch within an integrated analysis framework comprising a smartphone and a tablet for the implementation of a tremor assessment and monitoring system in a clinical setting. Shawen et al. (27) compared the performances of a smartwatch and a skin-mounted IMU in classifying tremor and bradykinesia severity in PD, demonstrating that smartwatch performance was comparable to that of a custom, specialized sensor.

By extending such localized measurement systems to a distributed configuration, other solutions have been devised, including more sensors displaced on several body points or limbs. Rigas et al. (15) developed a method based on features extracted from accelerometers mounted in different body segments, which produce data feeding two parallel hidden Markov models (HMM): the first one is used to quantify tremor severity and the second one to recognize body posture and action, thus providing a complete assessment of tremor activity. A preliminary study (16) used three electromagnetic motion capture sensors on different limbs of the arm. The aim of this study was to provide a model for tremor-suppression orthotic strategies in ET, but no progressions have been made so far in such direction. A more complex setup was proposed in a study by Lonini et al. (17), where PD subjects where instrumented with six multi-modal soft sensors

TABLE 1 | Classification of examined literature.

Assessment of tremor features	Sensors on fingers/hand/wrist	• Elble (6) • Heldman (7) • Dai (8) • Marino (9) • Hssayeni (10)	• Mahadevan (11) • Dai (12) • Sanchez-Perez (13) • Jeon (14)
	Sensors on multiple segments/whole body	• Rigas (15) • Charles (16) • Lonini (17)	• Huo (18) • Delrobaei (19)
	Smartphone based methods	• LeMoyne (20) • LeMoyne (21)	• Araújo (22) • Bhatti (23)
	Smartwatch based methods	• López-Blanco (24) • Varghese (25)	• López-Blanco (26) • Shawen (27)
	Other devices	• Zajki-Zechmeister (28)	
Continuous monitoring of tremor		• Cole (29) • Jeonghee (30) • Battista (31) • Battista (32) • Heijmans (33)	• San-Segundo (34) • McNames (35) • Kuosmanen (36) • Erb (37)
Differential diagnosis between tremors		• Vescio (38) • Hossen (39) • Ghassemi (40)	• Di Biase (41) • Bove (42)

(triaxial accelerometers and gyroscopes, with two-lead skin surface voltage), capable of acquiring accelerations, angular velocity, and EMG while deforming with skin. This setup was used to assess the performances of AI models in detecting motor symptoms (tremor and bradykinesia) during normal life activities. Huo et al. (18) introduced an even more complex suit, based on a force sensor, three IMUs, and four custom mechanomyography (MMG) sensors. The system was tested in its capacity to predict Unified Parkinson's Disease Rating Scale (UPDRS) scores based on quantitative assessment of bradykinesia, rigidity, and tremor in PD patients. Delrobaei et al. (19) performed a similar task using a distributed setup with 17 wireless IMUs, hinting at possible applications in home-monitoring settings. Another system, in the form of a pen, has been described by Zajki-Zechmeister et al. (28) and can provide information comparable to tremor scales, MDS-UPDRS for PD, and Essential Tremor Rating Assessment Scale (TETRAS) for ET. Despite the large diffusion of wearable sensors for the assessment of tremor features and for the evaluation of tremor severity, these technologies are still rarely used in clinical practice. It has been demonstrated that their evaluation of tremor severity and their test–retest variability are comparable to those of rating scales (6). These wearable solutions can reliably estimate only tremor frequency and amplitude and can be used as the basis for the development of more complex devices for the differential diagnosis of tremulous disorders and for the monitoring of therapies.

DEVICES FOR MONITORING TREMOR AND EFFICACY OF THERAPIES

Continuous monitoring of tremor symptoms has gained an increasing interest in the last years due to the continuous need for home-care solutions and smart services capable of reducing the burden of National Health Systems. Monitoring tremors during normal life activities can help in assessing the efficacy of therapies. It may be useful for understanding when tremor occurs and whether it is related to specific tasks or conditions. The main difficulty in daily life tracking is the reliable discrimination of tremor from other movements and artifacts. Therefore, a great effort has been dedicated to the development of signal processing and AI techniques.

Cole et al. (29) validated a network of eight wireless sensors with combined 3D accelerometry and surface EMG and tested several machine learning (ML) algorithms for the assessment of the presence/absence and severity of tremor and dyskinesia. They proved that their strategy achieved a small error rate and was robust to changes in the positioning of sensors. Kim et al. (30) used a wrist-worn device equipped with an IMU and statistical pattern recognition algorithms to discriminate upper limbs tremor from normal daily activities. Another watch-like device, based on a triaxial accelerometer, was introduced and validated by Battista and Romaniello (31, 32). Their device was used to identify tremor events by computing statistical indexes that were representative of motion patterns. In addition to a wrist IMU sensor, Heijmans et al. (33) used also a second IMU positioned on the chest, together with a questionnaire for annotating tremor events during the day. The annotated data were used to predict tremor severity. A wrist-worn accelerometer, together with a smartphone annotation app, was used by San-Segundo et al. (34). In this study, labeled data were collected in a laboratory setting and weak-labeled data were recorded during daily life. Several AI models were used to identify tremor occurrence and severity from different sets of extracted features.

McNames et al. (35) use two IMUs, one for each wrist, and a two-stage algorithm for refining tremor frequency

estimation during the normal activity of PD subjects for seven consecutive days. A smartphone-based solution for long-term monitoring was introduced by Kuosmanen et al. (36), consisting of an accelerometer-based ball game for quantifying patients' hand tremor, a medication journal for logging medication intake times, a daily survey for reporting the overall severity of PD symptoms, and reminder notifications. Erb et al. (37) introduced four different studies based on home monitoring by means of wearable sensors and self-reporting diaries. In this work, several sensing technologies were used: accelerometers, gyroscopes, magnetometers, barometers, electrocardiogram (ECG), EMG, and galvanic skin response (GSR) sensors. The main limitation of the proposed solutions is the accuracy in distinguishing between tremor and other movements or artifacts, due to the high variability of signals recorded during normal daily activity. Such monitoring devices seem to work better in combination with self-annotations. Achieving a good accuracy in identifying tremor and in assessing its severity during continuous, fully automated monitoring is still an open challenge.

DEVICES FOR DIFFERENTIAL DIAGNOSIS

Differential diagnosis between tremulous disorders is, perhaps, one of the most intriguing and challenging research tasks that have been carried on in recent times. A successful discrimination between neurological diseases based on tremor data only may avoid more complex, invasive, and expensive examinations. Hence, the interest for simpler instruments and methods may help even general practitioners in screening neurological disorders that exhibit tremor symptoms. Discrimination of ET from PD and other neurodegenerations often requires a DAT-SPECT imaging examination. Such examination is costly and invasive, as it employs a radioactive tracer. Essential tremor subjects have normal DAT-SPECT; therefore, abnormal DAT-SPECT can be considered as an exclusion criterion for ET (47). The increasing availability of cheap, non-invasive sensors and the development of ML and signal processing techniques have supported the search for alternative biomarkers in the huge amount of data that can be easily produced.

Nisticò et al. first discovered the usefulness of phase pattern in antagonistic muscle pairs as a powerful biomarker capable of discriminating ET from PD (48) and drug-induced Parkinsonism (DIP) from PD (49). Their work was based on EMG recordings and automatic evaluation of phase lags between bursts detected on the extensor carpi radialis (ECR) and flexor carpi ulnaris (FCU) muscles during rest tremor occurrence. It was observed that PD subjects exhibited an alternating activation pattern, with a marked phase shift between bursts corresponding to the alternating contractions of the antagonistic muscle pair. Non-PD subjects (ET and DIP) exhibited synchronous patterns, with no significant phase shift and muscles contracting at the same time. These findings have led to the development and validation of a wearable watch-like device (38), equipped with two EMG acquisition plates (one for each muscle) and with wireless connection to a smartphone and mobile app for real-time processing and fully automated evaluation (**Figure 1E**). The system is capable of characterizing rest tremor phase pattern in <1 min and to discriminate between PD and non-PD on an individual basis.

Other authors (39, 40) introduced AI-based analysis techniques for discriminating ET from PD using combined EMG and accelerometer signals acquired in a laboratory setting. Overall discrimination accuracies were 88.75 and 83%, respectively. However, such methods have not been implemented in any device yet.

Di Biase et al. (41) introduced another biomarker, called tremor stability index (TSI), evaluated by means of a triaxial accelerometer mounted on the wrist. Tremor stability index is evaluated as the interquartile range of the instantaneous frequency change. The authors tested this index on different datasets, achieving an accuracy between 82% (on a validation cohort) and 90% (testing cohort) in discriminating ET from PD. Bove et al. (42) used triaxial accelerometers worn on the proximal one-third of the metacarpals, and evaluated differences in frequency, amplitude, coherence, and peak dispersion of resting and action tremor between PD, ET, and dystonic tremor (DT) subjects. They combined these parameters into three sets of at most five discriminating criteria (one set for each disease), achieving, respectively, the following values of sensitivity and specificity: for DT, 85 and 87.5%; for ET, 95 and 90%; for PD, 100 and 93%. Diagnostic solutions based on inertial sensors have achieved a good discriminating performance. Wearable EMG devices, however, show the best accuracy in differential diagnosis between tremulous disorders, as they can evaluate tremor patterns.

CONCLUSION

Wearable sensors have undergone important developments in the last decade in an increasing number of areas of application. Healthcare is one of the most promising sectors, where new technologies are being used for sensing, acquiring, analyzing, and sharing data. Several wearable solutions have been implemented, either using commercially available devices or developing custom systems, for aiding clinical evaluation and diagnosis. In this short review, we have focused on devices and solutions for the assessment, continuous monitoring, and diagnosis of tremor in neurological diseases. As a first consideration, up to date, most wearable applications are mainly focused on tremor assessment and quantification of tremor severity. A minor number of solutions are dedicated to home monitoring of tremor symptoms in order to fully characterize their occurrence and severity during daily life tasks and to optimize therapies. The use of wearable technologies for differential diagnosis between tremulous disorders is very promising. In the next future, more efforts will be devoted to this field. Another consideration regards sensing technologies. Inertial sensing based on Micro Electro-Mechanical Systems (MEMS) is still the most used technology for wearable devices measuring tremor. This is mainly due to their physical properties: tremor is a rhythmic movement,

and these transducers sense motion. Moreover, they are nearly ubiquitous, as they are embedded in all mobile communication and entertainment devices, in smartwatches and smart bands used for sports and fitness. Last, they can be easily embedded in any wearable solution thanks to their small dimensions and low power requirements. However, in diagnostic applications, the accuracy that can be achieved using MEMS sensors is still lower than that of solutions that include EMG and tremor pattern analysis.

FUTURE PERSPECTIVES

The pervasive diffusion of mobile devices and network services, together with the advancement of signal processing algorithms, will allow for a wider diffusion of wearable solutions for diagnosing and monitoring tremors and other pathological conditions. Skin sensors, which can be used as patches, represent another emerging technology. They are at a very early stage but are very likely to be used in the next future for continuous monitoring applications. New devices will mainly follow three development directions: (i) smaller sizes, (ii) more complex and intelligent processing algorithms, and (iii) wireless interconnection to other devices and to more and more complex services on the Internet. The combination of these characteristics will allow for the development of new sophisticated devices for diagnostic and monitoring applications.

AUTHOR CONTRIBUTIONS

AlQ and RN: conception of the work. BV, AnQ, and MC: literature review. BV: first draft of the manuscript. AnQ, RN, and MC: contribution to the writing of all sections. AlQ and RN: critical review of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

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SYSTEMATIC REVIEW
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Imaging the Pathophysiology of Essential Tremor—A Systematic Review

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Background: The pathophysiology underlying essential tremor (ET) still is poorly understood. Recent research suggests a pivotal role of the cerebellum in tremor genesis, and an ongoing controversy remains as to whether ET constitutes a neurodegenerative disorder. In addition, mounting evidence indicates that alterations in the gamma-aminobutyric acid neurotransmitter system are involved in ET pathophysiology. Here, we systematically review structural, functional, and metabolic neuroimaging studies and discuss current concepts of ET pathophysiology from an imaging perspective.

Methods: We conducted a PubMed and Scopus search from 1966 up to December 2020, entering essential tremor in combination with any of the following search terms and their corresponding abbreviations: positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and gamma-aminobutyric acid (GABA).

Results: Altered functional connectivity in the cerebellum and cerebello-thalamico-cortical circuitry is a prevalent finding in functional imaging studies. Reports from structural imaging studies are less consistent, and there is no clear evidence for cerebellar neurodegeneration. However, diffusion tensor imaging robustly points toward microstructural cerebellar changes. Radiotracer imaging suggests that the dopaminergic axis is largely preserved in ET. Similarly, measurements of nigral iron content and neuromelanin are unremarkable in most studies; this is in contrast to Parkinson's disease (PD). PET and MRS studies provide limited evidence for cerebellar and thalamic GABAergic dysfunction.

Conclusions: There is robust evidence indicating that the cerebellum plays a key role within a multiple oscillator tremor network which underlies tremor genesis. However, whether cerebellar dysfunction relies on a neurodegenerative process remains unclear. Dopaminergic and iron imaging do not suggest a substantial overlap of ET with PD pathophysiology. There is limited evidence for alterations of the GABAergic

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neurotransmitter system in ET. The clinical, demographical, and genetic heterogeneity of ET translates into neuroimaging and likely explains the various inconsistencies reported.

Keywords: essential tremor, pathophysiology, magnetic resonance imaging (MRI), tremor network, PET, SPECT, gamma-aminobutyric acid

INTRODUCTION

Essential tremor (ET) is among the most common movement disorders in adulthood. Its prevalence in the general population is estimated at ∼0.5% (1). ET can manifest at any age, but there is a strong association with older age, as demonstrated by a much higher prevalence (4–5%) in people aged >65 years (2). ET can manifest sporadically, but 30–70% of ET cases have a positive family history, suggesting the disease has a genetic background (3). Familial cases usually show early disease manifestation in the first two to four decades (4). The clinical hallmark of ET is a symmetric action tremor of the upper limbs (5). However, tremor may spread to other regions, such as the head, tongue, torso, jaw, and legs or can manifest as voice tremor. In some patients, signs of cerebellar impairment, such as subtle oculomotor disturbances and gait ataxia are present. Cognitive impairment and psychiatric symptoms, such as depression also can occur in ET patients (4). The term "essential tremor plus" has been coined for ET cases presenting with these additional symptoms (5). Given the heterogeneity of clinical manifestation, the variable hereditary background, and wide range of age at onset, it is likely that ET does not constitute a single disease entity, but rather a disease spectrum (4).

Despite its high prevalence, the neuronal mechanisms underpinning ET are still not fully understood. Originally, the inferior olive nucleus (ION) had been considered the central oscillator of tremor genesis in ET (6); however, this hypothesis has since been disputed, and a multiple oscillator tremor network comprising the ION, brainstem, cerebellum, thalamus, and motor cortical areas has been indicated in tremor genesis (7). Moreover, a series of histopathological studies reporting a loss and morphological alterations of cerebellar Purkinje cells gave rise to the hypothesis that cerebellar neurodegeneration may be the primary cause of ET (8–10). However, this concept has been challenged by others (11, 12). In addition, there is mounting evidence that alterations in the integrity of the inhibitory gamma-aminobutyric acid (GABA) neurotransmitter system is a contributory factor in ET pathophysiology (13). Lastly, particularly in the early course of the disease, clinical differentiation of ET from Parkinson's disease (PD) can be challenging, and some authors have suggested common pathophysiological features of the two diseases (14).

In recent decades, a substantial number of imaging techniques have emerged that enable the assessment of structural, functional, and metabolic alterations of the ET brain in a non-invasive and easily accessible way, resulting in a large body of literature. Whereas some findings corroborate with current concepts of ET pathophysiology (15–17), others do not (18, 19). More recently, novel techniques have been established to assess distinct neurotransmitter systems and their role in tremor genesis *in vivo*. Furthermore, studies exploring the dopaminergic system and cerebral iron depositions have tried to establish a connection between ET and progressive neurodegeneration, particularly with PD, providing equivocal findings (14). Here, we systematically review the advances in structural, functional, and metabolic imaging and discuss pathophysiological concepts underlying ET based on evidence from neuroimaging.

METHODS

We conducted a PubMed and Scopus search, including publications from 1966 up to December 2020, entering "essential tremor" in combination ("AND") with any of the following terms and their corresponding abbreviations: positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), gamma-aminobutyric, and γ-aminobutyric acid (GABA). In addition, we browsed the reference lists of original and review articles retrieved in this primary search. We only considered articles that were (1) written in English, (2) included >5 ET subjects, (3) directly compared ET subjects with a healthy control (HC) cohort, (4) were performed on human subjects, and (5) provided quantitative or semiquantitative data analyses. We did not consider case reports, case series, or research papers that primarily focused on therapeutic interventions, such as thalamotomy, MRI-guided focused ultrasound, or deep brain stimulation (DBS). If ET patients were additionally compared with other disease groups (e.g., dystonic tremor), we solely considered comparisons with HC. We followed the PRISMA guidelines for systematic reviews (20).

We sought to address the following questions: (1) does evidence from neuroimaging support the hypothesis of cerebellar neurodegeneration in ET? (2) Do findings from neuroimaging corroborate with the postulated concept of a tremor network? (3) Is there support from neuroimaging for alterations of the GABAergic system in ET? (4) Is there evidence from neuroimaging for striatal dopaminergic degradation and nigral iron accumulation in ET as typically observed in PD?

RESULTS

Our search revealed 1,135 hits. References retrieved were imported into a reference manager (Endnote X8), and duplicates were removed. FH screened all titles and abstracts for eligibility. A total of 86 papers met our inclusion criteria. Fifteen additional abstracts were identified by browsing the reference lists of papers retrieved in the database search. The senior author (JS) cross-checked papers selected for qualitative data synthesis for

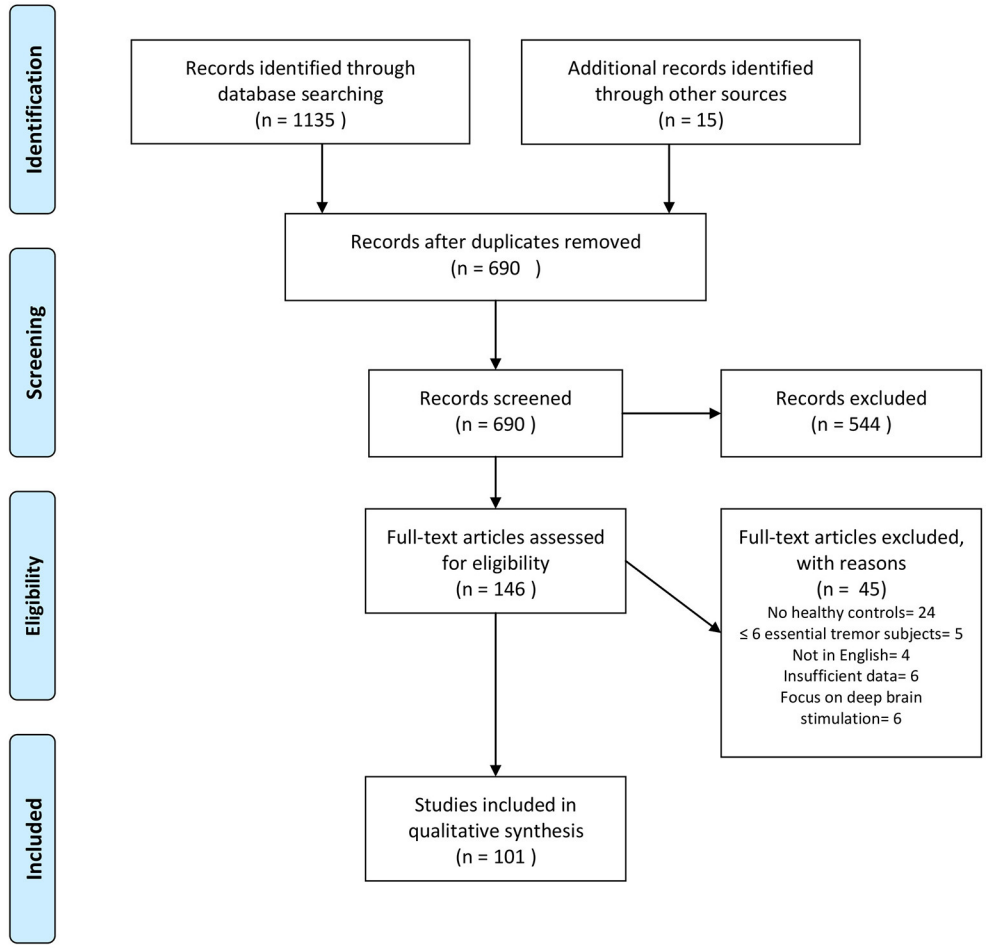

FIGURE 1 | Flowchart depicting the study selection process. Search was performed in PubMed and Scopus up to December 2020. Modified from Moher et al. (20).

eligibility. A flowchart of the selection process is presented in **Figure 1**. Thirty-one studies were assigned to volumetric MRI, 19 to diffusion tensor imaging (DTI), 26 to functional MRI (fMRI), six to MRS, six to imaging of brain iron, three to GABAergic imaging, 17 to dopaminergic imaging, seven to perfusion imaging (PET or SPECT), and five to metabolic radiotracer imaging. Some studies applied more than one modality and were assigned to different categories accordingly. A summary of all studies included is presented in **Table 1** (MRI and GABAergic imaging) and **Table 2** (radiotracer imaging).

Structural Magnetic Resonance Imaging

A number of imaging techniques have been applied to visualize the brain morphology of ET patients *in vivo*.

Volumetric Imaging

Voxel-based morphometry (VBM) allows for a voxel-based automated and rater-independent analysis of brain volumes between groups, either in specified regions-of-interest (ROI) or at a whole-brain level without *a priori* hypotheses (117). Alternatively, automated segmentation methods can be applied to quantitatively measure brain volumes, e.g., the cortical thickness, using freely available software, such as FreeSurfer (118).

Cerebellar atrophy is commonly reported in ET patients (15, 22, 26, 28–32, 36, 37, 43, 46, 48). However, an equivocal number of studies found no morphological cerebellar changes (18, 21, 25, 33–35, 38–42, 49), and even increased cerebellar gray matter volume in young ET subjects has been reported (27, 45). Findings of cerebral cortical and subcortical structural changes are even more heterogeneous. There is no consistent pattern of atrophy. Moreover, alongside volume loss, gray matter volume gain has been observed in various cortical regions, and some studies did not identify any cortical differences between ET patients and HC (15, 22, 23, 26, 33–36, 38, 41, 44, 45, 47). Of note, the clinical phenotype of ET is associated with distinct morphological brain changes. For example, ET patients presenting with additional head tremor display more pronounced or distinct patterns of cerebellar atrophy, as well as various cortical structural changes compared with classic ET (25, 26, 28, 30, 31, 46). Indeed, some of the studies reporting cerebellar atrophy found significant volume loss only in ET individuals exhibiting additional head or voice

TABLE 1 | Summary of MRI and GABAergic imaging studies.

References	Subjects (f)	Age (mean ± SD)	Main findings
Volumetric MRI			
Archer et al. (21)	ET 19 (12) HC 18 (10)	65.74 ± 11.56 63.66 ± 7.58	No difference
Bagepally et al. (22)	ET 20 (5) HC 17 (3)	38.2 ± 16.5 40.7 ± 16.5	GM of CER, frontal, occipital, L temporal, and R parietal regions ↓
Benito-Leon et al. (15)	ET 19 (10) HC 20 (10)	69.8 ± 9.4 68.9 ± 10.0	WM of R CER, L medulla, R parietal lobe, and R limbic lobe; and GM of bilateral CER, bilateral parietal lobes, R frontal lobe, and R insula ↓ No difference between hET and clET
Benito-Leon et al. (23)	13 (7) 17 (7)	67.8 ± 7.3 64.1 ± 11.9	GM (cortical thickness or volume) of both thalami, L PMC/SC, L temporal lobe, L occipital, L cingulate, bilateral entorhinal and ventral areas ↓ CER not assessed
Bhalsing et al. (24)	ET 25 (6) HC 25 (6)	45.0 ± 10.7 45.4 ± 10.7	GM of CER, R medial frontal gyrus in cognitively impaired ET patients ↓ GM of bilateral medial frontal gyrus, R SC, anterior cingulate and insula ↓ in cognitively impaired compared with cognitively intact ET group
Buijink et al. (25)	ET 36 (13) HC 30 (11)	56 ± 14 54 ± 15	No difference GM in bilateral PMC and SC, and L superior medial gyrus ↑ in hET compared with clET
Cameron et al. (26)	ET 47 (23) HC 36 (26)	76.0 ± 6.8 73.3 ± 6.5	GM of CER, posterior insula, superior temporal gyri, cingulate cortex, inferior frontal gyri, and parieto-occipital regions ↓ Pronounced atrophy in the hET subgroup
Cao et al. (27)	ET 17 (9) HC 17 (10)	39.65 ± 8.12 42.24 ± 9.47	GM of bilateral CER, occipital fusiform cortices, R inferior temporal gyrus, PMC, thalamus, midbrain, precuneus ↑ GM of L parietal lobe ↓
Cerasa et al. (28)	clET 27 (10) hET 19 (13) HC 28 (14)	65 ± 12.8 70.7 ± 7.8 66.5 ± 7.8	GM and WM of CER ↓ in hET only
Cerasa et al. (29)	ET 14 (6) HC 23 (10)	66.3 ± 9.1 64.4 ± 7.1	GM of CER in anterior lobe ↓ No difference in cerebral cortical thickness
Choi et al. (30)	ET 45 (13) HC 45 (13)	65.9 ± 6.8 67.6 ± 7.4	CER GM and WM ↓ in hET only
Daniels et al. (18)	ET 27 (9) HC 27 (9)	57.9 ± 12.2 n.a.[b]	No difference
Dyke et al. (31)	ET 47 (23) HC 36 (26)	76.0 ± 6.8 73.2 ± 6.7	GM of CER ↓ in hET and ET with voice tremor only
Espay et al. (32)	ET 16 (5)[a] HC 25 (21)	61.7 ± 9.3 48.6 ± 11.4	GM of L CER, and occipital cortex ↓ GM of R amygdala ↑
Fang et al. (33)	ET 20 (8) HC 20 (8)	50.3 ± 14.2 50.3 ± 14.2	No difference
Fang et al. (34)	ET 35 (13) HC 35 (13)	46.86 ± 11.3 44.46 ± 11.7	No difference
Fang et al. (35)	ET 26 (7) HC 26 (7)	47.3 ± 11.3 43.4 ± 14.4	No difference
Galazzo et al. (36)	ET 10 (4) HC 10 (5)	69.4 ± 8.9 67.7 ± 7.8	GM of CER and R occipital cortex ↓
Gallea et al. (37)	ET 19 (7) HC 19 (7)	50.4 ± 15.0 50.1 ± 16.4	GM of CER ↓ GM of SMA ↑
Klein et al. (38)	ET 14 (5) HC 20 (n.a.)	61.2 ± 12.0 60.2 ± 8.1	No difference
Lin et al. (39)	ET 10 (5) HC 13 (4)	63.4 ± 8.71 65.31 ± 11.09	GM of caudate, L temporal cortex, insular cortex, L precuneus, superior temporal gyrus ↓ No difference in cerebellar volume
Nicoletti et al. (40)	ET 32 (15) HC 12 (8)	69.7 ± 9.7 67.4 ± 4.8	No difference
Novellino et al. (49)	ET 60 (32) HC 50 (25)	67.11 ± 7.84 67.58 ± 6.14	No difference in CER, thalamus, hippocampus, frontal lobe
Pelzer et al. (41)	ET 19 (9) HC 23 (8)	49.47 ± 3.51 50.93 ± 3.33	GM precuneus ↑ No difference in cerebellar volume

(Continued)

TABLE 1 | Continued

References	Subjects (f)	Age (mean ± SD)	Main findings
Pietracupa et al. (42)	ET 19 (9) HC 15 (8)	67.00 ± 17.80 63.00 ± 9.00	Thalamic volume ↑ No difference in cerebral cortical thickness or cerebellar volume
Prasad et al. (43)	ET 40 (13) HC 37 (10)	44.95 ± 12.46 46.45 ± 9.93	Cerebellar GM and volume of MCP/ICP ↓, pronounced atrophy in ET with clinical cerebellar signs No difference in WM in CER
Prasad et al. (44)	ET 40 (12) HC 40 (10)	44.95 ± 12.46 46.30 ± 9.39	GM in bilateral thalamus, hippocampus, midbrain ↓ GM in R caudate nucleus, pallidum, amygdala, bilateral putamen, nucleus accumbens ↑ CER not assessed No difference between familial vs. sporadic or between clET and rET
Qi et al. (45)	ET 27 (13) HC 27 (12)	39.65 ± 8.12 42.24 ± 9.47	GM of bilateral CER, L temporal occipital fusiform gyrus, precentral lobe, R occipital fusiform gyrus, R inferior temporal gyrus, L thalamus, midbrain, medulla, bilateral precuneus ↑ GM of L parietal lobe, pons, L insula ↓
Quattrone et al. (46)	clET 30 (12) hET 20 (14) HC 32 (16)	61.5 ± 16.5 70.6 ± 7.6[c] 66.2 ± 8.1	GM of cerebellar anterior lobe, vermis, paravermal ↓ in hET only No difference between hET and clET
Serrano et al. (47)	ET 18 (8) HC 18 (9)	63.7 ± 10.5 63.3 ± 12.0	GM (cortical thickness or volume) in precentral, temporal, orbitofrontal, (para)hippocampal, entorhinal, posterior cingulate, and supramarginal regions ↓ CER not assessed
Shin et al. (48)	ET 39 (16) HC 36 (17)	63.7 ± 13.0 65.3 ± 6.8	GM cerebellar vermis ↓, more pronounced in clET
Diffusion tensor imaging			
Archer et al. (21)	ET 19 (12) HC 18 (10)	65.74 ± 11.56 63.66 ± 7.58	No difference in FA, MD not assessed
Bhalsing et al. (50)	ciET 33 (m:f 1:2.8) clET 22 (m:f 1:2.5) HC 55 (m:f 1:2.5)	47.03 ± 10.4 43.4 ± 13.4 46 ± 11	No difference in MD or FA between clET and HC MD in R cingulum and L precuneus ↑ in ciET No difference between clET and ciET
Caligiuri et al. (51)	clET 25 (14) rET 22 (11) HC 25 (11)	64.7 ± 10.9 63.7 ± 13.5 65.1 ± 6.7	Structural connectivity of thalamo-cerebello and thalamo-cortical tracts ↓ in rET and clET Structural connectivity in basal ganglia–cortical tracts ↓ in rET only
Gallea et al. (37)	ET 19 (7) HC 19 (7)	50.4 ± 15.0 50.1 ± 16.4	FA in CST ↑, no difference in tremor network-related connections
Jia et al. (52)	ET 15 (5) HC 15 (n.a.)	65.07 ± 11.41 62.07 ± 7.60	MD in red nuclei ↑, no difference in FA CER not assessed
Klein et al. (38)	ET 14 (5) HC 20 (n.a.)	61.2 ± 12.0 60.2 ± 8.1	MD in bilateral fronto-parietal and L temporo-occipital WM, and ICP ↑ FA in R ICP ↓
Martinelli et al. (19)	ET 10 (8) HC 10 (n.a.)	66 ± 11 60 ± 8	No difference in MD, FA not measured
Nestrasil et al. (53)	ET 12 (4) HC 10 (4)	45.5 ± 17.5 46.6 ± 14.8	MD in forceps minor and major, R CST, R inferior fronto-occipital fasciculi, R superior longitudinal fasciclus, R inferior longitudinal fasciculus, bilateral uncinate fasciculi, cingulum bundles, bilateral anterior thalamic radiation ↑ No FA assessment
Nicoletti et al. (54)	ET 25 (13) HC 15 (8)	62.9 ± 69.5 62.47 ± 5.4	FA in DN and SCP ↓ MD in SCP ↑
Novellino et al. (55)	ET 67 (29) HC 39 (18)	65.64 ± 10.48 64.56 ± 9.4	MD of GM in CER ↑ in ET and rET, but no difference between clET only and HC
Novellino et al. (49)	ET 60 (32) HC 50 (25)	67.11 ± 7.84 67.58 ± 6.14	MD in bilateral hippocampus, and cerebellar GM ↑
Pak et al. (56)	ET 40 (28) HC 40 (20)	44.23 ± 18.91 37.45 ± 10.95	FA in inferior longitudinal fasciculus, corpus callosum ↓ MD in inferior/superior longitudinal fasciculus, genu and corpus callosum ↑ CER not assessed
Pelzer et al. (41)	ET 19 (9) HC 23 (8)	49.47 ± 3.51 50.93 ± 3.33	MD in widespread WM including tremor network correlated with clinical tremor severity Positive correlation of callosal FA with verbal fluency test
Pietracupa et al. (42)	ET 19 (9) HC 15 (8)	67.00 ± 17.80 63.00 ± 9.00	FA ↓ and MD ↑ in multiple motor and non-motor tracts including MCP, SCP, CST, anterior thalamic radiation, longitudinal fasciculus, and inferior fronto-occipital fasciculus

(Continued)

TABLE 1 | Continued

References	Subjects (f)	Age (mean ± SD)	Main findings
Prasad et al. (57)	ET 40 (12) HC 40 (10)	44.95 ± 12.46 46.30 ± 9.39	FA in corpus callosum and CST in rET ↓ MD in CER ↑ in overall ET cohort and rET No differences of FA or MD between rET and clET
Revuelta et al. (58)	ET 18 (8) HC 10 (7)	71.1 ± 8.8 69.4 ± 9.0	MD in Vim-PMC, Vim-SMA, Vim-pre-SMA tract ↓ No difference in FA CER not assessed
Saini et al. (59)	ET 22 (5)[d] HC 17 (3)	38.2 ± 16.5 40.7 ± 16.5	Tract-based spatial statistics whole brain: no difference in FA; MD in R internal and external capsule, and R parietal WM ↑ No difference in CER ROI based: FA in L SCP and R CST ↓ MD in right internal capsule, and left CST ↑
Shin et al. (60)	ET 10 (5) HC 8 (5)	52.8 ± 11.5 51.3 ± 11.1	FA of WM in R pons, bilateral cerebellum, L retrorubral area of the midbrain, orbitofrontal, lateral frontal, parietal, and temporal WM ↓
Tikoo et al. (61)	ET 25 (11) HC 26 (17)	68.4 ± 9.7 63.2 ± 10.3	FA ↓ and MD ↑ in cerebellar peduncles
Functional MRI (task-based)			
Archer et al. (21)	ET 19 (12) HC 18 (10)	65.74 ± 11.56 63.66 ± 7.58	Complex changes of activity in the tremor and visual networks during a motor task that could be modulated by increased visual feedback
Broersma et al. (62)	ET 21 (9) HC 21 (7)	51.6 ± 17.8 50.6 ± 16.4	Tremor-associated activity in L/R cerebellum, and brainstem ↑ compared with mimicked tremor in HC
Bucher et al. (16)	ET 12 (4) HC 15 (7)	61.1 ± 11.9 58.2 ± 9.8	Bilateral activation of the cerebellar hemispheres, DN, and red nuclei, and unilateral activation of the contralateral PMC/SC, thalamus, and globus pallidus in ET during involuntary tremor Higher activation of cerebellar hemispheres and red nuclei during involuntary tremor in ET compared with mimicked tremor in HC
Buijink et al. (63)	ET 31 (10) HC 29 (9)	55.4 ± 15.8 52.6 ± 16.1	Activity in CER, parietal and frontal cortex, DN and ION ↓ during motor task
Buijink et al. (64)	ET 22 (10) HC 21 (7)	59.5 ± n.a. 56.5 ± n.a.	Cerebello-motor cortical FC ↓ during motor task
Cerasa et al. (65)	ET 12 (6) HC 12 (6)	62.2 ± 12.4 59.8 ± 10.7	Activity in dorsolateral prefrontal cortex and in the inferior parietal cortex ↑ during cognitive task
Espay et al. (32)	ET 16 (5)[a] HC 25 (21)	61.7 ± 9.3 48.6 ± 11.4	No difference during emotion processing and finger tapping task
Galazzo et al. (36)	ET 10 (4) HC 10 (5)	69.4 ± 8.9 67.7 ± 7.8	Activity in CER, sensory-motor cortex, and basal ganglia ↓ during motor task
Muthuraman et al. (66)	ET 34 (9) HC 34 (9)	58.9 ± 9 58 ± 9	Activity in CER associated with involuntary tremor mapped to motor cortex in ET, whereas it mapped to premotor cortex during mimicked tremor in HC Different topography of cerebellar activity sources in ET compared with HC
Neely et al. (67)	ET 14 (8) HC 14 (9)	61.7 ± 11.0 60.2 ± 9.2	Cerebello-cortical FC ↓ Cortico-cortical FC (PMC, SMA, premotor cortex) ↑ during motor task
Nicoletti et al. (40)	ET 32 (15) HC 12 (8)	69.7 ± 9.7 67.4 ± 4.8	Activity in CER and other nodes of the tremor network ↓ during motor task Activity in PMC and SC, precuneus and superior parietal gyrus ↑ during motor task Activity in widespread cortical regions, CER and internal globus pallidus ↑ during motor task in rET compared with clET
Passamonti et al. (68)	ET 15 (n.a.) HC 15 (n.a.)	61.6 ± 9.3 60.4 ± 7.3	FC between CER and various cortical regions implicated in focusing attention and with the DMN ↓ during cognitive task
Functional MRI (resting state)			
Benito-Leon et al. (69)	ET 23 (12) HC 23 (13)	63.3 ± 13.4 60.6 ± 13.2	FC in CER and visual network ↓ FC in DMN ↑
Benito-Leon et al. (70)	ET 23 (12) HC 23 (13)	63.3 ± 13.4 61.1 ± 13.1	Graph theory-based study showing complex alterations of various parameters inside and outside the tremor network in ET subjects
Fang et al. (33)	ET 20 (8) HC 20 (8)	50.3 ± 14.2 50.3 ± 14.2	Regional homogeneity in cerebellar lobes, bilateral thalamus, and the insular lobe ↓ Regional homogeneity in bilateral prefrontal and parietal cortices, L PMC, and L SMA ↑
Fang et al. (34)	ET 35 (13) HC 35 (13)	46.86 ± 11.3 44.46 ± 11.7	FC in sensorimotor network, salience network, and between anterior and posterior DMN ↑ FC in CER, and between CER and DMN and sensorimotor networks ↓
Fang et al. (35)	ET 26 (7) HC 26 (7)	47.3 ± 11.3 43.4 ± 14.4	Thalamus related FC in cerebello-thalamo-cortical network ↓ Thalamus related FC in primary and supplemental motor cortical areas ↑

(Continued)

TABLE 1 | Continued

References	Subjects (f)	Age (mean ± SD)	Main findings
Gallea et al. (37)	ET 19 (7) HC 19 (7)	50.4 ± 15.0 50.1 ± 16.4	FC between cerebellar hemispheres and ipsilateral DN, and between SMA and ipsilateral PMC ↓
Lenka et al. (71)	ET 30 (11) HC 30 (10)	45.4 ± 13.7 43.4 ± 9.2	FC of PMC and SC with R CER ↓ FC of bilateral thalamus with posterior CER ↑
Li et al. (72)	rET 20 (7) HC 27 (12)	48.32 ± 13.16 49.12 ± 11.81	Regional homogeneity in CER, putamen, and DMN ↓
Li et al. (73)	rET 19 (13) clET 31 (21) HC 25 (17)	46.58 ± 14.04 46.29 ± 14.30 49.88 ± 12.56	Activity in basal ganglia, inferior orbitofrontal gyrus, and insula ↓, activity in R CER ↑ in overall ET cohort In subgroup analysis, only clET patients showed ↑ activity in the CER Distinct differences of activity in various cortical regions and basal ganglia between rET and clET compared with HC
Mueller et al. (74)	ET 19 (4) HC 23 (n.a.)	55.5 ± 19.2 50.9 ± 18.0	Connectivity (eigenvector centrality) in cerebellar hemispheres ↓ Connectivity in the anterior cingulate and in the PMC bilaterally ↑
Nicoletti et al. (75)	ET 23 (10) HC 23 (12)	71.6 ± 10.5 70.3 ± 5.3	Complex alterations of (sensorimotor) cortico-cortical FC showing both ↓ and ↑ Cortico-cerebello FC ↓ Thalamico-cerebellar FC ↑
Tikoo et al. (61)	ET 25 (11) HC 26 (17)	68.4 ± 9.7 63.2 ± 10.3	FC of DN with L CER cortex, L caudate, L thalamus, L PMC and SC, bilateral frontal, and parietal cortices ↓
Wang et al. (76)	hET 20 (7) clET 27 (11) HC 27 (12)	51.00 ± 12.10 45.00 ± 14.43 45.00 ± 4.43	Activity in CER, bilateral caudate, R middle temporal gyrus, and L inferior parietal lobule ↑ in hET compared with HC Activity in R putamen, L precentral gyrus, and L SC ↓ in hET compared with HC Activity in thalamus, R middle temporal gyrus, R middle frontal gyrus, and R inferior parietal lobule ↑ in clET compared with HC Activity in thalamus, R middle temporal gyrus, R middle frontal gyrus, and R inferior parietal lobule ↓ in clET compared with HC
Yin et al. (77)	ET 24 (12)[e] HC 23 (12)	46.4 ± 14.2 47.2 ± 12.8	Activity in cortical regions, mainly related to motor function (e.g., pre- and postcentral gyrus, SMA) ↑ Activity in CER ↓
Magnetic resonance spectroscopy			
Barbagallo et al. (78)	rET 12 (6) HC 10 (2)	69.9 ± 8.3 64.1 ± 8.3	No difference in thalamic NAA/Cr or Cho/Cr ratios
Barbagallo et al. (79)	ET 16 (3) HC 14 (4)	65.5 ± 11.1 60.8 ± 10.2	No difference in thalamic NAA/Cr or Cho/Cr ratio Thalamic Glx and Glx/Cr ratio ↑
Kendi et al. (80)	ET 14 (8) HC 9 (n.a.)	38.64 ± 12.8 35.4 ± 11.7	No difference in thalamic NAA/Cr and Cho/Cr ratios
Louis et al. (81)	ET 16 (9) HC 11 (5)	66 ± 18 60 ± 24	Cerebellar NAA/Cr ratio ↓
Louis et al. (82)	ET 20 (10) HC 11 (4)	62.2 ± 19.4 59.6 ± 23.0	No difference in cerebellar NAA/Cr ratio NAA/Cr asymmetry index between R/L cerebellar hemispheres ↓
Pagan et al. (83)	ET 10 (n.a.) HC 10 (n.a.)	59.4 ± 18.7 57.2 ± 17.0	Cerebellar NAA/Cr and Cho/Cr ratios ↓
Imaging of brain iron			
Cheng et al. (84)	ET 9 (n.a.) HC 166 (104)	63.8 ± 8.6[f] 63.6 ± 6.1	No difference in nigral susceptibility-weighted imaging or nigrosome-1 integrity between ET and HC
Homayoon et al. (85)	ET 25 (10) HC 25 (12)	65.80 ± 12.82 64.60 ± 11	No difference in nigral R2* relaxation times between ET and HC
Jin et al. (86)	ET 25 (15) HC 34 (21)	61.12 ± 11.16 63.53 ± 7.81	No difference in nigral neuromelanin concentration or nigrosome-1 integrity between ET and HC
Novellino et al. (87)	ET 24 (10) HC 25 (12)	64.29 ± 10.02 64.16 ± 9.26	Higher T2* relaxation times of bilateral globus pallidus internus, substantia nigra, and R DN Only pallidal findings survived correction for multiple comparisons
Reimao et al. (88)	ET 15 (8) HC 10 (4)	70.5 ± 12.5[a] 61.2 ± 67.3	No difference in nigral neuromelanin in ET compared with HC
Wang et al. (89)	ET 18 (7) HC 21 (11)	62.56 ± 9.31 63.52 ± 8.34	No difference in nigral neuromelanin in ET compared with HC
Imaging of the GABAergic system			
Boecker et al. (90)	ET 8 (4) HC 11 (6)	65.5 ± 8.0 56.6 ± 4.3	^{11}C-flumazenil binding in CER, thalamus, and lateral premotor cortex ↑

(Continued)

TABLE 1 | Continued

References	Subjects (f)	Age (mean ± SD)	Main findings
Louis et al. (91)	ET 45 (19) HC 35 (25)[a]	74.98 ± 6.16 73.26 ± 6.06	No difference in DN GABA concentration between ET and HC Higher values in R compared with L DN in ET cohort, but no correlation with tremor scores
Tapper et al. (92)	ET 10 (3) HC 6 (1)	60.2 ± 9.7 62.2 ± 11.4	No difference in thalamic or CER GABA or Glx concentrations between ET and HC Positive correlation of GABA/Glx ratio with tremor severity

ET, essential tremor; clET, classical ET; hET, ET subjects presenting with head tremor; rET, ET subjects presenting with resting tremor; HC, healthy controls; ↓, lower compared with HC; ↑, higher compared with HC; R, right; L, left; GM, gray matter; WM, white matter; CER, cerebellum; CST, corticospinal tract; DN, dentate nucleus; ICP, inferior cerebellar peduncle; MCP, middle cerebellar peduncle; PMC, primary motor cortex; SC, sensory cortex; SMA, supplementary motor area; SCP, superior cerebellar peduncle; Cr, creatine; Cho, choline; FA, fractional anisotropy; FC, functional connectivity; GABA, gamma amino-butyric acid; Glx, glutamate/glutamine; MD, mean diffusivity; NAA, N-acetylaspartate; n.a., not available.

[a] *Groups not matched for gender and/or age.*

[b] *Age-matched, but no mean age for the cohort provided.*

[c] *hET significantly older than clET.*

[d] *Two ET subjects excluded from the final analyses because of extensive white matter lesions.*

[e] *Two subjects excluded due to excessive head motion.*

[f] *ET subjects were a subgroup of a larger cohort including atypical parkinsonian patients; no demographical data are provided for the ET group separately, but statistical analyses were performed for the ET subgroup.*

tremor (28, 30, 31, 46). Moreover, cognitive dysfunction in ET has been linked to specific cortical atrophy patterns not apparent in cognitively intact ET individuals (24). The heterogeneity of structural brain alterations reported in ET has been highlighted in a recent meta-analysis including 16 VBM studies and more than 350 ET individuals (119). The latter study did not identify any brain regions, including the cerebellum, that exhibited consistent gray matter volume loss in ET patients compared with HC (119).

Diffusion Tensor Imaging

DTI is utilized for the assessment of the brain's microstructural integrity and is particularly sensitive to alterations in cerebral white matter. DTI measures the random movement of water molecules, which is mainly directed along white matter fiber tracts (120). Two important measures are the mean diffusivity (MD) and the fractional anisotropy (FA). The MD depicts the average movement of water molecules in organic tissue, whereas the FA refers to the directionality of movement. FA values close to 1 reflect anisotropy, whereas values nearing 0 are isotropic and are suggestive of tissue damage. Conversely, high MD values are a surrogate for a loss of cellular integrity and indicative of neuronal damage (121).

Compared with conventional MRI, DTI studies more consistently point toward microstructural alterations of the cerebellum, particularly of the cerebellar peduncles and dentate nuclei (38, 49, 54, 55, 57, 59–61). In contrast to these 11 studies, only two studies, both employing an ROI-based approach, did not find any differences in DTI between ET patients and HC (19, 21). Beyond cerebellar changes, widespread microstructural alterations have been reported in various cerebral white matter tracts related to both motor and non-motor function and in the red nuclei (37, 38, 52, 53, 56, 59). For example, in a recent study by Revuelta et al., the authors reported decreased MD of fiber tracts connecting the ventral intermediate nucleus of the thalamus (Vim), the typical target for DBS in ET, with motor and supplementary motor cortical regions (58). Even though no alterations of FA were observed in the same tracts, both MD and FA in the Vim supplementary motor area tract correlated with tremor severity, suggesting a pathological reinforcement of this tract in ET (58). Similar to VBM studies, phenotype-specific changes of FA and MD have been reported. Specifically, ET patients presenting with additional resting tremor, but unremarkable dopamine transporter imaging, showed reduced structural connectivity in a network comprised of the globus pallidus, caudate nucleus, and supplemental motor area that was not apparent in ET patients without resting tremor (51). Moreover, distinct cortical microstructural changes, including the hippocampi, have been linked to cognitive dysfunction (41, 49, 50).

Functional and Metabolic Magnetic Resonance Imaging

The initial model of ET tremor genesis proposed that rhythmic discharges originating in the ION propagate tremor in ET (6). However, based on current research, it seems more likely that tremor genesis is not governed by a single oscillator, but is rather driven by a number of oscillators within a tremor network comprising the ION, cerebellum, thalamus, motor cortical regions, and the brainstem (7). This hypothesis is supported by evidence from neurophysiological studies confirming abnormal oscillatory activity within the tremor network in ET (122).

Functional Magnetic Resonance Imaging

fMRI measures the blood oxygen level-dependent (BOLD) contrast—generally called "the BOLD signal" (123). The BOLD signal is affected by hemodynamic, vascular, and metabolic factors, but is generally assumed to be closely related to neural activity (123, 124). The first task-based fMRI study in ET patients identified increased activity in the contralateral sensory and motor cortices, thalamus, and globus pallidus and bilateral overactivation of the cerebellar hemispheres and dentate nuclei during arm posturing. In contrast, the authors observed increased activity in the ION in only two out of 12 patients, supporting a pivotal role of the cerebellum in tremor genesis and refuting the single oscillator ION hypothesis (16). Subsequently, numerous task-based fMRI studies have confirmed that altered cerebellar and cerebello-thalamico-cortical activity is correlated

TABLE 2 | Summary of radiotracer studies.

References	Subjects (f)	Age (mean ± SD)	Main findings
Dopaminergic imaging			
Asenbaum et al. (93)	ET 32 (19) HC 30 (20)	45 ± n.a.[a] 63 ± n.a.	DaTScan Normal striatal uptake
Barbagallo et al. (78)	rET 12 (6) HC 10 (2)	69.9 ± 8.3 64.1 ± 8.3	DaTScan Normal striatal uptake
Benamer et al. (94)	ET 27 (9) HC 35 (20)	64.1 ± 8.8 61.1 ± 8.7	DaTScan Normal striatal uptake
Breit et al. (95)	ET 6 (4) HC 10 (5)	60 ± 5 58 ± 5	^{11}Cd-threo-methylphenidate PET Normal striatal uptake
Caligiuri et al. (51)	clET 25 (14) rET 22 (11) HC 25 (11)	64.7 ± 10.9 63.7 ± 13.5 65.1 ± 6.7	DaTScan Normal striatal uptake in clET and rET
Di Giuda et al. (96)	ET 15 (9) HC 17 (10)	52.5 ± 19.5 55.3 ± 13.7	DaTScan Normal striatal uptake
Fang et al. (97)	ET 33 (23) HC 28 (10)	72.1 ± 10.0 52.3 ± 15.7	[^{99m}Tc]-TRODAT SPECT Striatal uptake ↓
Gerasimu et al. (98)	ET 28 (18) HC 28 (16)	64 ± 15 63 ± 11	DaTScan Putamenal uptake ↓ No longitudinal change in 9/10 ET subjects with available follow-up scan
Isaias et al. (99)	ET 32 (10) HC 31 (18)	70 ± 7 64 ± 10	DaTScan Striatal uptake ↓
Isaias et al. (100)	ET 20 (8) HC 23 (13)	70.4 ± 9 70.5 ± 9	DaTScan Normal striatal uptake with a trend toward reductions in caudate nucleus No change over 3 years of follow-up
Lee et al. (101)	clET 9 (5) rET 6 (2) HC 21 (n.a.)	60.0 ± 11.4 68.3 ± 10.29 61.8 ± 9.7	DaTScan Normal striatal uptake in clET, ↓ in rET
Nistico et al. (102)	clET 14 (7) rET 14 (6) HC 16 (8)	68.29 ± 9.15 68.29 ± 9.15 66.37 ± 2.39	DaTScan Normal striatal uptake in clET and rET
Nistico et al. (103)	rET 10 (4) HC 20 (10)	60.60 ± 12.80 66.71 ± 4.02	DaTScan Normal striatal uptake
Novellino et al. (104)	ET 10 (6) HC 18 (9)	68.5 ± 5.13 64.06 ± 4.84	DaTScan Normal striatal uptake
Sun et al. (105)	ET 8 (n.a.) HC 11 (n.a.)	n.a.[c] n.a.[c]	^{11}C-CFT PET Normal striatal uptake
Waln et al. (106)	pET 9 (4) clET 22 (8) HC 13 (6)	67 ± 7.2 60.7 ± 8.5 63.2 ± 10.1	DaTScan Trend toward reduced striatal uptake predominantly in the caudate nucleus in both clET and ET-P
Wang et al. (107)	ET 12 (4) HC 10 (3)	52.1 ± 14.1 52.5 ± 10.7	[^{99m}Tc]-TRODAT SPECT Normal striatal uptake
Perfusion imaging			
Boecker et al. (108)	ET 6 (4) HC 6 (n.a.)	54 ± 13.8 45 ± 18.3	$H_2^{15}O$ PET rCBF in bilateral CER ↑, increase diminished after intake of ethanol and was accompanied by increased rCBF of the ION
Jenkins et al. (109)	ET 11 (5) HC 8 (4)	63.8 ± n.a. 57.1 ± n.a.	$C^{15}O_2$ PET rCBF of bilateral CER ↑ during rest, further ↑ during involuntary tremor with additional rCBF increases of the contralateral thalamus, striatum, and PMC/SC
Wills et al. (17)	ET 7 (3) HC 6 (n.a.)	49.4 ± n.a. 51.1 ± n.a.	$C^{15}O_2$ PET rCBF of CER and thalamus ↑ during rest, further increase during involuntary tremor with additional increase in the red nuclei No increase in rCBF in the ION
Wills et al. (110)	ET 7 (3) HC 6 (n.a.)	49.4 ± n.a. 51.1 ± n.a.	$C^{15}O_2$ PET rCBF in CER, midbrain, and thalamus ↑ during involuntary tremor
Sahin et al. (111)	ET 16 (9) HC 16 (9)	29.6 ± 10 28.0 ± 7.1	Technetium-99m HMPAO SPECT No difference in rCBF, inverse correlation of frontal cortical rCBF with cognitive function

(Continued)

TABLE 2 | Continued

References	Subjects (f)	Age (mean ± SD)	Main findings
Song et al. (112)	ET 16 (7) HC 33 (23)	68.44 ± 13.73 66.94 ± 5.40	Technetium-99m HMPAO SPECT rCBF in posterior CER, frontal gyrus, cingulate, insula ↓
Song et al. (113)	clET 13 (8) hET 10 (6) HC 33 (23)	63.54 ± 20.22 65.60 ± 8.96 66.94 ± 5.40	Technetium-99m HMPAO SPECT rCBF in posterior CER, frontal gyrus, cingulate, insula ↓ No difference between clET and hET
Metabolic imaging			
Hallett and Dubisnky (114)	ET 8 (3) HC 10 (2)	50 ± n.a. 40 ± n.a.	FDG PET rMRG of medulla oblongata and thalamus ↑ No difference in CER
Ha et al. (115)	ET 17 (0) HC 23 (n.a.)	67.29 ± 4.79 65.35 ± 6.11	FDG PET rMRG of medial frontal lobe, medial temporal lobe, and precuneus ↓ No difference in CER
Song et al. (116)	trET 8 (0) nrET 9 (0) HC 11 (0)	65.9 ± 0.7 68.6 ± 6.4 67.2 ± 1.5	FDG PET rMRG of CER, frontal, temporal, and occipital lobes, and right precuneus ↓ rMRG of right basal ganglia ↓ in trET compared with nrET
Sun et al. (105)	ET 8 (n.a.)[b] HC 11 (n.a.)	n.a. n.a.	FDG PET No difference in rMRG in basal ganglia, midbrain, and CER
Breit et al. (95)	ET 6 (4) HC 10 (5)	60 ± 5 58 ± 5	FDG PET No difference in rMRG in basal ganglia

ET, essential tremor; clET, classical ET; rET, ET subjects presenting with resting tremor; pET, ET individuals presenting with one cardinal parkinsonian feature (bradykinesia, rigidity, or rest tremor); trET, ET patients responsive to propranolol therapy; nrET, ET patients unresponsive to propranolol therapy; HC, healthy controls; ↓, lower compared with HC; ↑, higher compared with HC; n.a., not available; CER, cerebellum; ION, inferior olive nucleus; PMC, primary motor cortex; SC, sensory cortex; DaT, dopamine transporter; FDG, ^{18}F-fluorodeoxyglucose; PET, positron emission tomography; rCBF, regional cerebral blood flow; rMRG, regional metabolic rate of glucose; SPECT, single-photon emission computed tomography.

[a] *HC significantly older than ET.*

[b] *Only gender and age distribution of the entire cohort are provided, and it is not clear if cohorts were matched for gender and age.*

to clinical tremor manifestation and task performance (36, 40, 62–64, 66, 67). One study did not report a significant difference in functional connectivity during an emotion processing and finger tapping task in ET patients compared with HC. However, in the latter study, HC were not age matched to the ET cohort (32). In line with the findings from structural imaging, cognitive function has been associated with specific activity changes outside the classical tremor network (65, 68).

More recently, neuronal activity has been assessed in the resting state. Resting-state fMRI is advantageous over task-based paradigms in that it is independent of individual variability in task performance and interference of tremor with motor function. The most consistent finding reported by these studies was altered intrinsic cerebellar and cerebello-thalamo-cortical activation/connectivity, particularly of cerebello-motor cortical projections (33–35, 37, 61, 71–75, 77). There is also evidence that complex functional alterations outside the classical tremor axis are present in ET, including visual networks (69, 70). In this vein, Archer et al. have demonstrated that activity within the tremor and visual networks during a grip motor task could be modulated by visual feedback (21).

Of note, surgical interventions to treat ET, such as Vim-DBS or thalamotomy have been shown to restore connectivity in the tremor network partially and to cause widespread remodeling of other brain networks outside the classical tremor axis [e.g., (125, 126)]. In line with observations from structural MRI, the clinical phenotype appears to be associated with distinct functional brain changes. For example, ET individuals exhibiting head tremor showed distinct cerebellar activity compared with those who did not (76), and ET patients with resting tremor showed different activation patterns of various cortical and subcortical brain regions compared with classical ET (73).

Magnetic Resonance Spectroscopy

MRS is utilized to assess neurometabolic alterations in brain tissue *in vivo*. *N*-acetylaspartate (NAA) is an abundant amino acid derivative synthesized in neurons. A reduction of NAA, therefore, is indicative of neuronal damage. The choline (Cho) fraction comprises several soluble components mainly located in myelin and cell membranes. Conditions resulting in increased turnover or damage to cellular membranes and myelin, such as inflammation, tumor, or neurodegenerative processes, result in increased Cho concentrations. Creatine (Cr) is found in most neurons and astrocytes. The Cr peak is very robust, which is why Cr is commonly used as a denominator to offset changes of NAA and Cho (127). MRS can also be applied to measure GABA (please see below).

Few studies have exploited MRS to investigate neurometabolite changes in ET. Louis et al. were the first to report a reduced NAA/Cr ratio in the cerebellum of 16 ET patients compared with 11 HC that was inversely correlated to tremor severity (81). The same group later found that NAA/Cr changes were similar between cerebellar hemispheres, in accordance with the symmetric clinical manifestation of ET (82). Similarly, reduced NAA/Cr ratios have been reported by Pagan et al. in a small cohort of 10 ET patients (83). That

said, others found normal NAA/Cr ratios in the thalami of ET patients (78–80), whereas there was an increase in the excitatory neurotransmitter glutamate/glutamine evident in one of these studies (79).

Imaging of the GABAergic System

The role of GABA in ET has been a topic of ongoing discussion for many years (13), and different lines of research have vindicated the significance of the GABAergic system in ET pathophysiology.

ET patients show lower GABA levels in the cerebrospinal fluid (128), and GABA receptor density in the cerebellar dentate nucleus has been reported to be reduced (129). Alcohol has agonistic GABAergic properties and alleviates tremor in many patients with ET (130), and the majority of drugs used to treat ET act *via* GABAergic pathways (131). Moreover, GABA-A_1 receptor knockout mice develop an ET-like disease that responds to GABAergic drugs commonly used to treat ET (132). The impact of reduced cerebellar GABAergic tone on neuronal activity in cerebello-thalamico-cortical tremor network activity has also been highlighted in a recent study applying a complex computational simulation model of ET (133).

Very few *in vivo* imaging studies have explored the role of GABA in ET. Using PET and ^{11}C-flumazenil, a ligand of the benzodiazepine site of the GABA receptor, Boecker et al. observed increased cerebellar, thalamic, and premotor cortical tracer uptake in a small cohort of ET patients compared with HC, hinting at reduced GABAergic function (90). In contrast, a separate study employing MRS failed to demonstrate a significant difference in GABA concentration in the dentate nuclei between ET individuals and HC (91). Another MRS study reported a positive correlation of the cerebellar GABA/glutamate + glutamine ratio with clinical tremor scores in a small ET cohort. However, neither GABA nor glutamate/glutamine levels differed between ET patients and HC in the latter study (92). Given the limited number of available imaging studies focused on GABA, we would like to mention the work by Gironell et al. even though their study did not meet our inclusion criteria; they found a significant correlation of cerebellar ^{11}C-flumazenil uptake and tremor severity in a cohort of 10 ET patients (134).

Imaging of Brain Iron

Different MRI techniques, such as susceptibility-weighted imaging, T2*-weighted, or its inverse R2*-weighted gradient echo imaging, can be used to measure brain iron (135). More recently, novel methods, such as neuromelanin and nigrosome-1 imaging have been developed to visualize the neuronal integrity of the substantia nigra (136). These techniques have been extensively used to detect iron depositions, which are assumed to be a surrogate of cellular damage in neurodegenerative disorders, such as PD (137).

In one study comparing 25 ET patients with 25 matched HC, no significant difference was found in the R2* relaxation times of the substantia nigra (85). Similarly, three other studies reported normal nigral neuromelanin concentrations in ET patients (86, 88, 89), and nigral nigrosome-1 integrity has been found to be comparable with that of HC (84, 86). The focus of all these studies was on the substantia nigra, and only one study applied a whole-brain voxel-based approach (87). The authors reported increased iron levels in the bilateral pallidum, substantia nigra, and the right dentate nucleus. That being said, only the pallidal iron increase survived correction for multiple comparisons and was correlated to tremor severity (87).

Radiotracer Imaging

Alongside MRI, PET and SPECT have been applied using a variety of tracers to study the integrity of the dopaminergic axis, brain perfusion, and metabolism in ET.

Dopaminergic Imaging

Epidemiological studies suggest that ET populations have an increased risk of developing PD, and there is an ongoing controversy about a potential pathophysiological overlap between the two diseases (14).

FP-CIT SPECT (commercially known as DaTScan) is commonly used to assess the presynaptic striatal dopaminergic integrity (138). Striatal tracer uptake is significantly reduced in typical and atypical parkinsonism (138).

Most studies using FP-CIT SPECT or comparable techniques found no alterations of the dopaminergic system in ET (51, 78, 93–96, 100, 102–105, 107, 139). These findings were extended by two longitudinal studies showing constant tracer uptake over time (98, 100). Of note, a third longitudinal study not meeting our inclusion criteria did not reveal a decline of striatal dopamine transporter availability over a mean follow-up period of 28 months (140). One study reported normal DaTScan in classical ET patients, whereas tracer uptake was reduced in ET patients with additional resting tremor (101). However, resting tremor ET individuals were about 7 years older than the corresponding HC, and several subjects presented with subtle parkinsonian features, raising the question of whether they may have subsequently developed PD. Conversely, others have found normal striatal dopaminergic integrity in ET patients with resting tremor (102). That being said, some authors reported signs of slight striatal dopaminergic degradation in classical ET (97–99, 106). Of note, ET patients may show reductions of tracer uptake primarily in the caudate nucleus, contrasting the typical pattern of pronounced posterior putamenal reductions observed in PD (99, 106).

Perfusion Imaging

A series of small exploratory PET studies conducted in the 1990s, mostly using ^{15}O-labeled H_2O and PET, revealed increased regional cerebellar blood flow (rCBF) during both rest and posture in ET patients compared with HC (17, 109, 110). These studies showed overactivation of additional regions comprising the tremor network, whereas olivary overactivation was not present in any of these studies (17, 109, 110). Boecker et al. demonstrated that abnormally increased cerebellar rCBF decreased toward normal values after ingestion of ethanol, and this decrease was correlated to concurrent tremor alleviation (108). Furthermore, there was an increase in ION activation following ethanol ingestion, suggesting increased afferent olivary input as a consequence of normalizing synaptic

cerebellar activity (108). More recently, SPECT and ^{99m}Tc-hexamethylpropylenaminoxom (HMPAO) have been used to measure rCBF in ET cohorts. Sahin et al. did not observe any difference of rCBF between 16 ET patients and matched HC, but reported an inverse correlation of frontal cortical rCBF with tremor severity (111). Employing the same method, Song et al. found no significant differences in rCBF between ET patients with and without head tremor (113). Interestingly, rCBF was reduced in various brain regions, including the cerebellum, in the overall ET cohort compared with HC in the latter and in a subsequent study conducted by the same group (112, 113).

Metabolic Imaging

^{18}F-fluorodeoxyglucose (FDG) and PET can be used to quantitatively assess brain glucose consumption, which is largely equivalent to neuronal activity (141). FDG PET has been extensively used to characterize metabolic brain abnormalities in neurodegenerative disorders, such as PD, and has revealed disease-specific abnormal brain networks that correlate with disease severity and can discriminate PD from atypical parkinsonism (142).

Hallett and Dubisnky were among the first to report increased brainstem and thalamic activity in ET patients, whereas they did not observe significant changes in cerebellar metabolism (114). Similarly, two recently published studies did not find changes in cerebellar metabolism, but widespread cortical hypometabolism was reported in one of these studies (105, 115). In contrast, Song et al. found cerebellar hypometabolism accompanied by reduced tracer uptake in various cortical regions (116). In yet another study using an ROI-based approach, no metabolic differences were identified in ET patients compared with controls in the basal ganglia (95).

DISCUSSION

Whereas there is relatively little support from neuroimaging for the hypothesis that the ION is the primary oscillator of abnormal neuronal activity, there is robust evidence indicating that the cerebellum plays a major role in ET pathophysiology. Findings from volumetric MRI studies are, however, heterogeneous, and VBM studies do not unequivocally corroborate with histopathological findings of cerebellar neurodegeneration. Importantly, the topography of cerebellar regions displaying atrophy is inconsistent across studies, countering arguments in favor of a uniform pattern of cerebellar cell loss. DTI studies have more consistently revealed microstructural alterations of the cerebellum, and fMRI studies have clearly demonstrated abnormal cerebellar function and altered connectivity in cerebello-thalamico-cortical circuitry. Along these lines, radiotracer studies have shown increased cerebellar rCBF in ET patients, further underpinning a pivotal role of this structure in tremor genesis. That said, in view of the widespread functional alterations reported, it is likely that the cerebellum is not the sole driver of tremor genesis but rather constitutes a major hub within a multiple oscillator tremor network, thus validating neurophysiological data (122).

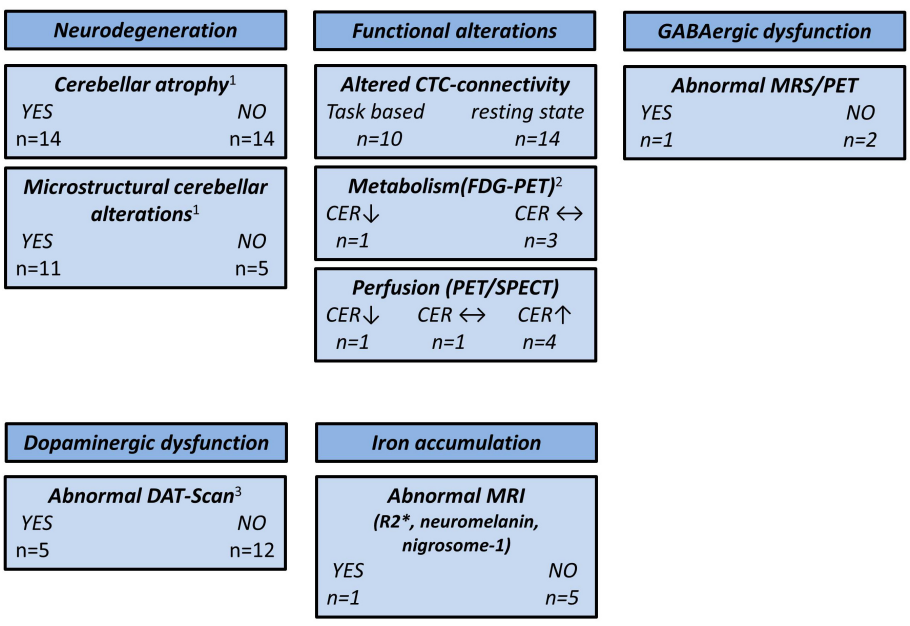

FIGURE 2 | Overview of neuroimaging studies in essential tremor. CER, cerebellum; CTC, cerebello-thalamico-cortical; DAT, dopamine transporter; FDG, ^{18}F-fluorodeoxyglucose; GABA, γ-aminobutyric acid; MRS, magnetic resonance spectroscopy; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography; ↑, higher compared with the healthy controls; ↓, lower compared with the healthy controls; ↔, no difference compared with the healthy controls. [1]CER not assessed by three studies. [2]CER not assessed by one study. [3]One study used ^{11}C-CFT PET and two studies used [^{99m}Tc]-TRODAT SPECT.

Findings from FDG PET studies are ambiguous. Some studies have reported extensive cortical hypometabolism, and there is evidence for increased thalamic activity. However, other studies have reported opposing results, and in particular, there are conflicting findings with respect to cerebellar metabolic activity. Data from MRS studies are scarce and insufficient to draw firm conclusions. However, the few available studies provide some evidence for thalamic and cerebellar neuronal damage.

The dopaminergic axis appears to be largely preserved in ET. This is also illustrated by the fact that DaTScan has been certified for use in the differentiation of PD from ET by both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA), and some studies on PD even use ET cohorts as "normal" controls [e.g., (143)]. That being said, some authors have suggested slightly reduced striatal dopaminergic integrity in ET subjects that does not, however, seem to decline over time.

With the exception of one study, there is no evidence for pathological nigral iron accumulation as typically observed in PD. However, only one study did not apply an ROI-based approach limited to the substantia nigra, and this study did observe a significant increase of iron accumulation in the bilateral globus pallidus internus. Therefore, it seems that there is no relevant nigral iron accumulation in ET, but this could well be the case for other brain regions not commonly assessed by imaging studies thus far, arguing in favor of neurodegenerative processes.

Finally, MRS and radiotracer studies lend some support to the hypothesis that dysfunction of the GABAergic system is involved in ET pathophysiology. It remains to be elucidated whether the reduced GABAergic tone is a primary contributing factor to ET pathophysiology or rather a consequence of disturbed Purkinje cell function or even cell death.

Based on the epidemiological, genetic, and clinical heterogeneity, it is likely that no single ET entity exists, but rather an ET spectrum. This is supported by the notion that clinical phenotype, e.g., the distribution of tremor manifestation, the presence of cognitive impairment, or resting tremor, is linked to specific functional and structural brain changes. A summary of the main findings reported in this review is depicted in **Figure 2**.

Taking genetic background (familiar vs. sporadic), age at onset, disease duration, therapeutic responsiveness, and clinical phenotype (e.g., presence of head tremor, symptoms of "ET plus") into account is important when studying ET populations, but these factors have not been consistently implemented in study designs so far. There are additional issues likely contributing to the heterogeneous findings from neuroimaging studies, such as limited sample size (this is particularly true for PET and SPECT studies), subject age (the mean age of ET cohorts included in this review ranged from 28 to 74 years), nature of the analytical approach (e.g., ROI-based vs. whole-brain analysis, statistical threshold applied), and the different field strengths of the MRI scanners. Moreover, several groups have published multiple papers on related topics using similar cohorts or did not specify if there was an overlap of cohorts across their studies, a potential source of reporting bias.

It is desirable that future studies more rigorously focus on the demographical, genetic, and clinical heterogeneity of ET. Multimodal imaging, including the simultaneous assessments of MRI, PET, and electroencephalography, may shed further light on the complex neuronal alterations underlying ET. Furthermore, the much higher spatial resolution of ultra-high field MRI may enable researchers to solve the remaining controversy of whether cerebellar neurodegeneration is the pathological foundation of ET.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

FH: study design, data collection and analysis, and drafting of the manuscript. NS: study design, revision of the manuscript, and supervision. Both authors contributed to the article and approved the submitted version.

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White Matter Hyperintensities Are Associated With Severity of Essential Tremor in the Elderly

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Background: Essential tremor (ET) occurs with steeply increasing prevalence in the elderly, and apart from disease duration, age is independently associated with an increase of tremor amplitude and a decrease of frequency. White matter hyperintensities (WMHs) are a common finding in the elderly, and their role in the pathophysiology of ET is unknown. The aims of this study were to examine whether ET patients differ in their total or region-specific WMH volumes from healthy controls and to determine the impact of WMH on tremor characteristics.

Methods: A total of 47 elderly ET patients with a mean age of 72 years and 39 age-matched healthy controls underwent a thorough clinical assessment and 3T MRI. Total WMH volumes were derived from T2-weighted fluid-attenuated inversion recovery (FLAIR) MR images. Additionally, region of interest-based WMH volumes for the Johns Hopkins University (JHU) white matter tracts and labels were calculated, and WMHs were assessed semiquantitatively using the Fazekas scale.

Results: Essential tremor patients and healthy controls did not differ in their total or tract-specific WMH volumes or Fazekas scores. However, WMH volume was significantly positively correlated with tremor severity on the TETRAS scale, and there was a significant negative correlation with the mean accelerometric tremor frequency. In a multiple linear regression model including disease duration, age, and age-adjusted total WMH volume, only the WMH volume significantly predicted tremor severity, while age and disease duration were not significant.

Conclusion: We found evidence for a direct association between WMH volume and tremor severity. If confirmed by larger studies, our findings could explain the well-known relation between age and tremor severity.

Keywords: white matter hyperintensities, essential tremor, senile tremors, accelerometric tremor frequency, tremor severity

INTRODUCTION

Essential tremor (ET) is the most common movement disorder, with steeply increasing prevalence in the elderly (1). According to the current classification, ET is considered a syndrome with clinical features described in axis I and the etiology in axis II (2). Although the etiology for the syndrome (axis II) remains unclear in the majority of patients, pathological oscillations within the cerebello-thalamo-cortical circuit are proposed as a common pathophysiologic correlate (3). The source for these oscillations has not been determined yet, but several imaging and pathological studies point toward a central role of the cerebellum for the pathogenesis (4–7).

Using linear regression analyses, epidemiologic studies have shown that apart from disease duration, age is independently associated with an increase in tremor severity as measured with clinical tremor scores and a decrease in accelerometric tremor frequency (8–11). Furthermore, older age of tremor onset is associated with a more rapid tremor progression, and patients with a tremor onset after the age of 60 have a shorter life expectancy (12–15). Such late-onset patients also show electrophysiological parameters for earlier aging, such as a prolonged latency of the pupillary response (15) and a different cerebral network of tremor (16). The underlying mechanisms for this relationship between biological aging and tremor progression are not understood yet, but a subtype of aging-related (senile) tremor is one explanation.

White matter hyperintensities (WMHs) on T2-weighted MRI are a very common finding in the elderly (17). Pathologically, they correspond to areas of demyelination and gliosis, mainly resulting from chronic diffuse subclinical ischemia (18). White matter hyperintensities affect cognitive functioning in normal aging and also in patients with mild cognitive impairment and dementia (17). Furthermore, there is growing evidence that WMHs affect motor performance in the elderly in several ways: WMHs are associated with a higher risk of developing gait disturbances in healthy elderly persons (19). In Parkinson's disease patients, WMHs are associated with an increased risk of progression from mild parkinsonian signs to severe gait and balance impairment, bradykinesia, and rigidity (20), and they mediate the effect of autonomic dysfunction on future cognitive decline (21).

To the best of our knowledge, only one study has examined the occurrence of WMHs in ET patients, finding that ET was associated with greater total WMH volume and greater cerebellar WMH volume compared to those in healthy controls (22). But these results have never been confirmed within a sample of ET patients that was diagnosed according to the current International Parkinson and Movement Disorder Society (IPMDS) tremor classification.

The objectives of this study were (1) to examine whether patients with ET differ in their total or region-specific WMH volumes from healthy, age-matched controls and (2) to examine the impact of WMHs on certain tremor characteristics (tremor amplitude, frequency, tremor score).

PARTICIPANTS AND METHODS

Clinical Assessment

Between 2017 and 2019, a sample of 55 ET patients and 41 healthy controls with at least 60 years of age was consecutively recruited from our outpatient clinic. Of these, eight patients and two healthy controls had incidental MRI findings and were excluded from all further analyses (see below).

Inclusion criteria for patients were a diagnosis of ET or ET plus according to the current diagnostic criteria of the IPMDS (2) and a minimum age of 60 years. Exclusion criteria were a history of clinically evident stroke, dementia, or other neurological diseases apart from ET or incidental MRI findings apart from WMH (see imaging exclusion criteria). Healthy controls were either spouses of patients ($n = 8$) or individuals who were registered within an in-house database for voluntary participation in research studies ($n = 33$). Patients and controls underwent a complete neurological examination by a movement disorder specialist, and patients were asked to pause any antitremor medication for at least 24 h before the examination. The presence of vascular risk factors (arterial hypertension, hyperlipidemia, diabetes mellitus) and vascular disease defined as a history of coronary artery disease (myocardial infarction, angina, atrial fibrillation, congestive heart failure) or cerebrovascular disease (carotid endarterectomy, carotid stent) was assessed based on a thorough review of the participant's medical history and medications. For each patient, a vascular burden score was calculated from vascular risk factors and vascular diseases, ranging from 0 to 5 (i.e., the sum of hypertension, hyperlipidemia, diabetes mellitus, coronary artery, and cerebrovascular diseases) (23). Cognitive functioning was tested using the Montreal Cognitive Assessment (MoCA) (24). In addition, semantic and verbal fluency was assessed with the Regensburger Wortflüssigkeits-Test (RWT), 2-min testing per task, no counting of errors (25). In all patients, tremor severity was rated according to the Essential Tremor Rating Assessment Scale (TETRAS) and by polygraphic tremor analysis (26).

The study was approved by our local ethics committee, and all individuals gave written informed consent prior to participation.

Electrophysiological Tremor Assessment

Tremor amplitude and frequency were assessed by polygraphic tremor analysis (27). Patients were seated in a comfortable chair in a slightly supine position. Both forearms were supported by firm armrests up to the wrist joints. During measurement, the hands were held outstretched against gravity. Tremor was recorded for 30 s by surface electromyography (EMG) from the extensor and flexor carpi ulnaris muscles using silver chloride electrodes and a piezoresistive accelerometer, which was placed on the third metacarpal bone about 2 cm proximal to the metacarpophalangeal joint bilaterally. All data were sampled at 800 Hz. The EMG was bandpass filtered between 50 and 350 Hz and full wave rectified. Spectral analysis was performed using a standard algorithm implemented in a commercially available tremor analysis software [as described in Lauk et al. (27)]. As a measure of tremor amplitude, the logarithmic total power of the accelerometrically measured tremor spectra was

calculated. The greatest peak power was considered to reflect the tremor frequency.

Magnetic Resonance Image Acquisition

Magnetic Resonance Image acquisitions were performed on a 3-Tesla whole-body MRI scanner (Achieva; Philips, Best, Netherlands) equipped with a 32-channel head coil. The imaging protocol consisted of the following:

I) A T1 MPRAGE sequence with a spatial resolution of 1.05 × 1.05 × 1.2 mm, 170 slices, a field of view of 256 × 256 mm, TR = 6.6 ms, TE = 3.1 ms, and a flip angle = 9°.
II) A T2 FLAIR sequence with a spatial resolution of 0.43 × 0.43 × 2.0 mm, 57 slices, a field of view of 528 × 528 mm, TR = 12,000 ms, TE = 160 ms, TI = 2,850 ms, and a flip angle of 90°.
III) A diffusion tensor imaging (DTI) dataset with 64 directions, a spatial resolution of 1.67 × 1.67 × 1.9 mm, a field of view of 144 × 144 mm, TR = 8,200 ms, TE = 75 ms, and a flip angle of 90°. Diffusion-weighted images were acquired in four consecutive scan sessions with intermitted B0 images. At the end of the acquisition, a reference scan with opposing polarities of the phase-encoding was added to correct susceptibility-induced distortions.

Additionally, a hemosensitive T2*-weighted sequence was acquired for clinical purposes.

Imaging Exclusion Criteria

All FLAIR and T2* sequences were screened by a board-certified radiologist with 10 years of experience in neuroradiology for incidental findings. Eight patients and two controls had incidental MRI findings and were excluded from further analyses: four patients had incidental embolic or lacunar stroke, one patient had a giant subarachnoid cyst preventing further processing of the MRI images, one patient had imaging evidence of idiopathic normal pressure hydrocephalus, two patients and two control subjects fulfilled imaging criteria for probable cerebral amyloid angiopathy.

Semiquantitative White Matter Hyperintensity Assessment

Periventricular and deep white matter signal hyperintensities were assessed semiquantitatively by a blinded examiner using the Fazekas scale on FLAIR images (**Table 1**) (28).

Automated Total and Region of Interest-Based White Matter Hyperintensity Assessment

1. FreeSurfer segmentation: A volumetric segmentation was applied to the structural T1 image using the FreeSurfer image analysis pipeline (recon-all). The technical details of these procedures are described in prior publications (29).
2. FLAIR-based WMH detection: Image intensity correction (bias field correction) was applied to the T1 and FLAIR images to get uniform image intensities (30). A rigid transformation estimated in a FLAIR to T1 registration step was used to align and transfer the FreeSurfer segmentation to the FLAIR image matrix (31). Based on FreeSurfer tissue segmentations projected onto the voxel of the FLAIR image, mean and standard deviation of the FLAIR intensities of gray matter were calculated, and an intensity threshold for WMHs was automatically determined by choosing the first upper quantile of the gray matter FLAIR intensities as a threshold for WMH regions.
3. DTI preprocessing: Images from the four consecutive DTI sequences were merged, and a brain mask was calculated using the FSL bet2 software (32). The FSL topup was applied to the B0 images with opposing polarities to estimate a distortion map. The method is described in Andersson et al. (33) and implemented in FSL (34). The distortion map and eddy correction were then applied to the DTI data to correct spatial and eddy distortions. After this correction, a new brain mask was calculated that respects the corrected image geometry. The corrected DTI dataset and the new brain mask were then piped into FSL's DTIFIT to calculate individual fractional anisotropy (FA) and mean diffusivity (MD) maps.

The individual FA maps were registered with the JHU atlas FA maps to assign detected WMH voxels to specific JHU tracts using the JHU max probability map (JHU ICBM tracts maxprob thr0 1 mm) (35). Additionally, WMH voxels were assigned to the JHU labels atlas (36). Whole-brain and tract-/label-specific WMH volumes were automatically calculated in mm^3. **Figure 1** summarizes major steps of the preprocessing pipeline.

Statistical Analyses

IBM SPSS Statistics (Version 24.0; IBM Corp., Armonk, NY) was used for statistical analyses. *t*-Tests were applied for group comparisons of baseline clinical characteristics and total or ROI-based WMH volumes. Nonparametric Mann–Whitney–U-test was applied for group comparisons of the Fazekas scale and vascular burden score. Pearson's chi-square-test was used to test categorical variables. Results were considered significant for $p < 0.05$.

To examine whether WMHs are associated with tremor severity and frequency in ET patients, a multiple linear regression model was compiled. The total WMH volume was adjusted for age to allow including both as independent variables into this model. To identify strategic white matter tracts in which WMHs are associated with tremor severity independently of global WMH volume, assumption-free ROI-based analyses were performed. Therefore, the tract-specific WMH volume was adjusted for total WMH volume, and bilateral JHU tracts/labels were merged into a single ROI. The regional WMH volumes of these 11 white matter tracts/27 JHU labels were entered separately into linear regression models as independent variables with TETRAS part 2 scores or tremor frequency as dependent variables. Bonferroni correction was applied for multiple comparisons.

TABLE 1 | Baseline characteristics.

	ET $n = 47$		Controls $n = 39$		*t*-test
	Mean	**Std. Deviation**	**Mean**	**Std. Deviation**	***p*-value**
Age	72.36	6.76	71.54	6.96	0.567
School years	10.37	1.92	10.87	1.60	0.194
Body mass index	25.54	3.52	26.94	5.55	0.173
MoCA	24.28	2.84	26.02	2.70	**0.005**
MoCA age adjusted	−0.15	0.83	0.38	0.86	**0.004**
RWT semantic	31.18	9.79	34.57	8.84	0.100
RWT phonematic	18.31	8.61	20.31	8.50	0.285
BDI	3.36	4.29	2.37	3.21	0.244
TETRAS part 1	22.71	7.05			N/A
TETRAS part 2	19.67	4.06			N/A
	Median	**Range**	**Median**	**Range**	**Mann–Whitney–U-test, *p*-value**
Vascular burden score (0–5)	1	4	1	3	0.128
Fazekas periventricular white matter (0–3)	1	3	1	2	0.301
Fazekas deep white matter (0–3)	1	2	1	2	0.951

BDI, Beck's Depression Inventory; MoCA, Montreal Cognitive Assessment; RWT, Regensburger Wortflüssigkeits-Test; TETRAS, Tremor Research Group Essential Tremor Rating Assessment Scale; Significant values are marked in bold.

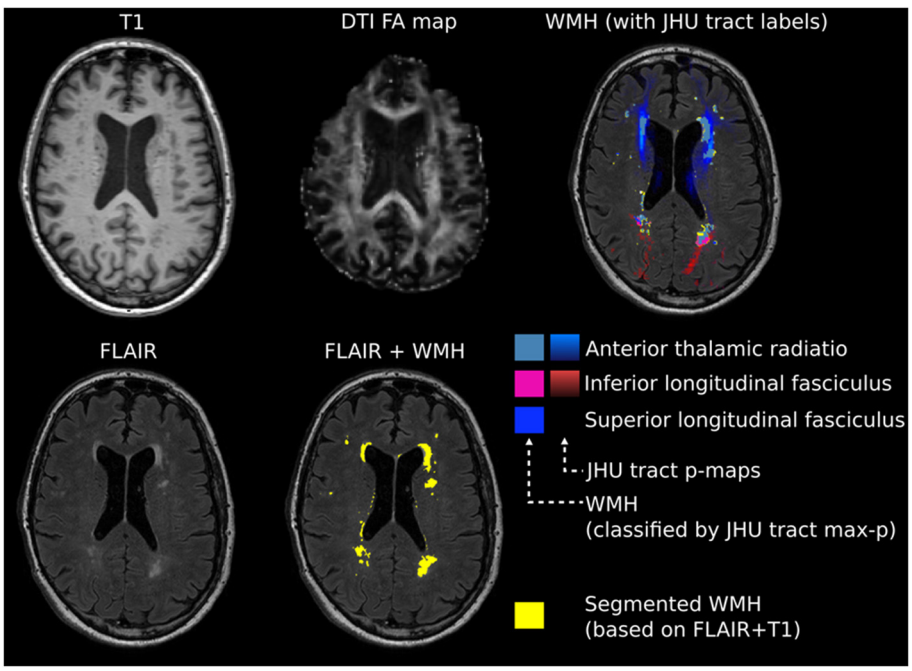

FIGURE 1 | Exemplary image processing of a single patient for region of interest (ROI)-based white matter hyperintensity (WMH) assessment. Intensity threshold for WMHs was automatically determined by choosing the first upper quantile of the gray matter as a threshold. Individual fractional anisotropy (FA) maps were coregistered with the Johns Hopkins University (JHU) atlas FA maps. Whole-brain and tract-specific WMH volumes were automatically calculated in mm^3.

RESULTS

Baseline Characteristics

A sample of 47 ET patients and 39 healthy controls, both groups >60 years of age, was included in the study. **Table 1** summarizes the baseline characteristics of the study cohort. In 20 of the 47 ET patients, additional neurological signs of uncertain significance were found (e.g., questionable dystonic postures, mild gait ataxia, etc.) and these patients were labeled as ET plus accordingly. Since no group differences were found between patients with and

those without additional soft signs regarding total or ROI-specific WMH volumes, all ET patients were pooled for further analyses to increase statistical power.

Essential tremor patients had a significantly lower MoCA score than that in healthy controls even after correction for age (**Table 1**). Both groups did not differ in their verbal fluency measures. Patients and controls did not differ in their vascular burden score ($p = 0.128$, Mann–Whitney–U-test), although patients had a slightly wider range (**Table 1**).

Within the group of ET patients, the TETRAS motor score (TETRAS part 2) was significantly negatively correlated with tremor frequency (mean value of left and right upper extremity; $r = -0.39$, $p = 0.009$), but there was no significant correlation of TETRAS part 2 with the logarithmic accelerometric total power (mean value between left and right upper extremity; $r = 0.166$, $p = 0.326$). However, total power and tremor frequency were significantly negatively correlated ($r = -0.33$, $p = 0.043$).

White Matter Hyperintensity Volumes

Vascular burden score was significantly correlated with total WMH volumes (Spearman rho = 0.270, $p = 0.012$). Patient groups and healthy controls did not differ significantly with regard to the total volume of WMH nor to the ROI-specific WMH volume (mean values of left/right side ROI; **Figure 2**). These results remained not significant when taking the vascular burden score, age, and age-adjusted MoCA score as covariates into the analysis. The semiquantitative assessment of the Fazekas scale confirmed these results (no significant group differences; **Table 1**). When splitting the sample of ET patients into a group with early (<40 years, $n = 23$) and late (≥60 years, $n = 12$) onset of symptoms, no significant differences for total or ROI-specific WMH volumes were found between these groups or in comparison to healthy controls after age correction. Both groups also did not differ regarding TETRAS part 2 scores or mean tremor frequency, although patients with late symptom onset had a significantly shorter disease duration (11.4 vs. 51.3 years, $p < 0.001$).

White Matter Hyperintensities and Tremor Characteristics

Age and disease duration were not significantly correlated with each other ($r = -0.267$, $p = 0.07$), and both age and disease duration were not directly correlated with tremor severity on the TETRAS scale (correlation analysis for age/TETRAS: $r = 0.08$, $p = 0.590$; duration: $r = -0.03$, $p = 0.858$) nor the logarithmic total power of postural tremor (age: $r = -0.146$, $p = 0.297$; duration: $r = 0.060$, $p = 0.667$). However, age was significantly correlated with the total WMH volume ($r = 0.328$, $p = 0.009$). Therefore, the WMH values were controlled for age to allow including both into a linear regression model.

The total WMH volume was significantly positively correlated with tremor severity on the TETRAS scale (TETRAS part 2: $r = 0.482$, $p = 0.001$; **Figure 3**), and there was a significantly negative correlation with the mean accelerometric tremor frequency ($r = -0.372$, $p = 0.012$; **Figure 3**), but there was no significant correlation between WMH volume and mean logarithmic total power.

A multiple linear regression model was compiled to predict tremor severity (TETRAS part 2) based on disease duration, age, and age-adjusted total WMH load. The adjusted R^2 for the entire model was 0.279 [$F_{(3,44)} = 5.685$, $p = 0.002$; **Table 2**].

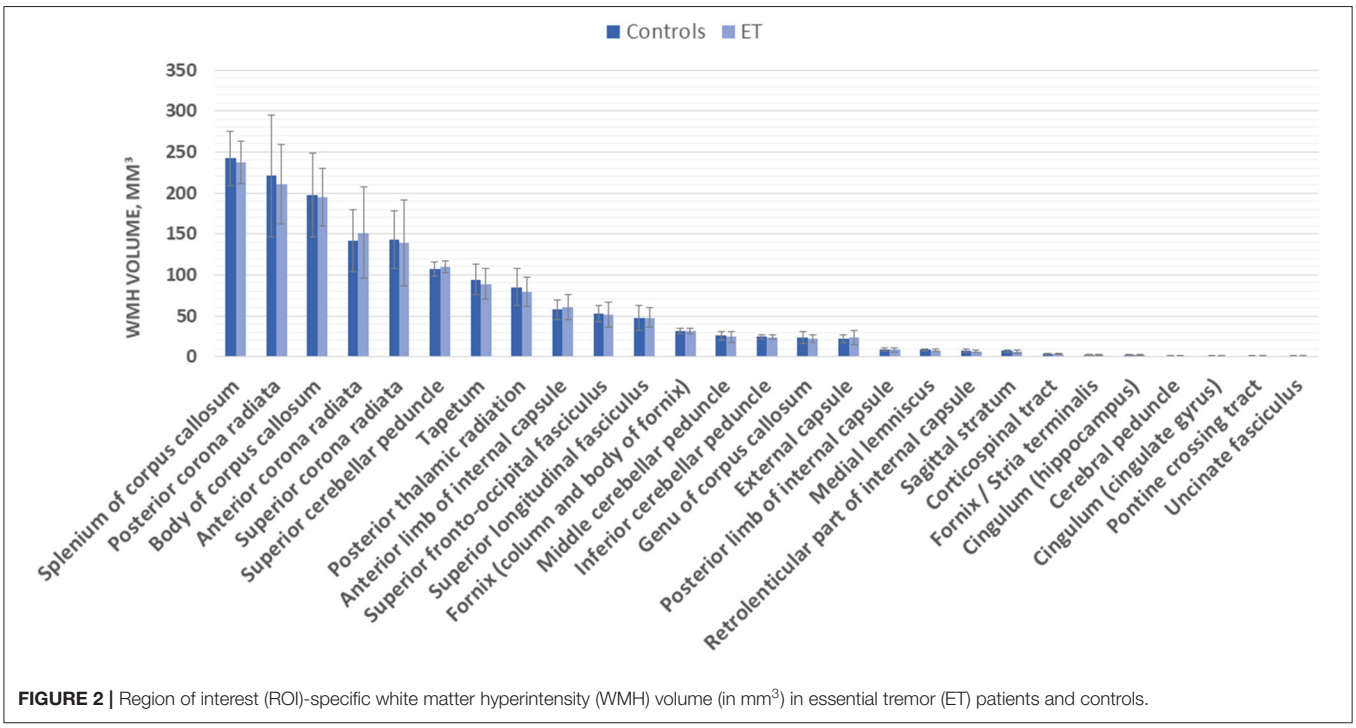

FIGURE 2 | Region of interest (ROI)-specific white matter hyperintensity (WMH) volume (in mm^3) in essential tremor (ET) patients and controls.

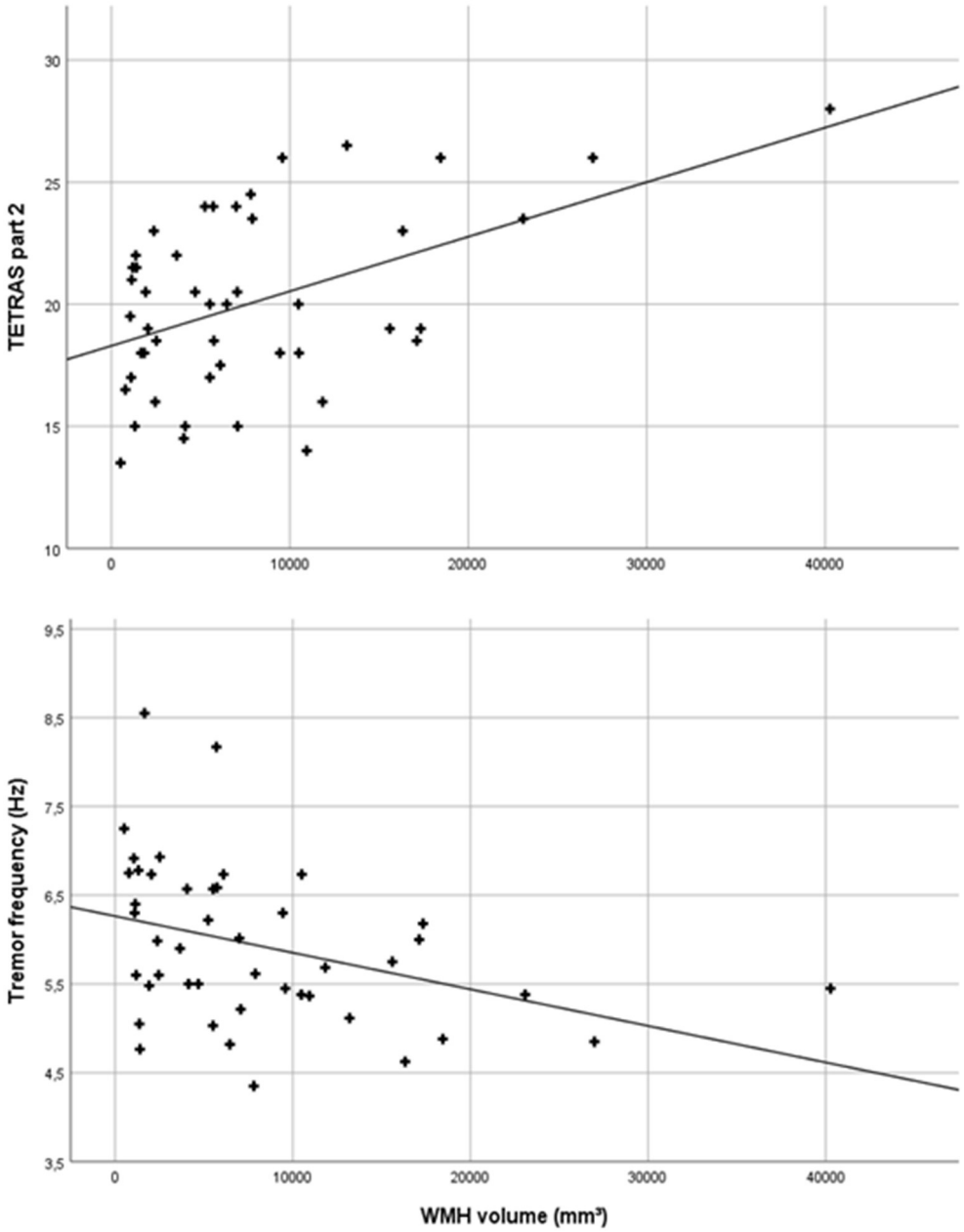

FIGURE 3 | Scatter plot of total white matter hyperintensity (WMH) volumes and Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) part 2 scores ($r = 0.482$, $p = 0.001$) and mean accelerometric tremor frequencies ($r = -0.372$, $p = 0.012$) of essential tremor (ET) patients.

Only the WMH volume significantly predicted tremor severity ($\beta = 0.517$, $p < 0.001$), while age and disease duration were not significant (each $p > 0.05$), meaning that higher WMH load was associated with more severe tremor. The same regression model with the mean tremor frequency as dependent variable showed an adjusted R^2 for the whole model of 0.113 [$F_{(3,44)} = 2.873$, $p = 0.048$; **Table 2**], and again, only the WMH volume significantly predicted tremor frequency (ß = 0.341, $p = 0.02$), while age and disease duration were not significant (each $p > 0.05$).

The results of the assumption-free ROI-based analysis to identify strategic white matter tracts associated with tremor severity are shown in **Table 2** and **Supplementary Table 1**. Age and disease duration do not significantly predict tremor severity or frequency (Regression-model 1, **Table 2**). After entering the age-adjusted WMH volume, the model becomes significant (Regression-model 2). Separate regression models for 27 white matter tracts after correction for total WMH volume were performed (significance level for model 3.1–3.27, $p < 0.0019$). After multiple comparison

TABLE 2 | Assumption-free ROI-based analysis to identify strategic white matter tracts that are associated with tremor severity (TETRAS part 2) and accelerometric frequency based on the JHU labels atlas.

		TETRAS part 2		Frequency	
Regression model	**Independent variables**	R^2	p-value R^2	R^2	p-value R^2
1	Age, disease duration	0.089	0.265	0.067	0.422
2	Model 1 + total WMH volume	**0.279**	**0.002**	**0.113**	**0.048**
3.1	Middle cerebellar peduncle	0.013	0.485	0.000	0.939
3.2	Pontine crossing tract	0.001	0.814	0.001	0.819
3.3	Genu corpus callosum	0.000	0.928	0.004	0.724
3.4	Body corpus callosum	0.100	0.047	0.045	0.201
3.5	Splenium corpus callosum	0.170	0.008	0.035	0.262
3.6	Fornix	0.004	0.712	0.006	0.644
3.7	Lemniscus medialis	0.025	0.329	0.000	0.984
3.8	Inferior cerebellar peduncle	0.008	0.590	0.000	0.925
3.9	Superior cerebellar peduncle	0.091	0.059	0.005	0.667
3.10	Cerebral peduncle	0.020	0.381	0.015	0.463
3.11	Anterior limb of CI	0.052	0.159	0.031	0.294
3.12	Posterior limb of CI	0.011	0.521	0.015	0.462
3.13	Retrolenticular part CI	0.047	0.178	0.02	0.325
3.14	Anterior corona radiata	0.078	0.081	0.042	0.216
3.15	Superior corona radiata	0.063	0.119	0.050	0.178
3.16	Posterior corona radiata	0.108	0.038	0.108	0.044
3.17	Posterior thalamic radiation	0.004	0.715	0.015	0.457
3.18	Sagittal Stratum	0.048	0.176	0.076	0.095
3.19	Cingulum	0.095	0.054	0.065	0.123
3.20	Cingulum hippocampal part	0.040	0.214	0.011	0.538
3.21	External Capsule	0.008	0.589	0.001	0.871
3.22	Fornix stria terminalis	0.011	0.516	0.002	0.805
3.23	Tapetum	0.000	0.906	0.001	0.850
3.24	Superior fronto-occipital fasciculus	0.224	0.002	0.093	0.063
3.25	Corticospinal tract	0.010	0.889	0.014	0.480
3.26	Superior longitudinal fasciculus	0.007	0.670	0.000	0.960
3.27	Uncinate fasciculus	0.007	0.607	0.008	0.596

JHU, Johns Hopkins University; ROI, region of interest; TETRAS, Tremor Research Group Essential Tremor Rating Assessment Scale; WMH, white matter hyperintensity; CI, capsula interna; Significant values are marked in bold.

correction, none of the ROI significantly predicted the tremor measures.

DISCUSSION

In this study, the total and tract-specific amounts of WMHs were studied in a large sample of elderly ET patients between 60 and 84 years of age and age-matched healthy controls. While no group difference between ET patients and controls for total or ROI-based WMH load was found, there was a direct correlation between WMH load and tremor severity. Moreover, a multiple linear regression model showed that only the WMH load significantly predicted tremor severity and frequency, while age and disease duration had no significant effect.

Our study for the first time found evidence for a direct association between WMH and tremor severity. Within our sample of elderly ET patients, age *per se* was not directly associated with tremor severity, but the WMH load was. Our data suggest that WMHs contribute to the variability of tremor severity in the elderly and that WMH could be one factor among others mediating the relationship between biological aging and worsening of ET. Interestingly, we found no group differences between early-onset and late-onset ET patients and healthy controls regarding total or ROI-specific WMH volumes after age correction. This would imply that differences of WMH are not a relevant factor for the development of ET, no matter if earlier or later tremor onset. However, in patients with ET, the presence of WMH may impact the tremor severity.

DTI studies have shown widespread white matter microstructural alterations localized to cerebellar peduncles and pontine tracts as well as corticospinal tract and thalamo-cortical visual pathways in ET patients compared with healthy controls or patients with Parkinson's disease tremor (37–40). These studies differ methodologically from our study, since they examined DTI measures, while we quantified FLAIR hyperintensities and located them to certain fiber tracts. It is unclear if lesions localized on these specific tracts that were found abnormal in ET patients compared with healthy controls or patients with PD

tremor are responsible for the association with tremor severity. Therefore, we chose an assumption-free ROI-based analysis using the JHU tracts and JHU labels atlases, but we were not able to localize strategic white matter tracts after adjusting for the total WMH volume. Therefore, pathophysiological conclusions from our findings remain limited.

To interpret these results appropriately, the relation of the physiological features of tremor frequency and amplitude and the morphological features of WMHs and brain lesions have to be considered: For ET, several studies have shown that aging is associated with an increase of tremor amplitude and a decrease of tremor frequency, independent of disease duration (8–10), but the underlying mechanism for this is not clear. Elble (8, 9) proposed that biological aging influences the symptom progression of ET by causing a gradual reduction in tremor frequency, which secondarily increases the amplitude of tremor. Tremor amplitude, frequency, and motor unit entrainment are logarithmically related to each other, and frequency and motor unit entrainment make comparable and independent contributions to tremor amplitude (41).

It is well-documented that strategic lesions can produce different kinds of tremors (42). Lesions within the cerebellum and particularly the upper cerebellar peduncle may cause intention-tremor syndromes (43–45). Midbrain lesions near the rubral and subthalamic nucleus have long been described to produce specific rest and intention tremors as documented by Benedikt (46) and Holmes (47). Thalamic lesions may produce similar tremors (48), although they are mostly accompanied by dystonic or other hyperkinetic symptoms. The tremor-producing effect of lesions is usually explained by destruction of motor centers being responsible for damping oscillations like the cerebellum or the pallidum (3, 49). On the other hand, brain lesions can abruptly stop tremors. Lesions, particularly ischemic strokes in specific areas like the ventrolateral thalamus, can alleviate preexisting ET well-known from neurosurgical interventions (50). More generally, if such lesions occur along the pathway of the tremor network of ET (16, 51), the cerebello-thalamo-cortical projection or within the cortico-spinal tract, a preexisting tremor can be extinguished (52). The tremor reduction following lesions is assumed to result from destruction of pathways that mediate tremor excitations (53).

The mechanism underlying the tremor-modulating effect of WMH is likely to differ from these better established mechanisms and is mostly speculative: WMHs correspond pathologically to areas of demyelination and gliosis (18). Axonal demyelination causes a decrease in nerve conduction velocity or even a total conduction block of action potentials. Partial conduction blocks are typically frequency related. While high-frequency impulses are not transmitted, low-frequency impulses may still reliably pass through (54). Essential tremor in elderly patients is characterized by low-frequency tremor (8). This low frequency leads to an elevated tremor amplitude, which causes the functional impairment. Increased WMH load reflects locally distributed demyelination and gliosis (18), and it is conceivable that this leads to an abnormal processing of high-frequency impulses. The result would be a decrease of tremor frequency and increase of tremor amplitude and functional impairment. Thus, WMHs might directly modulate centrally generated tremor frequencies. Of course, this explanation remains speculative and requires further investigations.

The limitations of our study are that no longitudinal data have been recorded to support the potentially causative relation between WMH and tremor severity. Apart from disease duration, age, and WMH, several other factors that have not been identified yet might potentially affect tremor severity in the elderly and these might not be captured by our regression models. Disease duration was calculated retrospectively from the patient-reported age at symptom onset, but this information typically does not mirror the "real" disease onset because many patients do not recognize their condition when it is mild (55). We included ET patients with and without additional neurological signs of uncertain significance (ET plus), and subgroups of ET patients were carefully compared with each other regarding total or ROI-specific WMH volumes. But since we found no group differences, all ET patients were pooled for further analyses to increase statistical power. So far, it is not clear if certain ET plus subtypes differ from ET patients regarding total or regional WMH load, and our study is not powered to finally answer this question. Therefore, future studies should explore brain structural differences in larger subgroups of ET patients. Our patient and control groups differed in their MoCA scores, even after correction for age and school education. These findings are in line with the literature, since several clinical and epidemiological studies have shown poorer cognitive performance in ET patients compared with healthy controls and additionally, an increased risk to develop dementia (12, 56–58). A concerning limitation is that we cannot reproduce the previous finding of a higher WMH load in patients compared to controls. (22). A possible explanation is the smaller sample size in our study. *Vice versa*, the previous study (22) did not report the tremor amplitude/WMH relation, which was not part of their protocol and the diagnosis of ET was established on handwriting samples. Apart from the clinical tremor assessment (TETRAS), we performed a polygraphic tremor analysis, since we aimed for an electrophysiologic outcome parameter as well. Interestingly, tremor frequency seemed to more adequately reflect tremor severity, since TETRAS scores and frequency measures were significantly negatively correlated in our patients. Therefore, we chose to consider tremor frequency instead of accelerometric total power as an electrophysiological parameter additionally to the TETRAS score. Finally, we were not able to localize the clinical effect of WMH on tremor characteristics to a strategic white matter tract of the JHU atlas. Most possibly this is due to the small sample size. Lesion–symptom studies on WMHs typically require hundreds of individuals (59).

We conclude that total or ROI-specific WMHs are not differing between ET patients and controls, but we have a relatively robust relation between tremor severity and the WMH load. Our data provide the first evidence for a worsening of ET in the presence of WMHs in the elderly. The WMH load might be one factor among others mediating the tremor severity in (disposed) elderly ET patients, and this could at least partly explain the well-established relation between aging and increase

of tremor severity. However, these findings need to be confirmed in larger studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Christian Albrechts University Kiel. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GD, DB, KZ, and JSB designed the study. JSB, JB, UJ-K, and SW organized and executed the study. JSB, OG, and IT performed analysis and interpreted the results. JSB and JB wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.694286/full#supplementary-material

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Pathophysiology of Cerebellar Tremor: The Forward Model-Related Tremor and the Inferior Olive Oscillation-Related Tremor

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Lesions in the Guillain–Mollaret (G–M) triangle frequently cause various types of tremors or tremor-like movements. Nevertheless, we know relatively little about their generation mechanisms. The deep cerebellar nuclei (DCN), which is a primary node of the triangle, has 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 inhibitory path contributes to the dentato-olivo-cerebellar loop (the short loop), while the excitatory path contributes to the cerebrocerebellar loop (the long loop). We propose a novel hypothesis: each loop contributes to physiologically distinct type of tremors or tremor-like movements. One type of irregular tremor-like movement is caused by a lesion in the cerebrocerebellar loop, which includes the primary path. A lesion in this loop affects the cerebellar forward model and deteriorates its accuracy of prediction and compensation of the feedback delay, resulting in irregular instability of voluntary motor control, i.e., cerebellar ataxia (CA). Therefore, this type of tremor, such as kinetic tremor, is usually associated with other symptoms of CA such as dysmetria. We call this type of tremor forward model-related tremor. The second type of regular tremor appears to be correlated with synchronized oscillation of IO neurons due, at least in animal models, to reduced degrees of freedom in IO activities. The regular burst activity of IO neurons is precisely transmitted along the cerebellocerebral path to the motor cortex before inducing rhythmical reciprocal activities of agonists and antagonists, i.e., tremor. We call this type of tremor IO-oscillation-related tremor. Although this type of regular tremor does not necessarily accompany ataxia, the aberrant IO activities (i.e., aberrant CS activities) may induce secondary maladaptation of cerebellar forward models through aberrant patterns of long-term depression (LTD) and/or long-term potentiation (LTP) of the cerebellar circuitry. Although our hypothesis does not cover all tremors or tremor-like movement disorders, our approach integrates the latest theories of cerebellar physiology and provides explanations how various lesions in or around the G–M triangle results in tremors or tremor-like movements. We propose that tremor results from errors in predictions carried out by the cerebellar circuitry.

Keywords: tremor, cerebellum, Guillain–Mollaret triangle, predictions, forward model

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INTRODUCTION

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 (1).

Deep cerebellar nuclei 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 inhibitory path contributes to the dentato-olivo-cerebellar loop (we call it the short loop), while the excitatory path contributes to the cerebrocerebellar loop (we call it the long loop).

We propose a hypothesis according to which each loop contributes to physiologically distinct type of tremors or tremor-like movements. One type of irregular tremor-like movement is caused by a lesion in the cerebrocerebellar loop, which includes the primary path. The second type of regular tremor is correlated with synchronized oscillation of IO neurons due to reduced degrees of freedom in IO activities.

SECTION I. PHENOMENOLOGY OF CEREBELLAR TREMORS

Cerebellar tremors include diverse phenotypes (2). However, Louis (3) pointed out that, nowadays, "cerebellar tremor is equated exclusively with intention tremor" in an "oversimplified manner" (4). Besides, pathomechanisms underlying essential tremor (ET) have been a focus of debate (2), and thereby roles of IO have likely been overstressed in tremor pathogenesis (5). Due to such a simplification, seminal works by Gordon Holmes appear to be underestimated. This section aims to provide a brief overview of the historical backgrounds and phenomenology of cerebellar tremors.

Kinetic Tremor and Static Tremor in Holmes' Classic Study

Studies of human cerebellar tremors originate from Holmes' works who carefully examined tremor phenomenology in patients with spatially confined lesions in the cerebellum and described two types of tremors, namely, kinetic tremor and static tremor, in the Croonian lectures given in June 1922 (**Table 1**). Their clinical phenotypes appear different from those we imagine now from the terminology of kinetic or static. Thus, we cite his original descriptions to elucidate their phenomenology (6, 7). One can read his classic papers in an article of *Cerebellar Classic* (8). It should be acknowledged that these two types of tremors occur concomitantly with deterioration of coordination.

Kinetic Tremor in Holmes' Classic Study

Holmes described the tremor during active movement (attempts to bring finger from nose to three points in succession or attempts to touch a series of points alternatively) as follows: "At the commencement of the movement the finger or toe may sway from side to side, or the movement may be broken and jerky, especially when performed slowly (**Table 1**) (1). There is little irregularity as a rule during its course, but in slow and deliberate movements the rate is irregular or discontinuous, or the finger may swing in any plane from the correct line [page 151 in a reference of Cerebellar Classic (8)]." In addition to the irregular and discontinuous sways, he emphasized the association of two additional features. First, terminal tremor (irregular terminal jerks) occurs, associated with hypermetric and hypometric, for example, "in the former case the finger that has shot past its mark is brought back too far and sways or oscillates about its aim until it touches it; in the latter the limb which is arrested before it has reached it is advanced by a series of irregular jerks" (page 151). Second, continuous sways occur at the target. He described that "Even when the finger comes in contact with the patient's nose or other object it may continue to sway from side to side or in the direction of previous movement owing to inability to maintain the attitude steadily" (page 151).

Notably, this kinetic tremor "was less prominent" in most of his cases with local lesions of the cerebellum than in patients with "the primary atrophies (**Table 1**) (2)." In other words, this type of tremor is prominent in degenerative cerebellar ataxia (CA), suggesting that its developments might be dependent on cerebellar residual functions. Indeed, Holmes hypothesized kinetic tremor, or tremor during active movement, as follows: tremor "naturally results from the irregularities in the rate of muscle contractions, but errors in the range and direction of movement, necessitating correction, are also factors."

Static Tremor in Holmes' Classic Study

Holmes described two types of static tremor.

The first subtype has irregular nature (**Table 1**) (3). Holmes observed this tremor when his patients extended both upper limbs. He described that "Its oscillations are mostly in the line of gravity, and can be seen on careful inspection to be due to a failure in the tonic contractions of the muscles that maintain the attitude, with the result that the limb falls with gravity and is replaced by voluntary efforts" (page 146). It should be noted that the maintenance of the attitude is a highly voluntary process.

The other subtype is characterized by regular oscillations (**Table 1**) (4). Holmes described conditions in which this tremor preferably occurs: "Another type of tremor, characterized by more regular oscillations of a limb or some of its segments, occurs when the patient attempts to maintain the limb accurately in certain positions, or in postures necessary for the performance of some act" (page 146). Moreover, "It is usually only in attitudes determined by the tonic contractions of opposing groups of muscles that this *regular* form of tremor develops" (page 146). The lesions of the regular static tremor were ascribed to "the superior peduncles" and "mid-brain lesions that involve these peduncles."

In summary, the latter type of regular static tremor appears to occur during co-contraction of agonist and antagonist muscles, while the former type of irregular static tremor appears to occur during reciprocal muscle activities for feedback control.

After Holmes

For instance, in the "Handbook of Clinical Neurology" published in 1969, Garcin attributed features of kinetic tremor and irregular

TABLE 1 | Clinical features of various forms of tremors described by Holmes: summary of Holmes' Croonian lectures given in June 1922.

	Holmes' description	Static/ kinetic	Regularity	Target oriented	Reciprocal muscle activities	Contribution of visual feedback	Special features
(1)	Kinetic tremor during motion	Kinetic	Irregular (especially during slow movement)	Yes	Not typical	Yes	Prominent when superior peduncles are damaged. Proximal > distal
(2)	Intention tremor	Kinetic	Irregular	Yes	?	Yes	Tremor associated with disseminated sclerosis. Less sharp than kinetic tremor.
(3)	Static tremor/Gravitational irregular tremor	Static/ postural	Irregular	?	No	Yes	Prominent in the extension of both upper limbs. Contribution of fatigue. Proximal joints.
(4)	Static (postural)/Regular oscillatory tremor with reciprocal activities of agonists and antagonists	Static/ postural	Regular	Yes	Yes	Yes	Prominent in precise maintenance of the limbs accurately in certain positions. "Terminal tremor"-like tremor. PD rest tremor-like tremor. Easily induced in co-contraction of agonist/antagonist.

static tremor in Holmes' classic study to "disturbed continuity of movement" (9). In this regard, he described more clearly features of irregular static tremor as follows: "the static effort of maintaining posture in fact produces tremors to the same extent as does movement," and "The tremor is more marked when more motor segments are involved, and this explains the difficulty of maintaining immobility in standing or in keeping the arms widely extended" (page 327). He stressed that irregular static tremor is mostly observed in the initial static phase. For example, he described that "at the moment when a hand grasps the glass: when the first clumsy movement is over there may be a few oscillations of pronation and supination occurs, but the patient can grasp the glass without jerking." This classification of cerebellar tremor by Holmes appears to be used until the 1970s. However, distinction of these two types of tremors are getting rarer in recent textbooks and review articles (2).

Intention Tremor

Intention tremor was first described by Jean-Martin Charcot. In a well-documented lecture on multiple sclerosis (MS) delivered in 1868, he described the presence of CA in patients with MS, now known as the Charcot's triad (intention tremor, scanning speech, and nystagmus) (10).

A consensus statement of the Movement Disorder Society characterizes features of intention tremor as "amplitude increases during visually guided movements toward a target at the termination of the movement" (11) or "a crescendo increase in tremor occurs as the affected body part approaches its visual target" (12). Furthermore, intention tremor is exaggerated in a visually guided target pursuit task but diminished in a memory-guided task (11, 13). In order to emphasize these pathophysiological features, a term of tremor during target-directed movements has been utilized. Thus, intention tremor can be observed in the finger-to-nose maneuver, which requires precise feedback control. Its frequency is mainly <5 Hz, and "the possibility of a position-specific tremor or a postural tremor produced at the beginning or end of a movement is excluded" (11). Rest tremor is commonly not identified (14). There is a consensus that that intention tremor is caused by a lesion in the cerebellothalamic pathway (12, 14, 15). The lesions are usually in the brainstem in the vicinity of the RN (16) or the posterior thalamus (17, 18). Therefore, another term of cerebellar outflow tremor has also been introduced to stress the neural structure for the genesis of intention tremor (19). In contrast, focal lesions in the cerebellar cortex alone usually do not cause this tremor (20).

In Holmes' classic papers, he described both of his kinetic tremor and regular static tremor occurred in patients with lesions in the superior cerebellar peduncles, suggesting that intention tremor has common features with these Holmes' tremors. Notably, there is a description that "In the tremor that is a prominent feature when the superior peduncles are damaged, the deviations are more abrupt and are terminated more suddenly" (page 151).

Late-Onset Cerebellar Tremors: "Holmes' Tremor" and Palatal Tremor

The onset of cerebellar tremor after a stroke is diverse, ranging from the day of a stroke to a few years later (14). The above kinetic and static tremors in Holmes' classic study and intention tremor seem to be present in the acute phase. However, the two types of cerebellar tremors also occur characteristically with some

delay after the onset of pathologies (21): "Holmes' tremor" and palatal tremor.

"Holmes' Tremor"

"Holmes' tremor," as a modern term, is a rare tremor characterized by the following three features: (1) a concomitant expression of rest tremor and intention tremor, involving the proximal and distal part of the upper limbs with large amplitudes, usually associated with postural tremor; (2) slow frequency, usually <4.5 Hz; and (4) in a case when the preceding lesion (e.g., strokes) is identified, a variable delay (usually 4 weeks−2 years) (11, 14). This unique tremor was previously labeled under rubral tremor or midbrain tremor. However, this tremor is also induced by lesions outside these classic locations. For example, one study of three patients with "Holmes' tremor" following stroke showed that the lesions were located in the superior cerebellar peduncle, midbrain tegmentum, and posterior thalamus (22). To avoid topographic names, therefore, "Holmes' tremor" is now used in honor of his first description (11). Holmes' tremor is frequently accompanied by hypertrophy of the inferior olive nucleus (ION) (23).

Palatal Tremor

Palatal tremor is characterized by slow, rhythmic movements of the soft palate (usually, at a frequency of 1–3 Hz) and sometimes of other muscles in the pharynx, larynx, lower face, and trunk (24, 25). Palatal tremor comprises idiopathic and symptomatic types. The causes of symptomatic palatal tremor include stroke, trauma, MS, Behçet's disease, and encephalitis (24), and the most common causes are strokes in the brainstem and the cerebellum (24). The symptomatic palatal tremor usually develops some time (1–49 weeks) after the lesion onset (26), which is associated with cerebellar symptoms (25) and hypertrophy of ION (24, 25).

Taken together, the late-onset nature and the associated ION hypertrophy suggest underlying secondary and compensatory pathological mechanisms in "Holmes' tremor" and palatal tremor (21). The hypertrophy of ION is usually observed as a high signal on T2- or proton density-weighted MR image with the enlargement (24, 25).

Essential Tremor

According to a consensus statement of the Movement Disorder Society, ET is defined by bilateral, largely symmetric postural, or kinetic tremor, at the frequency of 4–12 Hz, involving hands and forearm, with or without head tremor and tremor in other locations (11, 12). The primary clinical phenotype is the postural tremor of the hands (11). The tremor generally persists, although the amplitude fluctuates (11). The tremor may or may not produce disability (11); however, ET is progressive in nature (27). Concomitant manifestation of intention tremor and rest tremor is observed in 50 and 20% of the patients, respectively (27). Due to the heterogeneity, it is proposed that ET comprises a family of diseases rather than a single entity (27). In other words, ET is overlapping clinical phenotypes.

In the 2018 statement, the notion of ET plus was introduced to include patients with neurological signs of uncertain relationship to tremor (i.e., "soft neurological signs"). Notably, soft neurological signs include cerebellar symptoms such as a mild degree of ataxic gait, oculomotor deficits, and impaired motor timing (27). Due to the clinical heterogeneity, Louis et al. (28) proposed that ET may represent a family of diseases rather than a single clinical–pathological entity (28). Our current understanding of the mechanisms behind ET has evolved quickly, thanks to the works of Louis' group with the elucidation that cerebellar cortex shows abnormal features in postmortem material (29). These authors have shown abnormalities in Purkinje cells (PCs: axonal swellings, swellings in and regression of the PC dendritic arbor, and PC death), basket cells, and climbing fibers in individuals with ET.

In conclusion, cerebellar tremors gather various phenotypes (**Table 2**). Two clinical features will be summarized:

1. Tremor is generally defined as the "involuntary, rhythmic, oscillatory movement of a body part" (11, 12). However, the irregularity in cycle and amplitude is evident in kinetic tremor and irregular static tremor in Holmes' classic study, and sometimes in intention tremor, compared with other types of cerebellar tremors.
2. In the condition of "Holmes' tremor" and ET, plural pathophysiological mechanisms appear to contribute to their phenotypes of tremor either concomitantly or with the lapse of time.

From physiological and control engineering points of view, difference in regularity and voluntariness strongly suggests contribution of distinct control mechanisms. In addition, difference in onset also suggests distinct pathomechanisms to be factored in. Overall, the three factors, i.e., regularity, voluntariness, and onset, may be key clues for understanding pathophysiology of diverse cerebellar tremors. We will address this issue in section Physiological Backgrounds of Two Types of Cerebellar Tremors.

SECTION II. PHYSIOLOGICAL BACKGROUNDS OF TWO TYPES OF CEREBELLAR TREMORS

In the previous section, we traced the historical backgrounds and phenomenology of cerebellar tremors as far back as the original descriptions by Holmes (6, 7). We realized that various phenotypes of "cerebellar tremors" may contain two distinct conditions: involuntary regular tremors and voluntary irregular tremors (or more precisely, tremor-like movements), and each condition may be related to distinct pathology of distinct neuron circuitries. In this section, we will address the two tremor generation mechanisms based on recent physiological, morphological, and clinical findings.

Two Loop Circuitries in the Dentato-Rubro-Olivary (Guillain–Mollaret) Triangle and Their Functions

It has long been established that patients with lesions in or in the vicinity of the G–M triangle (**Figure 1**) frequently show various types of tremors or tremor-like movements (14). Previous studies

TABLE 2 | Phenotypes in cerebellar tremors.

Type of cerebellar tremor	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 1: 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 during visually guided movements toward a target at the movement termination	The dentato-rubro-thalamic tract
"Holmes' tremor"	• Concomitant expression of rest tremor* and intention tremor with/without postural tremor* • Slow frequency, usually <4.5 Hz • Late onset of pathologies	Superior peduncle, midbrain tegmentum, and posterior thalamus
Palatal tremor	• Rhythmic movements of the soft palate • Late onset of pathologies	The brainstem and the cerebellum
Essential tremor	• Bilateral, largely symmetric postural tremor or kinetic tremor* • Involving hands and forearm, with or without head tremor and tremor in other locations	Cerebellar cortex

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 completely supported against gravity.
**Definition by Consensus Statement of the Movement Disorder Society on Tremor (11).*

established that the G–M triangle contains two distinct loop circuitries: (1) the dentato-olivo-cerebellar loop (we call it *the short loop*, **Figure 1**) and (2) the cerebrocerebellar loop (we call it *the long loop*, **Figure 1**).

Anatomy of the Long Loop

The long loop is almost identical to the cerebrocerebellar loop (30–32). Larger excitatory dentate nucleus (DN) cells, after passing through SCP (**Figure 1**, sp) and crossing the midline, project to the contralateral RNp and the thalamus (**Figure 1**, Th) with collaterals. Thalamocortical neurons relays the cerebellar inputs to various cortical areas (**Figure 1**, Cx). The return path to the cerebellum is the cortico-ponto-cerebellar tract, which originates from various parts of the cerebral cortex (30–32). The corticofugal axons project directly to the pontine nuclei (PN, **Figure 1**, P) and finally arrive at the contralateral cerebellar hemisphere (**Figure 1**, Cbl-h) as mossy fibers (MFs) via the middle cerebellar peduncle (**Figure 1**, mp) to close the loop (30, 31).

Physiological Operation of the Short Loop

The DN contains two distinct types of neurons. Larger excitatory neurons project to the parvocellular part of the red nucleus (RNp) and the thalamus (Th), while smaller inhibitory (GABAergic) neurons project directly to the IO to inhibit IO neurons (33). The GABAergic terminals in IO are concentrated around gap junctions between the IO neurons (34) and reduces their conductance, thereby reducing synchronous activities of the IO neurons (35). On the other hand, IO neurons also receive excitatory inputs from PNp (35–37). The excitatory terminals are concentrated around the gap junctions and are presumed to facilitate synchronous activities of the IO neurons (34, 35). In summary, the IO neurons receive two distinct types of inputs; one facilitates, and the other suppresses synchronous activities of IO neurons.

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

In physiological conditions, the inhibitory input from DN and the excitatory input from RNp to the gap junctions between the IO neurons appear to be balanced. For instance, when DN cells get more active, the direct inhibition from DN to IO increases, while the disynaptic excitatory input from RNp to IO 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 from RNp to IO decreases concomitantly. In summary, regardless of the alteration of output from DN, modulations of inhibitory and excitatory inputs to IO appear to cancel each other. Overall, the synchrony between IO neurons appears to be limited within a certain range in physiological conditions with this servo-like mechanism.

Physiological Operation of the Long Loop: the Cerebrocerebellum as a Site of Forward Models

One critical problem in biological motor control is that afferent sensory signals have inevitable temporal delays in reaching the central nervous system. In other words, the brain always observes "the past" of its own body and environments. A visual signal, for instance, arrive at the primary visual cortex about 30 ms later and at the parietal cortex about 80 ms later than an onset of the signal (38). Among the factors contributing to the feedback delay, such as a synaptic delay or an electro-mechanical delay, the dominant factor is the nerve conduction delay, ranging about 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.

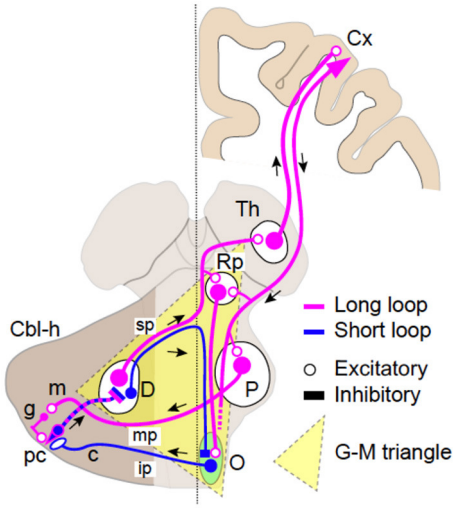

FIGURE 1 | Schematics of the two loop circuits in the Guillain–Mollaret triangle. The dentato-olivo-cerebellar loop (short loop, blue) and the cerebrocerebellar loop (long loop, magenta). Smaller GABAergic (inhibitory) cells in the dentate nucleus (D) pass through the superior cerebellar peduncle (SCP) (sp), cross the midline, and project directly to the contralateral inferior olivary nucleus (O). Efferent fibers from IO pass through the inferior cerebellar peduncle (ip) and project to Purkinje cells (PC, pc) in the contralateral cerebellar hemisphere (Cbl-h). PCs then project to DN cells to close the loop. The long loop is almost identical to the cerebrocerebellar loop. Larger excitatory DN cells pass through (SCP, sp), cross the midline, and project to the contralateral parvocellular red nucleus (RNp), and the thalamus (Th) with collaterals. Thalamocortical neurons relay the cerebellar inputs to various cortical areas (Cx). The return path to the cerebellum is the cortico-ponto-cerebellar tract, which originates from a various parts of the cerebral cortex. The corticofugal axons project directly to the PN (P) and finally arrive at the contralateral cerebellar hemisphere (Cbl-h) as mossy fibers (MFs) via the middle cerebellar peduncle (mp) to close the loop.

The delay in sensory feedback is problematic not only in sensing the body and the environments but also in controlling the body. It is well known in control engineering that feedback control based on a previous state causes oscillatory and unstable movements if the delay in feedback control is of the order of or larger than a time constant of a controlled plant (39). 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 of saccadic eye movements (typically <50 ms). Therefore, in biological motor control, feedback control based on delayed sensory signals would result in unstable movements. Nonetheless, animals can perform a fast movement without losing its stability. Biological motor control must be equipped with a mechanism to compensate 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 (40, 41). 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 internal forward model is called internal feedback. There are lines of evidence supporting the hypothesis of predictive forward model and internal feedback from neuroimaging studies (42, 43), non-invasive stimulation studies (44, 45), and psychophysics studies (46–48) 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., (39, 49–52)]. A forward model requires two distinct inputs: (a) a set of sensory feedback signals, which are necessary to update the forward model and (b) the copy of descending motor commands. The two inputs are integrated in the forward model to generate the state estimate. In fact, the cerebellum receives both of these inputs. It receives inputs from cortical motor areas via the PN (53, 54), and these inputs represent the efference copy of descending motor commands (55–57). 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. However, 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 (58), 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., (59)] of the cerebellar cortex. Therefore, one may expect a convergence of the two MF inputs only in a minor part of the intermediate zone. Unfortunately, the simple summation of the two MF inputs is not consistent with their asymmetric roles in the forward model. The efference copy plays an essential role in a state prediction, while the sensory input plays a critical role in an update of 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 (39). In principle, we should examine the output from the cerebrocerebellum in the DN because it is the sole output node from the cerebrocerebellum. Nevertheless, previous studies tried to address this issue by analyzing the PC activities. Note that the PCs' activity represents an intermediate representation of the cerebellar circuitry and is not suitable for characterizing the output of a forward model. In this regard, few studies are eligible to discuss the output of the cerebellar forward models (60–62).

System Identification of the Transformation in the Cerebrocerebellum—Its Similarity to 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 (63, 64), we examined the relationship between activities of MFs (cerebellar inputs), PCs (intermediate representation), and DNCs (cerebellar outputs) (**Figure 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 DNCs were reconstructed strictly as a weighted sum of those of PCs and MFs. We further proved that the activities of DNCs contained predictive information about future MF inputs (63, 64). Namely, the output from the cerebrocerebellum is capable of predicting 200 ms into the future to compensate for the delay of sensory feedback. We finally note that the linear relationship between MF, PC, and DNC activities resemble an optimal linear estimator known as the Kalman filter [(63–65)].

The functional similarity of the cerebellum to the Kalman filter has already been suggested in some previous studies. Most notably, Paulin (66, 67) indicated that the cerebellum could be a neural analog of a Kalman filter. Droulez and Cornílleau-Pérèz (68) drew attention to the relevance of multisensory integration in the moving organism to the Kalman filter. Nevertheless, the suggested analogy was only at the functional level and totally lacked correspondence to the cerebellar network. In our study, we demonstrated the three computational steps in the cerebellar circuit that are compatible with the Kalman filter (63, 64) (**Figure 2**): (1) the PCs compute a predictive state from a current estimate conveyed by the MFs (prediction step); (2) the DNCs combine the predicted state from the PCs and sensory feedback from the MFs (Filtering step); and (4) the DNCs represent future activities of MFs (cerebellar prediction).

Overall, 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 Kalman filter as demonstrated in Tanaka et al. (63, 64) (**Figure 2**).

Interaction Between the Two Loops

It should be noted that the two loops are not independent to each other as clearly depicted in **Figure 1**. First, they share the same PCs in the hemispheric part of the cerebellar cortex. Second, the long loop has a side path to modulate activities of IO cells through RNp. Therefore, the two loops are interactive and dependent to each other. An unstable loop may therefore impact on the physiological behavior of the second loop. Abnormal discharges may emerge from altered PCs (see the example of ET), and this will impact on both loops.

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 has a neural mechanism to avoid synchronous discharges of IO neurons, while the long loop has evolved to function as a forward model to avoid instability of control. Nevertheless, in pathological conditions, each safety mechanism fails, resulting in the generation of a characteristic type of tremor.

Failure of the Short Loop Results in Regular Oscillatory Tremors

As reviewed in section Phenomenology of cerebellar tremors, the modern definition of the term "tremor" is "the involuntary, rhythmic, oscillatory movement of a body part" (11, 12). Naturally, a number of previous studies, both basic and clinical, addressed the location of the oscillator. There is a consensus that IO plays an essential role in the generation of the regular tremors (35, 70, 71). For instance, harmaline-induced tremor in rodents has been extensively used as an animal model for ET. Cheng et al. (72) made a subcutaneous injection of harmaline hydrochloride (20 mg/kg) in mice and then videotaped the responses. Regular action and postural tremors in the mouse began no more than 5 min after harmaline injection and peaked at approximately 30 min. The forelimb tremor was postural or action tremor, similar to that observed in ET. In these model animals, a large population of IO neurons appear to discharge in synchrony and rhythmically (73–75), thereby inducing synchronized complex spikes (CSs) of Purkinje cells. Then, the synchronized CSs ignite synchronized rebound excitation of DN cells (71, 76), and the cerebellar output finally induces, through the thalamocortical pathway, rhythmical and reciprocal discharges of agonists and antagonists muscles, i.e., tremor. As described in *Physiological operation of the short loop*, there is a mechanism to avoid synchronous discharges of IO neurons in physiological conditions. Nevertheless, in pathological conditions and for specific posture and/or movement, IO neurons are somehow switched into a synchronization mode to induce rhythmical discharges, resulting in regular tremors. We infer that involuntary and regular tremors, such as static tremor described by Holmes (6, 7), rest tremor and postural tremor of "Holmes' tremor," and ET, are likely to depend on the same mechanism described above. We also infer that "Holmes' tremor" and palatal tremor depend on the same mechanism, although the efferent pathway of the palatal tremor appears to spare the Vim nucleus of the thalamus because Vim thalamotomy is ineffective to palatal tremor, while it is effective to "Holmes' tremor" (77).

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 section Phenomenology of Cerebellar Tremors) as noted by Holmes himself (6, 7). The irregularity in cycle and amplitude is crucial because it strongly suggests different generation mechanisms from that of the regular tremors described above. Moreover, it should be noted 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 malfunction of the cerebellar forward model.

In our previous study (69), we demonstrated a clinical evidence that supported the cerebellar forward model hypothesis [e.g., (44, 51)]. A series of studies from our group confirmed the impaired predictive control in movements of patients with degenerative 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), each of which represented the predictive control and the feedback correction, respectively (69). Then, for each component, we identified a recipe of muscle activities by analyzing a relationship

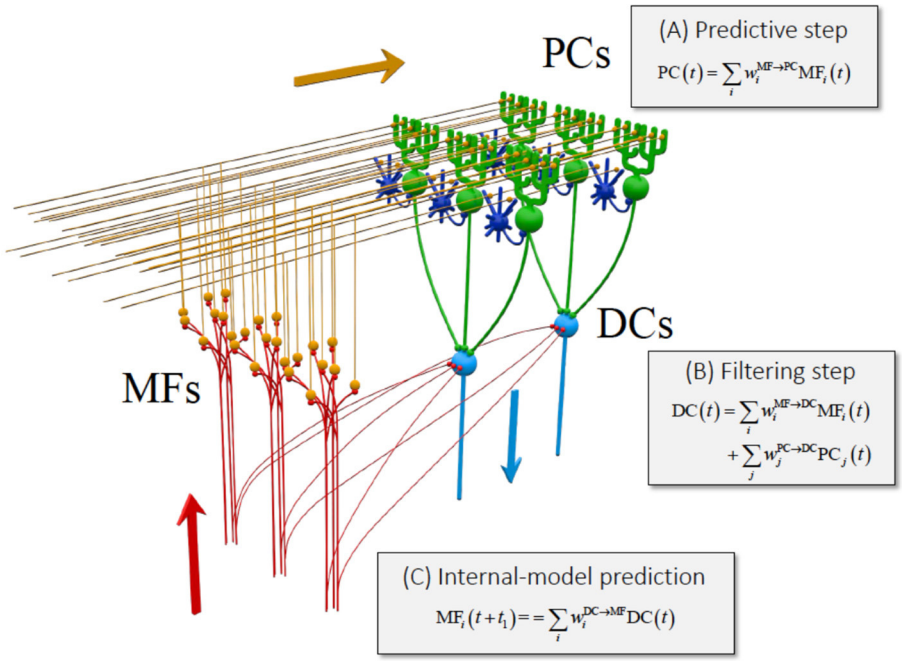

FIGURE 2 | Equivalence of the cerebrocerebellar circuitry to a Kalman filter [reproduced with permission from Tanaka et al. (63)]. Schematic of the Kalman filter model of the cerebrocerebellum overlaid on the cerebellar circuit. MF, mossy fiber (red); PC, Purkinje cell (green); DC, dentate cell (light 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 are accompanied with the three types of computation of Kalman filter explained in the text. Reproduced from Tanaka et al. (63) under CC-BY license.

between the muscle tension and movement kinematics [the wrist angle θ (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) (69, 78–80). Importantly, the ratio of B_r/K_r characterized the recipe of muscle activities for the predictive and corrective components. In control subjects, the B_r/K_r ratio for the predictive (F1) component demonstrated a higher value (**Figure 3A**), suggesting the velocity control dominance. On the other hand, the B_r/K_r ratio for the corrective (F2) component demonstrated a much smaller value (**Figure 3A**), suggesting the role of F2 component in correction of positional errors (69). In contrast, CAs showed a selective decrease in the B_r/K_r ratio for the predictive (F1) component (**Figure 3A**), suggesting poor recruitment of the predictive velocity control and compensatory dependence on the position-dependent pursuit (69). The loss of component-specific differences in the B_r/K_r ratio suggests impairment of predictive control in CA. Indeed, the decrease in B_r/K_r ratio in CA correlated with the increase in error in the predictive (F1) movement (**Figure 3B**) (69). Another critical difference between the control and CA was the increased delay of the predictive (F1) component in CA (**Figure 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 (i.e., a proof of prediction) (69). 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 lack of compensation of feedback delay in CA patients. In summary, ataxic movements are consistent with an impairment of a forward model in terms of accuracy and delay of state prediction. 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 uncertainty of each corrective (i.e., feedback) movement unreliable due to increased uncertainty of both current and future states. The residual errors trigger a chain of irregular corrective movements around the target trajectory (**Figure 3D**, CA wrist movement). Note that the chain of corrective movements (i.e., the tremor-like movement in **Figure 3D**) is voluntary in nature, although it must be far from what CA patients intended to do.

As demonstrated in **Figure 1**, the long loop 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 a complete disruption, malfunction of the forward model may be irreversible, and the resultant irregular tremor must be severe and persisting because the cerebellar reserve (81) is unavailable. In contrast, in case of a partial disruption, the initial irregular tremor may recover partially or completely 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 CA for many months (82, 83). When the lesion involved both DN and interpositus nuclei (IN), the monkeys revealed typical cerebellar symptoms, hypotonia, asthenia, awkwardness, dysmetria, and

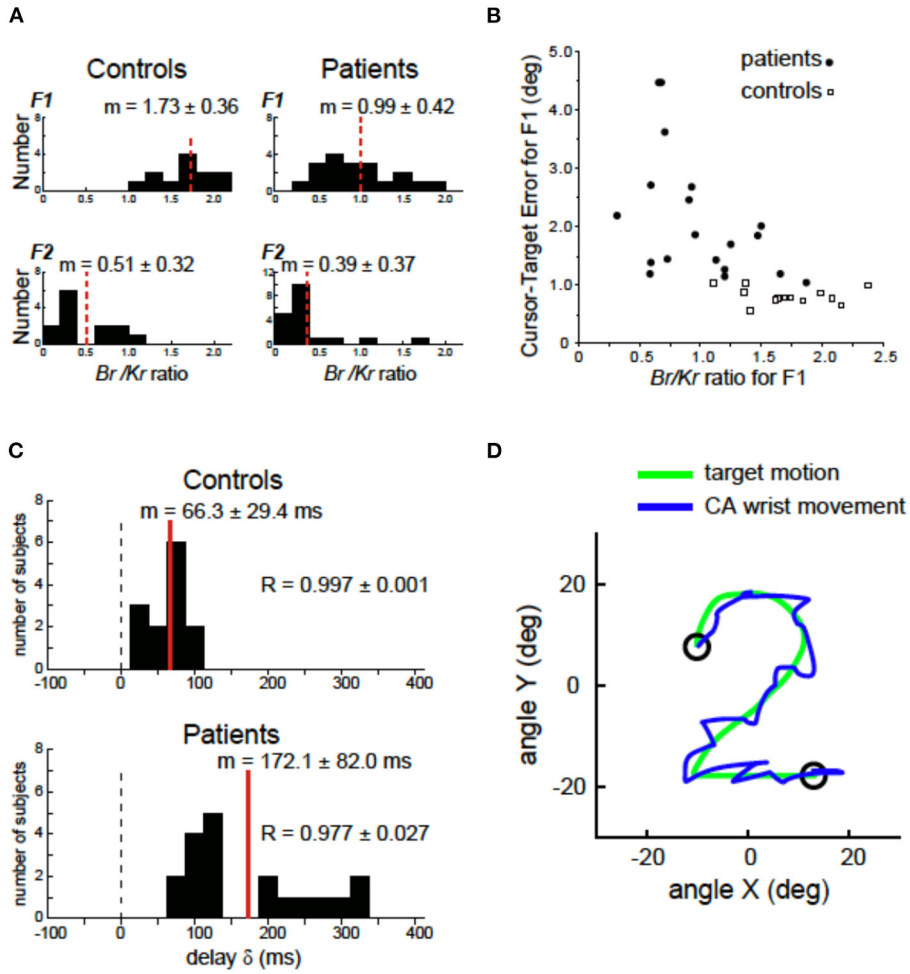

FIGURE 3 | Deficits of forward models in patients with cerebellar ataxia (CA). **(A)** Comparison of the Br/Kr ratios that represents recipe of the motor commands for the F1 and F2 components between the controls and the cerebellar patients. Controls: Br/Kr ratios of the control subjects for the F1 component (top) and the F2 component (bottom) ($n = 13$). Note the highly significant difference between the two components. Patients: Br/Kr ratios of the patients for the F1 (top) and the F2 (bottom) components ($n = 19$). Note the selective decrease in Br/Kr ratios for the F1 component in the patients. **(B)** Correlation between the Br/Kr ratios for F1 component and cursor–target error for F1 (F1 error, in short). The F1 error is defined as an average error between the target motion and the F1 component of the movement. Note the negative correlation. **(C)** Delay of the predictive (F1) component of the movement relative to the target motion calculated 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. (69) under CC-BY license.

kinetic and/or static tremor. These symptoms lasted for several months until the animals were sacrificed. 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 is damaged more severely in a lesion in the SCP than in a lesion in the cerebellar hemisphere. Thus, tremor in the former lesion (e.g., intention tremor) develops more irregular and abrupt natures compared with tremor in the latter lesion (e.g., kinetic tremor in Holmes' classic study). In this regard, 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.

Impairments in "G–M Triangle"

Disruptions of the Two Loops in the "G–M Triangle"

The G–M triangle includes vital parts of the long loop and the short loop. In particular, both loops are packed into the same bundle in SCP (**Figure 1**, sp). On the other hand, after crossing the midline, SCP is divided into the ascending branch and the descending branch (84). The ascending branch mainly contains thicker excitatory fibers from DN, while the descending branch mainly contains finer inhibitory fibers from DN (34). 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 branch or the descending branch may disrupt the long loop or the short loop separately.

For instance, a selective disruption of the long loop disorganizes the online operation of cerebellar forward model and leads to manifestation of irregular tremors, including kinetic tremor in Holmes' classic study and intention tremor, 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 neurons) shifts IO activities toward the synchronous mode like a local injection of bicuculine into IO (85) to cause regular tremors such as regular postural tremor in Holmes' classic study.

It has been a focus of debate why "Holmes' tremor" exhibits diverse types of tremors (i.e., rest, postural, and intention tremors) after a period of time. "Holmes' tremor" (midbrain tremor) was previously called cerebellar outflow tremor, whose causal lesions include SCP, midbrain tegmentum, or posterior thalamus. These foci are aligned on the dentato-thalamic (DN-Th) tract and are in or close to the G–M triangle (**Figure 1**). A lesion in the G–M triangle may well disrupt the two loops in a complicated manner, causing the diverse types of tremors (**Figure 4**).

Reorganization and Maladaptation in the G–M Triangle

Reorganization in the Short Loop

Emergence of regular rest or postural tremors in "Holmes' tremor" needs several weeks or longer (usually 4 weeks−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 neurons, i.e., reduction or disappearance of inhibitory terminals and concomitant sprouting of excitatory terminals (86, 87). However, this hypothesis does not exclude possibility of regular tremors during acute phases (14). For instance, the above-mentioned harmaline-induced tremor model clearly suggests the existence of a switch to ignite regular tremors without chronic reorganizations of neuron circuitries.

Induction of Maladaptation Caused by Regular Tremors

The regular tremor is accompanied by abnormal synchronized IO activities. The aberrant IO activities (i.e., aberrant CS activities) may induce secondary maladaptation of cerebellar forward models through aberrant patterns of LTD and/or LTP of the cerebellar circuitry (**Figure 4**, dashed arrow). The problem may be twofold. First, during a regular tremor, average CS activities (>4 Hz) are much higher than normal levels of CS activities (∼1 Hz). Therefore, CS activities are corrupted by increased noise (i.e., low S/N ratio) during regular tremors. Second, Hoang et al. (85) recently found that high coupling strengths of IO neurons induce their synchronous firing and decrease the amount of information encoded by firing dynamics of IO neurons. The two mechanisms may gradually deteriorate the forward model and increase its prediction error, resulting in irregular tremor. In this regard, it may be possible to explain the intention tremor of "Holmes' tremor" with this mechanism.

In conclusion, it is important to note that in "Holmes' tremor," or more generally tremors induced by lesions in the G–M triangle, disruptions of the two loops coexist and induce the regular and irregular types of tremors in various combinations depending on the location and size of the lesion. In addition, the complex pathological condition is further prone to secondary changes such as reorganization and maladaptation.

Consideration of Neuroimaging Studies

Our proposal of a dual pathogenesis will now require an in-depth multimodal assessment to establish how it can be translated into a 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 to assess the morphological and functional aspects in cerebellar tremor patients. Structural imaging by MRI provides insights for focal or diffuse anatomical lesions, complemented in particular by diffusion imaging (DTI), fMRI, and assessment of metabolic brain networks (88, 89). Diffusion tractography shows the neuronal connections in the brain and allows to draw conclusions in terms of deafferentation following a focal lesion such as a stroke and infer on remote effects of this connection.

One typical example was provided by Seidel et al. who reported the case of a 20-year-old patient with right-sided Holmes' tremor 9 months after a midbrain/pontine hemorrhage (90). Tractography demonstrated a reduced fiber connectivity of the superior and middle cerebellar peduncles on the lesioned side. The hemorrhage affected the RN directly and impacted on nigro-striatal projections and the cortico-rubro-cerebellar loop, underlining that tremor was probably due to a deafferentation mechanism (88). These findings are coincident with the present proposal of reorganizations in the short loop (see section Reorganization and Maladaptation in the G–M Triangle). 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 (91).

In ET, a functional disconnection of dentate nuclei with cortical, subcortical, and cerebellar areas has been demonstrated recently (92). Changes in the cerebellum positively correlated with tremor amplitude, in contrast with changes in the bilateral thalamus that 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 tremor genesis. These, from imaging studies, favor the present hypothesis that a pathological synchronization of IO neurons sparks a chain reaction in the cerebello-cerebral circuits (e.g., synchronous CS, rebound potentiation of DN neurons, and finally rhythmical activation of M1 through the cerebello-thalamo-cortical pathway) (see section Failure of the Short Loop Results in Regular Oscillatory Tremors). In the systematic literature search by Ceresa–Quattrone, who combined the terms ET 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 (93). The studies showed similar findings but without defining a clear topography of the neurodegenerative process. The majority

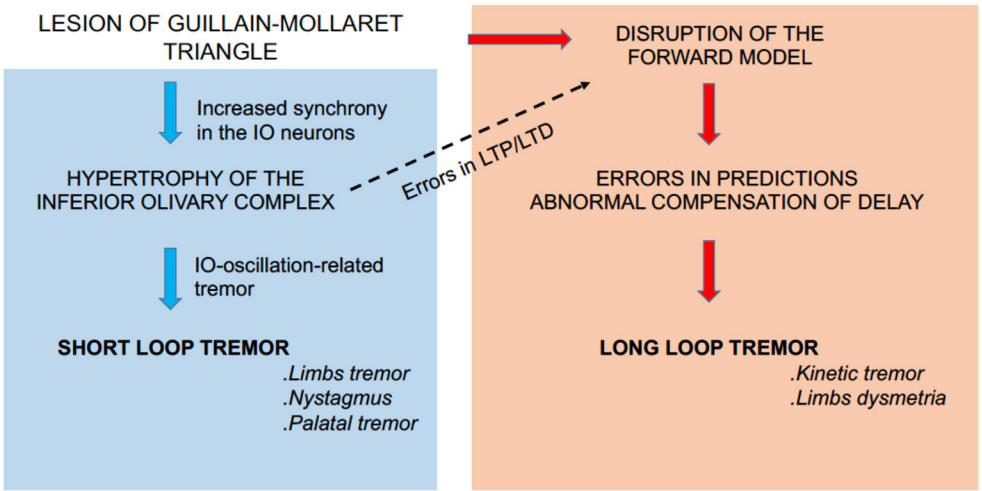

FIGURE 4 | Summary diagram. A lesion in the G–M triangle may well-disrupt the short loop (left panel) and the long loop (right panel) to cause the diverse types of tremors. In addition, the aberrant activities in the short loop (i.e., aberrant complex spike activities) may induce *secondary* maladaptation of cerebellar forward models through aberrant patterns of LTD and/or LTP of the cerebellar circuitry (dashed arrow).

of studies identified functional and structural abnormalities in several portions of the anterior and posterior cerebellar lobules, but 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 the central tegmental tract, the dentatorubrothalamic tract, the transaxonal degeneration, and Wallerian degeneration [see the recent work of Raeder et al. (94) focusing on imaging characteristics of transaxonal degenerations involving cerebellar connections].

CONCLUSION

We tried to explain complex phenotypes of tremors or tremor-like movements with two physiological principles related to the G–M triangle, pointing out the abnormal motor behavior on the basis of errors in feedforward and feedback loops. The G–M triangle appears in our view as an interface between sensory and motor processes. Tremor is viewed as 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 and provides explanations how various lesions in or around the G–M triangle results 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 reverberation (95). We did not speculate on the neurobiological mechanisms underlying the aberrant synaptogenesis in the G–M triangle (96).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Tremor Syndromes: An Updated Review

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Tremor is the most commonly encountered movement disorder in clinical practice. A wide range of pathologies may manifest with tremor either as a presenting or predominant symptom. Considering the marked etiological and phenomenological heterogeneity, it would be desirable to develop a classification of tremors that reflects their underlying pathophysiology. The tremor task force of the International Parkinson Disease and Movement Disorders Society has worked toward this goal and proposed a new classification system. This system has remained a prime topic of scientific communications on tremor in recent times. The new classification is based on two axes: 1. based on the clinical features, history, and tremor characteristics and 2. based on the etiology of tremor. In this article, we discuss the key aspects of the new classification, review various tremor syndromes, highlight some of the controversies in the field of tremor, and share the potential future perspectives.

Keywords: tremor, essential tremor plus, action tremor, rest tremor, dystonic tremor, neuropathic tremor, myorhythmia, orthostatic tremor

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INTRODUCTION

Tremor is an involuntary, rhythmic, and oscillatory movement which may involve one or several body parts (1, 2). After leg stereotypy syndrome (3), tremor is the most commonly observed movement disorder in adults (4, 5). Tremor can be an isolated manifestation of a disease such as essential tremor (ET) or it can be a part of other neurological disorders. The task force on tremor of the International Parkinson and Movement Disorders Society (IPMDS) proposed a classification scheme based on two axes; axis 1- emphasizing the clinical features, history, and tremor characteristics and axis 2- emphasizing the potential etiologies of tremor (1). One of the major aims was to redefine ET ("bilateral upper limb action tremor" of "at least 3 years' duration") and to introduce the concept of ET plus (ET with additional neurologic soft signs such as dystonia, ataxia, parkinsonism) (1). The publication engendered a great deal of controversy about the definition of ET and related syndromes. Since tremor has a vastly heterogeneous etiological spectrum, it is important to fully appreciate the phenomenology of tremor in various tremor syndromes and other neurological features associated with those syndromes.

The major objective of this article is to provide an updated review of various tremor syndromes with special reference to the new bi-axial classification system. We also highlight some of the controversies in the field of tremor, and share our perspectives for the future research.

METHODS

For this narrative review, the literature search in PubMed was done in January-April 2021. A broad search strategy was used with several keywords and combinations related to tremor ("Tremor," "Tremor syndrome," "Essential tremor," "Action tremor," "Rest tremor," "Intention tremor," "Postural tremor," "Kinetic tremor," "Isometric tremor," "Task-specific tremor," "Focal tremor," "Palatal tremor," "Tremor AND genetics," "Tremor AND etiology," "Tremor AND neurodegeneration," "Tremor AND Toxins," "Tremor AND Neuropathy." Titles and abstracts were reviewed and when appropriate from the standpoint of the theme of the current review topic, articles were shortlisted, reviewed in detail, and used for the references.

TYPES OF TREMOR BASED ON THE ACTIVATION PATTERN

Based on the activation pattern, tremor is broadly categorized into rest tremor or action tremor (**Figure 1**) (1). As evident from the name, action tremor manifests only during any activity. It is further divided into postural tremor, kinetic tremor, and isometric tremor. Postural tremor may occur in specific positions (position-dependent tremor) or may occur independently of any specific position (position-independent tremor). Kinetic tremor is further divided into simple kinetic tremor (non-specific to any activity), task-specific tremor (while doing a specific task-writing, playing musical instruments, etc), and intention tremor (while performing goal-directed activities such as finger-to-nose test). Isometric tremor occurs during sustained muscle contraction without any gross movement of the body part other than the tremor (**Table 1**).

These tremors have marked etiological heterogeneity and the tremor task force of IPMDS recommends searching for those etiologies as noted in the axis-2 classification (**Table 2**). The following discussion largely focuses on the key aspects of various axis-1 tremor syndromes and some of the common axis-2 nosologies that may present with tremor in the background of other neurological features.

OVERVIEW OF THE AXIS-I TREMOR SYNDROMES

Action and Rest Tremor

Essential Tremor and Essential Tremor Plus

One of the key proposals of the tremor task force was the introduction of a new definition of ET. Accordingly, 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 (1). This may or may not be associated with tremor involving the voice, head, and lower extremities. Previously, several neurological soft-signs such as tandem gait impairment, subtle dystonic posturing, and memory problems were considered to be in the clinical spectrum of ET. However, as per the new classification scheme, ET patients with any such neurological soft signs are now categorized as "ET plus." The validity of this nomenclature has remained a matter of debate in recent times and we have elaborated on this issue in the latter part of this article (6, 7).

There are no prevalence studies on this newly defined "ET" or "ET plus." However, according to the previous diagnostic criteria, ET was one of the commonly observed movement disorders among adults. Several movement disorder centers have reclassified their ET patients using the new diagnostic criteria and have reported that ET plus outnumbers the isolated (pure) ET patients after such re-classification (8–10). As mentioned above, one of the core features of ET is action tremor (kinetic > postural) of both upper extremities. Patients subsequently may develop vocal tremor, tongue tremor, head tremor, and lower extremity tremor. The usual frequency of the action tremor of the upper extremities in ET is 4–12 Hz. Postural tremor is conventionally examined by outstretching the hands in front of the body or with arms abducted at shoulders and flexed at elbows with hands held pronated in front of the chest ("wing-beating" position), whereas kinetic tremor is best evaluated during finger-nose-finger maneuver, by drawing spirals on a paper, or by pouring water between two cups (11). While the upper extremities in patients with ET have similar tremor frequencies (12), several studies, based on both objective (12) and subjective assessments (13), have reported that there may be asymmetry in tremor amplitude between the upper extremities. Although may not be universally present, alcohol responsiveness is one of the well-known characteristics of tremor in ET patients (14). While alcohol responsiveness and family history have been traditionally considered important features of ET, these were not included in the definition of ET according to the "consensus statement" (1). Tremor in ET may be difficult to differentiate from dystonic hand tremor, especially when the dystonia is subtle. In such cases, certain clinical clues that include irregularity of tremor with jerky component, abnormal hand posturing, sensory trick, null point phenomenon, and lack of a clear axis while drawing spirals may be helpful as these are commonly observed in dystonic tremor (15).

Tremor in ET patients tends to worsen over time in terms of severity as well as in the number of body parts involved and, as discussed below, may become associated with parkinsonism, dystonia, ataxia and other motor disorders (16). In addition to tremor, patients with ET may develop several non-motor symptoms (NMS) such as cognitive impairment, anxiety, depression, apathy, and sleep disturbances (17). Hence, neurologists should evaluate all ET patients for both motor and NMS.

There is growing body of evidence that some ET patients when followed longitudinally develop PD (10, 18, 19). Based on many clinical, epidemiologic, imaging, genetic and pathologic studies, a subset of ET patients appears to be at a high risk of developing PD. Besides PD with antecedent ET, ET may follow the onset of PD (ET with antecedent PD). These ET-PD patients seem to have a slower progression and more favorable prognosis than PD in general, similar to tremor-dominant PD as compared to postural instability gait difficulty subtype of PD (20). Neurologists should be aware of the difference in the NMS profile of ET and PD

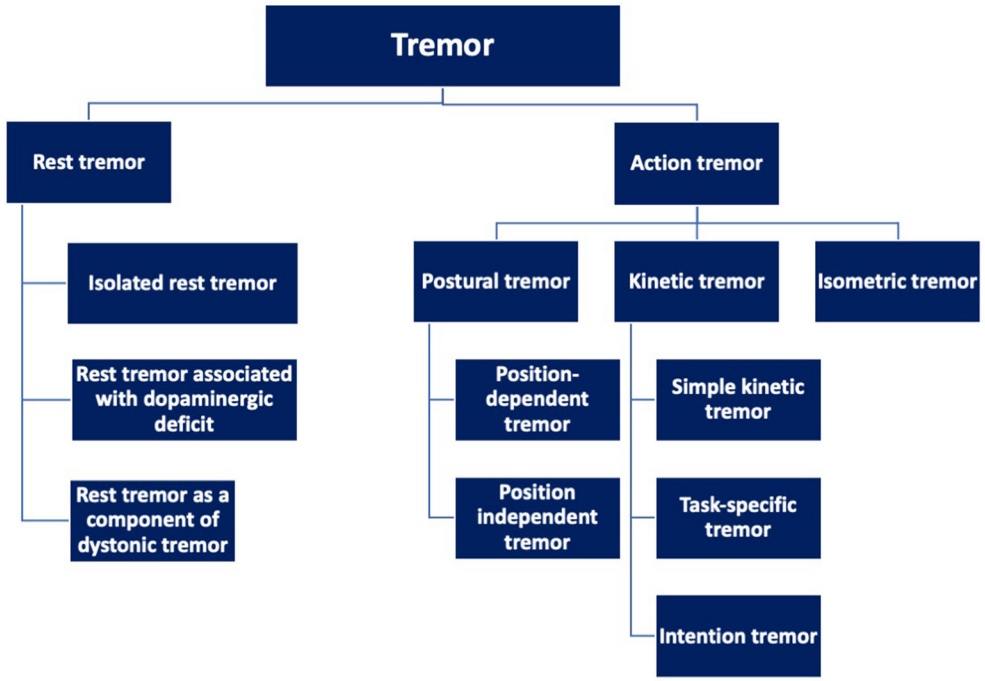

FIGURE 1 | Categories of tremor based on the activation pattern.

patients. While the NMS mentioned above in the context of ET can also be commonly observed in PD patients, there are several other NMS which are relatively more specific to PD. These include hyposmia, rapid eye movement sleep behavior disorder (RBD), dysautonomia, visual hallucinations, impulse control disorder, and constipation (21). Therefore, emergence of these NMS should prompt detailed evaluation to explore the possibility of PD or co-existent PD. The exact relationship between ET and PD is not well-understood but better understanding of the etiopathogenesis of ET and PD and their subtypes should lead to better insights into the relationships between these two common, but not well-defined movement disorders (10, 18).

Besides a link between ET and PD, there is a well-recognized link between ET-like phenotype and dystonia (see below discussion of tremor associated with dystonia). Several early studies have demonstrated that about 25% of patients with cervical dystonia had tremor in their hands that is phenomenologically similar to ET (22). In a more recent study of 2,362 patients enrolled in the Dystonia Coalition project, 53.3% had tremor, mostly involving the head, followed by the upper limbs and other body regions (23). Dystonic tremor (DT) occurred in 36.9–48.4% of patients, but others had ET-like tremors. The frequent co-existence of dystonia and ET-like tremor, and family history of both or either suggests that the two disorders share some pathophysiologic mechanisms, but the nature of the relationship is still poorly understood.

Pathogenesis of Essential Tremor

Although the exact pathogenesis of ET is still unknown and its detailed discussion is beyond the scope of this review, growing body of evidence suggest an alteration in the cerebello-thalamo-cortical circuit (24–26). While inferior olive was thought to play an important role in the pathogenesis of ET, a histopathological study of 14 ET patients did not reveal any abnormality compared to 15 control brains (27). Similarly, abnormalities of Purkinje cells have been observed in some (24, 25) but not (28) all post-mortem brain pathological studies. Hence, the cerebellar and olivary model of ET has remained controversial. Advanced neuroimaging studies have provided valuable insights into the putative neuroanatomical corelates of ET. Most of the studies based on structural or functional neuroimaging have identified abnormalities in the components of the cerebello-thalamo-cortical network, suggesting that ET might not be a disease associated with a particular brain region, rather associated with abnormalities in the neural network level (29).

Since a majority of ET patients have a family history of ET suggestive of an autosomal dominant transmission, attempts have been made to identify genetic abnormalities associated with ET. Although no single gene has been found to be causally linked to ET a number of genes (*ETM1, ETM2, ETM3, ETM4, ETM5, SORT1, SCN4A, SCN11A, HTRA2, CACNA1, SCNA, MTHFR, LINGO1, LINGO2, LRRK2, MAPT, TREMT, HMOX1, HMOX2; BACE2*, *LRRN2*, *DHRS13*, and *LINC00323*) have been identified in the last 3–4 decades as possibly related to ET (30). Further linkage, whole exome or genome sequencing, genome-wide association studies (GWAS), and other genetic studies are needed to elucidate the genetic mechanisms of ET.

Other Isolated Action Tremor Syndromes

As per the consensus statement, certain tremor syndromes may not fulfill the criteria of any of the established tremor syndromes

TABLE 1 | Tremor syndromes based on the predominant manifestation of the tremor (Axis-1).

Tremor category based on activation/position	Tremor subcategories	Key features
Action/rest tremor	Essential tremor	Body parts involved: Bilateral upper extremities involvement for 3-years is mandatory for diagnosis. Voice, head, lower extremities may be involved. Key features: 4–12 Hz action tremor
	Essential tremor plus	Tremor fulfilling the criteria of ET along with additional neurological signs (dystonia, rest tremor, impaired tandem gait)
	Enhanced physiologic tremor	Body parts involved: Bilateral hands and fingers Key features: Low amplitude, high frequency tremor (8–12H z). Can be precipitated or exacerbated by anxiety, caffeine, and hypermetabolic states.
	Isolated action or rest tremor syndromes	Additional clinical features in axis-1 should be explored to reach at the diagnosis. Isolated rest tremor usually affects the upper extremities and may evolve into Parkinson's disease.
Focal tremor	Voice tremor	Body parts involved: Vocal cord, larynx, oropharynx, palate, tongue, lip) Key features: Frequency range 3.8–5.5 Hz
	Head tremor	Body parts involved: Head/neck Key features: Yes-yes or no-no or diagonal direction of tremor, often associated with cervical dystonia or essential tremor
	Palatal tremor	Body part involved: Soft palate (may be associated with myorhythmia in other body parts) Key features: Rhythmic, 0.5–5Hz tremor, may be present during sleep, may be associated with audible clicks
Task specific tremor	Primary writing tremor	Body part involved: Hand used for writing Key features: Tremor only while writing (type-A) or while adopting the hand in writing position (type-B)
	Other tremors in musicians and sports persons	Body part involved: Hand used for the specific task Key features: may be associated with focal dystonia and a compensatory posture
Orthostatic tremor	Primary orthostatic tremor	Body part involved: legs and trunk Key features: 13–18Hz, low amplitude tremor only while standing, associated with subjective unsteadiness
	Pseudo orthostatic tremor	Body part involved: legs Key features: <13 Hz low amplitude tremor, only while standing, associated with subjective unsteadiness
Tremor with additional prominent neurological signs	Re-emergent tremor	Body parts involved: Upper extremities, rarely tongue Key features: Form of postural tremor (3–5 Hz) which emerges after a latency of a few seconds when hands are kept in an anti-gravity posture. Typically present in Parkinson's disease
	Dystonic tremor	Body parts involved: Any of the body parts with dystonia Key features: Irregular, jerky tremor; worsens while resisting dystonic pull and subsides or resolves in maximal dystonic posture ("null point").
	Holmes' tremor	Body parts involved: Bilateral upper extremity Key features: Present at rest, worsens when holding a posture, intensifies during action
	Myorhythmia	Body parts involved: Cranio-facial and limb muscles Key features: Slow, rhythmic, repetitive movements (1–4 Hz); associated with lesions of the brainstem and/or diencephalic structures
	Wing-beating tremor	Body parts involved: Upper extremities Key features: High amplitude proximal tremor when arms are in abducted position; may be present in Wilson's disease or cerebellar-outflow pathways
Others	Functional tremor	Body parts involved: Any the body part Key features: Abrupt onset, variable in frequency and amplitude, distractible, entrainable; incongruous with organic tremors.

and such cases should carry the label "indeterminate tremor syndrome" during the observation period (1). For example, isolated action tremor of both upper extremities with a duration < 3 years (otherwise fulfilling the criteria for ET) should be labeled as "indeterminate tremor" during the observation period. Some of the isolated action tremor syndromes which get the label of "indeterminate tremor" may subsequently evolve and fulfill the definition of ET or may develop additional neurological signs and meet the diagnostic criteria of other diseases. For example, anoctamin 3 gene (*ANO3*) mutation which is known to cause an autosomal dominant cranio-cervical dystonia (DYT24) may initially present only with action tremor of upper extremities (31). Tremor in DYT24 commonly involves bilateral upper extremities and head; the tremor in extremities is usually asymmetric. As DYT24 was identified less than a decade ago, details about the natural course of the tremor and the exact neural correlates remain elusive. Patients with certain subtypes of spinocerebellar ataxias (SCA), especially SCA12 and SCA 40, may initially present with action tremor of the limbs, followed by the emergence of ataxia (32–34) (described in detail in

TABLE 2 | A summary of common diseases/etiologies manifesting predominantly with tremor.

Neurodegenerative
• Parkinson's disease
• Essential tremor
• Corticobasal syndrome
• Progressive supranuclear palsy
• Multiple system atrophy
Genetic diseases/mitochondrial diseases
• ANO3 (Anoctamin) mutation or DYT24
• Spinocerebellar ataxia type-12, type 40
• Klinefelter syndrome
• Fragile-X tremor ataxia syndrome
• Hereditary chin tremor
• Charcot-Marie-Tooth disease
• Leigh's disease
• Mitochondrial polymerase gamma mutation
Metabolic diseases
• Wilson's disease
• Hyperthyroidism
Drugs and toxins
• Anti-seizure medications: Phenytoin, valproate
• Beta-2 agonists
• Thyroid hormone replacement
• Dopamine receptor blockers: Neuroleptics, metoclopramide
• Lithium
• Amiodarone
• Chemotherapeutic agents: Tacrolimus, vincristine, cisplatin, methotrexate
• Toxins: Mercury, lead, manganese, arsenic, cyanide, carbon monoxide, naphthalene, toluene, lindane
Neuropathic
• Charcot-Marie-Tooth disease
• Acute inflammatory polyradiculoneuropathy
• Chronic inflammatory polyradiculoneuropathy
• Multifocal neuropathy with conduction block
• Monoclonal gammopathies
Other causes
Any space occupying lesions, stroke in the basal ganglia or in the cerebello-thalamo-cortical network may result in tremor, albeit along with other focal neurological deficits

a latter section). It is possible that the tremors observed in patients with DYT24, SCA12, and SCA40 are not completely "isolated" during the initial stages as the patients may have subtle dystonia and/or ataxia. Thus, the various tremor syndromes should be thoroughly investigated using accelerometry and electromyogram (EMG) as accurate distinction of these conditions may not always be possible solely by clinical examinations.

Isolated Rest Tremor

Rest tremor has been classically described in patients with PD; however, it has also been reported in ET patients, especially in those with a long duration of disease, and a variety of parkinsonian disorders. Suppression of rest tremor during initiation of voluntary movements of the affected body part usually indicates a state of dopaminergic deficiency such as PD. In a study on 44 PD patients and 22 ET patients, rest tremor suppression was observed in 39/44 PD patients and in 2/22 ET patients (35). As many of the patients with isolated rest tremor develop PD in the future, the term "benign tremulous parkinsonism" was used by several groups in the past (36, 37). Isolated rest tremor of at least 2 years duration was referred to as monosymptomatic rest tremor by the first consensus statement on tremor by the IPMDS (38). These patients should be followed closely because many subsequently develop additional signs of PD in the future (36). It should be noted that re-emergent tremor (discussed below) is viewed by some as a variant of rest tremor. Patients with dystonia may exhibit rest tremor in body parts not obviously affected by dystonia. Although this may possibly represent a form of dystonic tremor, when such rest tremor appears in a hand it may lead to a misdiagnosis of PD. In a study on 473 consecutive patients with adult-onset primary dystonia, 55.4% were tremulous and, of those, 40.7% had rest tremor (unilateral > asymmetric bilateral) (39). This observation highlights the fact that patients with isolated rest tremor should be thoroughly examined for additional signs of PD, ET, and dystonia.

It is important to note that to label rest tremor as "isolated," the presence of subtle postural tremor should be ruled out objectively through accelerometry or surface EMG. In the absence of objective examination, it would be preferable to use the term "clinically isolated rest tremor."

Enhanced Physiologic Tremor

As the name suggests, enhanced physiologic tremor can be observed in normal individuals during enhanced muscle activity such as while exercising or immediately thereafter, probably related to increased sympathetic activity. This is a form of action tremor which may not be visible to the naked eye because of its low amplitude and high frequency (8–12 Hz, slower in children and elderly) (1). Enhanced physiologic tremor usually involves both hands and all fingers symmetrically and is perhaps the most commonly observed postural tremor. Unilateral postural tremor mimicking enhanced physiologic tremor was reported in patients with reflex sympathetic dystrophy (40). If not very obvious to the naked eye, a sheet of paper may be placed on the outstretched hands to amplify the tremor to make it more evident (41). Vigorous exercise, fatigue, anxiety, stress, excess caffeine consumption, and conditions associated with a hypermetabolic state such as hyperthyroidism can make the enhanced physiologic tremor more obvious (42). Diagnosis of enhanced physiologic tremor is contingent upon the fact that other etiologies (axis-2 classification of consensus statement) of tremor are excluded. Considering the benign nature, this non-bothersome tremor usually does not warrant any pharmacotherapy. However, if bothersome, patients may obtain benefit from propranolol (2, 43). Similar to the isolated tremor syndromes described above, accelerometry and EMG can be used to confirm the nature of the tremor objectively. The objective confirmation of enhanced physiologic tremor requires the demonstration of the presence of tremor on both accelerometry and EMG (enhanced muscle activity via a recruitment of mechanical reflex loop i.e., both central and peripheral involvement) which cannot be demonstrated solely by clinical observation.

Isometric Tremor

This form of action tremor is observed when muscle forcefully contracts without moving the limb or the involved body part. For example, it is noted while holding a heavy object, while making a fist or tightly squeezing examiner's finger, or while contracting abdominal and truncal muscles when patient while seated flexes the hips and holds the legs against gravity (1). Isometric tremor may be isolated or noted in certain movement disorders such as PD, ET, orthostatic tremor, and dystonic tremor (44). Hence, individuals who exhibit isometric tremor should be thoroughly examined to explore the aforementioned disorders. There are two case reports of "shopping bag" tremor which phenomenologically is similar to isometric tremor (45, 46).

Focal Tremors

The commonly reported focal tremors include voice tremor, head tremor, and palatal tremor, although the latter is also often referred to as palatal myoclonus since it is typically caused by rhythmical contractions of tensor veli palatine or levator veli palatine, rather than an oscillatory movement produced by antagonist contractions (see below).

Vocal/Voice Tremor

Vocal tremor or voice tremor (VT) occurs due to tremor of any of the anatomical components of the vocal apparatus. VT without any dystonia of the affected component of vocal apparatus or tremor in any other body part is referred to as isolated VT. Several studies have explored whether isolated VT is a unique category of tremor or a type of focal ET or a manifestation of laryngeal dystonic tremor (47, 48). VT results in periodic fluctuations in the pitch and loudness of voice, including voiceless pauses; the latter typically occurs as a compensatory phenomenon when vocalis muscles voluntarily contract in an attempt to suppress the VT. The latter is particularly common and troublesome when VT evolves into or becomes combined with laryngeal dystonia, also referred to as spasmodic dysphonia. Based on objective analyses of the VT of 160 subjects, one study reported that the normative frequency range of VT is 3.8–5.5Hz (49). A VT scoring system (VTSS), used to document the severity of VT based on a scale of 0–3 (maximum score 18), assesses six different components of the vocal apparatus (palate, the base of the tongue, pharyngeal walls, larynx, supraglottis, true vocal cords) (50). In addition to ET and laryngeal dystonia, VT may occur in the context of oro-facial dystonia and essential head tremor (HT), but it is relatively rare in patients with PD unless they also have co-existent ET (51, 52). A recent study based on the acoustic analysis of the voice of 240 subjects revealed the presence of VT in a number of neurological diseases with the following frequency- Huntington disease- 65%, ET- 50%, multiple system atrophy (MSA)-40%, cerebellar ataxia-40%, amyotrophic lateral sclerosis- 25%, progressive supranuclear palsy-25%, PD-20%, cervical dystonia- 10%, and multiple sclerosis-8% (53).

Head Tremor

HT is commonly seen in the context of ET and cervical dystonia. HT in the absence of any obvious cervical dystonia or any tremor of other body parts is described as isolated HT. Several studies have found that HT is often associated with cervical dystonia, neck pain, hand tremor and family history of tremor or other movement disorders, suggesting marked heterogeneity of underlying mechanisms (54, 55). In a series of 241 first-degree relatives of ET patients, isolated transient HT was observed in 21% (vs. controls 2%) which provides support for the observation that HT with or without hand tremor may be a manifestation of ET (56). In ET, based on the direction of the head movement, HT can be of 3 types- "Yes-Yes" (affirmation), "No-No" (negation), a mixed type, or "round-round" (diagonal) (57). In a series of 234 patients, HT was the presenting feature in more than two thirds of the patients (58). In the same study, ET patients with HT seem to have distinct characteristics as HT was often seen in the female patients, especially in those above 50 years of age (with a unimodal peak of age distribution), and patients with HT had a later onset of tremor (58). While this information support HT as a different "trait," the increased prevalence of HT in patients with a long duration of ET also favors the concept that it could be both a "state" and "trait" dependent feature (59).

Several studies have drawn attention to HT in patients with cervical dystonia. Pal et al in a series of 114 patients with cervical dystonia observed HT in approximately two thirds of the patients; in one third HT was the presenting symptom (55). HT in cervical dystonia may be associated with the direction of pull resulting from dystonia and also with the duration of dystonia. There is discordance in the results of studies that explored the association of subtypes of cervical dystonia with the presence of HT. While a study on 185 patients with cervical dystonia reported that patients with retrocollis/anetrocollis had a higher likelihood of developing HT (60), another study on 293 patients reported that torticaput variety of cervical dystonia is more likely to be associated with HT (61). Duration of dystonia was the common factor related to HT in both these studies. Similar to that ET, there is evidence to suggest that HT in cervical dystonia has some unique features. In a large multi-center study comparing the clinical characteristics of tremulous (HT at disease onset) and non-tremulous cervical dystonia patients, the former group more frequently affected older women, had a higher prevalence of ataxic features and had milder dystonia (62). A structural imaging study revealing greater cerebellar vermian atrophy in cervical dystonia patients with HT compared to those without HT further reinforces the fact that HT represents a unique cerebellar phenotype of cervical dystonia (63). One characteristic feature that helps to differentiate between HT due to cervical dystonia vs. ET is the presence of "null point," a position of the head and neck when the head tremor diminishes or resolves as the head and neck are allowed to assume the maximal dystonic position (64). Assessment of tremor in the supine position may provide a clue toward the nature of HT. HT in patients with ET tends to disappear in supine position whereas HT associated with cervical dystonia persists in the supine position and may be associated with the abnormal dystonic posture (65).

Palatal Tremor

This is a rare form of tremor that involves the soft palate. It was previously known as "palatal myoclonus" but it was renamed "palatal tremor" during the first International Congress

of Movement Disorders in 1990 as the term "tremor" represents the continuous, rhythmic nature of the palatal movement (66). However, the term myoclonus may still apply since the movement is produced by contractions of only agonist muscles (either tensor veli palatine or levator veli palatine), rather than alternating, oscillatory antagonist contractions which produce typical oscillatory movement characterizing tremor. Furthermore, in contrast to typical tremor, this focal movement disorder often has a jerky and arhythmic component, particularly when present as a functional (psychogenic) movement disorder (67, 68).

Based on the absence or presence of additional neurological signs and symptoms palatal tremor is categorized into two groups, essential palatal tremor (EPT), and symptomatic palatal tremor (SPT). EPT, in a true sense, is an isolated focal tremor as the sole manifestation of this entity is palatal tremor, often with audible clicks. The clicks are presumably secondary to rhythmic contraction of tensor veli palatini muscle. No demonstrable etiology is found in patients with EPT. The frequency of EPT may vary from <1 to 7 Hz (69). SPT, which is more frequently reported compared to EPT, refers to the conditions where palatal tremor coexists with other neurological signs and symptoms. SPT is reported to have lower frequency than that of EPT, in the 1.5–3 Hz range, and may be associated with myorhythmia (see below) involving other head and neck structures (69). While EPT may have complete cessation during sleep, SPT usually persists during sleep, albeit with a lower frequency (69, 70).

In addition to functional (psychogenic) palatal tremor (71), there are many other etiologies. Previous case series have documented vascular abnormalities (posterior circulation strokes, aneurysms, arterio-venous malformation), genetic abnormalities (polymerase gamma-related mitochondrial disease, SCA type 20, Alexander disease), and traumatic brain injury as the commonest etiologies of SPT (67, 72). In addition, there are reports of an array of neurodegenerative (progressive ataxia with palatal tremor), infectious (Whipple disease, tuberculosis, toxoplasmosis), inflammatory/demyelinating (neurosarcoidosis, multiple sclerosis, Behcet's disease) and neoplastic conditions (posterior fossa tumors) associated with SPT (67, 72, 73). Although not universal, MRI of the brain often reveals hypertrophic degeneration of the olive and other focal lesions in the Guillain-Mollaret triangle (formed by the ipsilateral red nucleus, inferior olivary nucleus, and contralateral dentate nucleus).

Task-Specific Tremor

Task-specific tremor is a type of action tremor that emerges while performing or attempting to perform specific motor tasks such as writing and playing musical instruments. Primary writing tremor (PWT) is one of the commonly reported task-specific tremors. It is described as a tremor of the hand only while writing or while attempting to write (74). Based on the timing of the tremor, PWT is divided into two categories- type-A (tremor while actively writing) or type-B (tremor while adopting the hand position used for writing). Hence, type-B PWT is a position-specific tremor rather than a true task-specific tremor (74). Although PWT affects the hand used for writing which is often the dominant hand, it may subsequently affect the other hand also (75). The abnormal movement or position in the opposite, unaffected, hand may be observed as a mirror dystonia or tremor (76). The frequency of PWT is 5–7 Hz and it often has a jerky component (77). Etiopathogenesis of PWT remains elusive. Several structural and functional neuroimaging studies have suggested a putative role of the cerebellum in the genesis of PWT (78, 79). Although it has been categorized as "tremor," there is controversy whether PWT is truly an isolated tremor or it is a dystonic tremor associated with the writer's cramp (80, 81). Electrophysiological assessment comparing several characteristics of PWT and dystonic tremor (DT) provided evidence for marked similarity of these two conditions in several electrophysiologic indices, including reduced eyeblink classic conditioning learning, reduced blink recovery cycle inhibition, and a lack of effect of paired-associative plasticity on long-interval intracortical inhibition (82). While additional studies are warranted to confirm and establish these findings, these findings certainly reinforce the notion that PWT is a phenotype of task-specific dystonia.

Many examples of task-specific tremor have been reported, including task-specific tremors in musicians (83, 84), oro-lingual tremor only while drinking (85, 86), chin tremor only while brushing teeth (87), finger tremor in carrom players (88) and many others. Patients with task-specific tremor should be followed up periodically to assess the emergence of additional neurological signs. This is important as there are reports to suggest that some of these patients subsequently develop PD (89, 90). In a recently published case series, 11 patients with various types of task-specific tremor of the arm went on to develop PD with a mean duration between onset of task-specific tremor and the onset of PD 13.66 $\pm$ 14.36 years (89).

Orthostatic Tremor

Orthostatic tremor (OT) refers to a high-frequency (13–18 Hz) tremor of the legs upon standing. Rarely, trunk and abdomen may be involved. When OT is the only clinical feature, i.e., an isolated tremor syndrome, it is termed a primary OT. The key phenomenological characteristics include high frequency, low amplitude tremor when the individual stands up and tremor resolves immediately after sitting or lying down (91). Very low amplitude and high frequency of OT may not be often obvious to the eyes and in such cases, surface EMG may be useful. Hence, for an accurate correct axis I classification of OT objective physiological assessment should be performed. Palpation and auscultation of the leg muscles may reveal the presence of thrill, and a continuous thumping sound (Helicopter sign), respectively (91). Most of the patients with OT report subjective unsteadiness and/or cramp in the distal legs upon standing and recent studies also provide objective evidence of ataxia in patients with OT (92). The mechanism of subjective unsteadiness in OT is not well-understood but has been attributed to a tremulous disruption of the proprioceptive feedback from the lower limbs (93). It is not clear whether the disruption is altered by trans-spinal direct current stimulation, which has been recently found to provide modest improvement in OT (94). The term "OT plus" is used to describe a situation when OT co-manifests with

additional neurological conditions such as parkinsonism, ataxia, dementia. In a recently published series of 27 patients with OT, neurological comorbidities preceding the onset of OT were present in 30% of the patients (95). The exact etiopathogenesis of OT is unclear and several hypotheses which include altered cerebello-thalamo-cortical circuit, cerebellar neurodegeneration, dopaminergic deficit, and presence of a central oscillator have been proposed (91). OT must be differentiated from other leg tremors, including leg tremors present in patients with ET or PD (96).

Although 13–18 Hz tremor is characteristic of OT, there are several reports of OT with frequency < 13 Hz (slow OT). There are reports of slow OT as an isolated syndrome as well as in the context of other neurological disorders (97, 98). A retrospective analysis of 28 patients revealed the presence of slow OT (<13 Hz) in 14 patients and among 8 of those with slow OT had a tremor frequency of <10 Hz (97). Interestingly, low (<10 Hz) and intermediate frequency (10–13 Hz) of OT in the same study were associated with more subjective unsteadiness, abnormal gait examination, and falls (97). Slow OT is also referred as to pseudo OT and in addition to fast OT (99), it has also been reported in patients with ET and PD (100, 101).

TREMOR IN THE SETTING ADDITIONAL NEUROLOGICAL FEATURES

Tremor Associated With Parkinsonism

Rest Tremor

Tremor-at-rest or rest tremor is one of the hallmark clinical features of PD. In a study on autopsy-confirmed PD cases, 69% had rest tremor at the time of presentation and 75% had it during the course of the disease (102). Rest tremor in PD is typically asymmetric, has a frequency of 4–6 Hz, commonly involves the hands, in a "pill-rolling" pattern, but may involve other body parts, and is often exacerbated during walking or while performing physical or mental tasks. Inhibition of the tremor during voluntary movements is a characteristic feature of rest tremor in PD (103). There are several paradoxical aspects of rest tremor in PD including lack of correlation with the degree of nigrostriatal degeneration, occasional occurrence on side contralateral to predominant parkinsonian features (bradykinesia/rigidity), resolution of rest tremor in some patients with progression of disease, and inconsistent response to levodopa (104, 105). Although the accurate neuroanatomical corelates of rest tremor is yet to be fully understood, there is evidence suggesting that both basal ganglia and cerebello-thalamo-cortical circuits are involved in the generation of rest tremor (104).

Re-Emergent Tremor

The term "re-emergent tremor" was coined by Jankovic et.al (106) to describe a form of postural tremor in patients with PD that emerges after a latency of a few seconds when hands and arms are held in an anti-gravity horizontal posture. The readers are referred to published video demonstration of the examination for re-emergent tremor (107). Although most often re-emergent tremor coexists with observable rest tremor, it may rarely emerge independently in PD patients without rest tremor (108). Previous cross-sectional studies have documented re-emergent tremor in 20–25% of PD patients (109, 110). An EMG study exploring the nature of postural tremor in PD revealed two pathophysiologically distinct clusters: 81% had re-emergent tremor and 19% had a pure postural tremor (111). The exact neural correlates of re-emergent tremor remain elusive; however, there is evidence to suggest that it overlaps with parkinsonian rest tremor in terms of frequency (both are of 3–5 Hz), the direction of movement (occasional supination-pronation), and response to dopaminergic medications (106, 111, 112). A recent study based on transcranial magnetic stimulation demonstrated that re-emergent tremor and rest tremor have common pathophysiological mechanisms in which the motor cortex plays an important role (113). The amplitude of re-emergent tremor and the tremor pause duration (latency) was demonstrated to have an inverse relationship and both are also modulated by levodopa (114). Amplitude and latency are also affected by provocative measures or distractions as noted by increase in amplitude and a decrease in latency when the patients count out loud backward from 100 (115). Patients with PD may rarely present with re-emergent tremor of the tongue (116–118). Re-emergent tongue tremor has also been reported in conditions other than PD (119, 120). Re-emergent tremor of the jaw was reported both in idiopathic PD (121) and vascular parkinsonism (122). Re-emergent tremor was also described while drawing a spiral (123).

Dystonic Tremor and Tremor Associated With Dystonia

Dystonic tremor (DT) represent a condition where dystonia is the predominant neurological feature and tremor manifests in the body part associated with dystonia. If a patient with dystonia has a tremor in a non-dystonic body part, the tremor is described as "tremor associated with dystonia" (TAWD) (15). For example, a hand tremor in a patient with cervical dystonia would be classified as TAWD. Occasionally, patients may develop DT as well as TAWD (124). While DT can affect any body part, it is most frequently found in patients with cervical dystonia (as head tremor) (124–126). The onset of DT usually either coincides with or occurs after the onset of dystonia. Rarely, DT may precede the onset of dystonia (127). One of the key features of DT is irregularity and variability in the frequency and amplitude. DT can be of postural, kinetic, or rest in nature and can manifest with varied combination of these phenomenologies (39) (**Figure 1**). DT can be reduced or completely eliminated by alleviating maneuver (128, 129), also referred to as "sensory trick" "geste antagoniste," and when the affected body part is positioned in the direction of dystonia and the movement, tremor or abnormal posture stop, this is referred to as "null point" (64). Conversely, the severity of DT worsens with the voluntary orientation of the affected body part against the main direction of dystonia pull (e.g., a patient with right torticollis may have an increase in DT while turning the head to the left or while trying to maintain primary head position) (130).

Holmes Tremor

Holmes tremor was first described by Gordon Holmes in reference to a 3–4 Hz tremor which is usually of high amplitude, irregular, present at rest, worsens with posture, and additionally intensifies with action (131). Holmes tremor predominantly affects the proximal upper extremities unilaterally or asymmetrically. There are several synonyms for Holmes tremor, including rubral tremor, thalamic tremor, midbrain tremor, mesencephalic tremor, and cerebellar outflow tremor (131, 132). Holmes tremor almost always occurs in the context of pathologies in the brainstem or diencephalon. A recent connectivity-based study analyzed the pattern of structural pathology in previously published case reports and suggested that the affected brain legions are connected to a common brain circuit with nodes in the red nucleus, thalamus, globus pallidus, and cerebellum (133). As per the new "consensus" tremor classification (1), it is one of the tremor syndromes which is associated with additional neurologic signs. In a series of 29 patients, the common co-existing neurologic abnormalities were hemiparesis (62%), ataxia (51.7%), hypoesthesia (27.6%), and dystonia (24.1%) (132). While stroke and traumatic brain injury are leading causes of Holmes tremor (132), it has also been reported in patients with multiple sclerosis (134), brain tumor (135), intracranial hypotension (136), and CNS infections (137). There may be a latency of a few weeks to few years between the precipitating events and the onset of the tremor. Holmes tremor may be associated with myorhythmia (below). A recently published study on 17 patients with Holmes tremor suggested the existence two phenotypically distinct types of Holmes tremor i.e., midbrain Holmes tremor and thalamic Holmes tremor (138). While the former was characterized by myorythmic rest tremor with or without distal dystonic posturing, the latter had distal choreo-athetoid movements, marked dystonic posturing, and proprioceptive sensory deficits.

Myorhythmia

As per the consensus paper, myorhythmia is classified as a tremor syndrome with prominent additional signs (1). The term "myorhythmia" was first coined by Herz in 1931 in reference to a slow tremor in a patient with dystonia. This is an uncommon movement disorder which is characterized by slow, rhythmic, repetitive jerky movements of 1–4 Hz frequency, involving the cranial or limb muscles (1, 70). It is frequently associated with other neurological signs such as dystonia, palatal tremor, and eye movement abnormalities, and can affect cranial, branchial and limb muscles along with the additional neurological signs (70). Rarely it can manifest as isolated facial slow rhythmic movement (139).

The precise neural mechanism of myorhythmia remains elusive but the main significance of recognizing this movement disorder is that it is almost always associated with an identifiable pathology typically involving the upper brainstem and thalamus. Myorhythmia has marked etiological heterogeneity. It has been frequently reported as oculo-masticatory myorhythmia in the context of Whipple's disease, caused by the infection of the central nervous system by *Trophyrema whipplei* (140). Other conditions where myorhythmia has been reported are stroke (139), anti-NMDA encephalitis (141, 142), anti-IgLON5 disease (143), interferon alpha-2a use (144), Hashimoto encephalopathy (145), and X-linked dystonia-parkinsonism (146). As myorhythmia is often associated with conditions that are potentially treatable, it is important to be familiar with this phenomenology and its differential diagnoses.

Wing Beating Tremor

This form of tremor often overlaps with Holmes tremor. It has been classically described in patients with Wilson's disease (WD), but there are many other forms of tremor associated with WD. Wing beating tremor is a low frequency, high amplitude postural tremor which is usually elicited by sustained abduction of the arms with flexed elbows and palm facing downwards (147). Considering frequent association with WD, patients with this form of tremor should be thoroughly investigated for WD. It usually coexists with several other neurological signs such as dystonia, Kayser-Fleischer ring in the cornea, cognitive impairment in patients with WD (148). Wing beating tremor was reported recently in a case of Creutzfeldt-Jakob Disease (CJD) (149).

FUNCTIONAL TREMOR

Functional or psychogenic tremor is the most commonly reported functional movement disorder, accounting for approximately half of the cases (150, 151). There are no set diagnostic criteria for functional tremor and the diagnosis is based on a careful history and neurological examination. Among the commonly described characteristics of functional tremor are variability, distractibility, entrainability, and coherence; and higher prevalence in females compared to males (152). The onset of tremor is usually sudden and there is variability in the amplitude, frequency, and direction of the tremor. In one study designed to determine which clinical features help distinguish functional tremor from ET, a "blinded" rater evaluated video segments of subjects using a standardized protocol with special attention to distractibility, suggestibility, or entrainment (153). Patients with functional tremor were significantly more likely to have sudden onset, spontaneous remissions, shorter duration of tremor, and lower prevalence of family history of tremor. Furthermore, patients with functional tremor had more distractibility with alternate finger tapping and mental concentration, suggestibility with a tuning fork, and exacerbation with hyperventilation. Although functional tremors can affect any of the body parts, hands are the most commonly reported body involved in functional tremor. A tremor in multiple body parts occurring with similar frequencies (coherence) is a clue toward functional tremor. Careful assessment of these features may help in distinguishing functional tremor from other common diseases presenting with tremor including ET and PD (152). Electrophysiological assessment, using a scoring system, may provide additional information to support the diagnosis of functional tremor (150, 154). However, it needs to be emphasized that the positive signs on the clinical examination mentioned above are the key to the diagnosis of functional

tremor. The readers are referred to two published articles with video demonstration of examination of functional tremor (152, 155).

OTHER RARE FORMS OF TREMOR

In this section, we describe some of the rare axis-2 tremor syndromes which are likely to be encountered in the general neurology and movement disorders practice, often on the background of other neurological problems or movement disorders.

Neuropathic Tremor

A neuropathic tremor is a form of tremor observed in some patients with severe peripheral neuropathies in the absence of any other movement disorders (156). Certain peripheral neuropathies, especially demyelinating polyneuropathies, have a higher predilection than other neuropathies for neuropathic tremor. The commonly described tremor frequency is 3–6 Hz, it usually affects the arms and/or hands, and does not vary with weight loading (156). In a series of 89 patients with polyneuropathy, 59.5% during clinical evaluation and 74% during objective assessment through surface EMG recording were noted to have tremor (157). Postural tremor (70%) was the commonest, followed by rest (51%) and kinetic tremor (32%). A study on 43 patients with inflammatory neuropathies revealed that tremor was most common in IgM paraproteinemic neuropathies, followed by chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multifocal motor neuropathy with conduction block (158). Several studies have reported that patients with a specific subtype of CIDP which is associated with the presence of neurofascin155 (nfasc155) IgG4 antibodies develop disabling low-frequency, high-amplitude action tremor of the upper limbs (159, 160). Head, voice, and tongue tremor have also been reported in this subtype of CIDP (161, 162). There are several reports of a high prevalence of tremor in patients with various forms of Charcot-Marie-Tooth disease (CMT), in the past referred to as the Roussy-Levy syndrome (163, 164). In a survey of 201 patients, 40% of the CMT patients reported the presence of tremor of hands (164). Because of frequent involvement of hands, presence of postural tremor, presence of a family history of ET, and lack of correlation of tremor severity with neuropathy severity, it was presumed that tremor in CMT may pathophysiologically overlap with that of ET. A study based on the neurophysiological evaluation, however, did not find any evidence of cerebellar dysfunction in CMT patients with tremor (165).

Tremor in Spinocerebellar Ataxias

Various ataxias may be also associated with tremor. For example, SCA 12 is an autosomal dominant progressive degenerative ataxia that is commonly reported among the "Agarwal" community in northern India (32). SCA12 is due to the abnormal CAG repeats expansion in the 5' untranslated region of PPP2R2B gene at locus 5q32. The most common presenting symptom of SCA12 is action tremor of both upper extremities, often misdiagnosed as ET. Subsequently, patients develop appendicular and gait ataxia. In a series of 21 consecutive patients, postural tremor was observed in 17 patients (81%), followed by head tremor in 13 (62%), intention tremor in 12 (57%), and rest tremor in 10 (48%) (34). Upper extremity tremor in SAC12 is slow compared to that in ET and has more proximal involvement. A recent study noted the presence of action tremor in all and an asymmetry of the tremor amplitude in 91% of the patients with SCA12 (166). A patient with SCA40 was reported to have an ET-like syndrome for years, requiring treatment with deep brain stimulation, before the genetic cause was confirmed (33).

Fragile-X Tremor Ataxia Syndrome

FXTAS is a neurodegenerative disorder that results due to CGG repeat expansion in the premutation range (55–200) in the fragile X mental retardation 1 gene (*FMR1* gene) (167). Tremor and ataxia are the predominant clinical features along with a repertoire of other symptoms that include cognitive dysfunctions, parkinsonism, peripheral neuropathy, anxiety, depression, and apathy (168). Although action tremor in both upper limbs is the common type of tremor in FXTAS, patients may also have rest tremor (169). Because of a mixed phenomenology of tremor along with mild parkinsonian signs, FXTAS may be confused with ET or PD. However, the presence of early ataxia and cognitive impairment usually differentiates it from ET or PD. Previous studies have reported a correlation of the CGG repeat length with the onset of the motor symptoms.

Other Genetic Forms of Tremor

Klinefelter syndrome (47, XXY) (KS) is a chromosomal variation leading to the presence of an extra X-chromosome in males (170). Patients usually have an array of symptoms related to endocrine, metabolic, and reproductive functions. Commonly reported features include tall stature, micro-orchidism, gynecomastia, azoospermia, sparse body hair, and osteoporosis (170). There are several reports of a high prevalence of tremor in patients with KS. In a series of 44 patients with KS, more than half (51%) of the patients reported tremor, and 10% were previously diagnosed as ET (171). Although bilateral or unilateral action tremor of the upper extremities is commonly reported, some patients may present with rest tremor (172). The exact pathogenesis of tremor in KS is not fully understood.

Spinal and bulbar muscular atrophy or Kennedy disease, a rare X-linked neuromuscular disease caused by a CAG repeat expansion in the first exon of the androgen receptor gene, is manifested by bulbar symptoms, muscle cramps, leg weakness, and tremor (173). The patients have evidence of small or large nerve fiber neuropathy and, therefore, the observed tremor may be a neuropathic tremor.

Hereditary chin tremor (HCT), also known as hereditary geniospasm, hereditary quivering of the chin, hereditary essential chin myoclonus, is a benign genetic condition which manifests only with chin tremor. HCT is linked to chromosome 9q13-q21 (174). It follows autosomal dominant transmission and has high penetrance. Chin tremor may be visible in patients with HCT from childhood and it peaks during early adulthood. One of the key features of HCT is the intermittent nature of the tremor

that is triggered by emotional stress or anxiety and lasts for few seconds to a few hours. The frequency of HCT varies from 2 to 11 Hz (175). This disease is usually non-progressive and does not have any long-term complications. It can be effectively treated with local injections of botulinum toxin (176).

There are several other genetic disorders that may have tremor as one of the clinical features (177), but detailed discussion of all the those syndromes is beyond the scope of this article.

CURRENT CONTROVERSIES

ET Plus- the Controversial Category

One of the most recently debated issues in the field of tremor is the introduction of the term ET plus by the "consensus" statement (1). As discussed earlier, ET with additional neurological soft signs is now labeled as ET plus, as per the new tremor classification. This categorization has its own merits and limitations (10). The classification defines isolated ET which is helpful for genetic studies and for selection of a homogenous population of patients in interventional trials. However, the presence of poorly defined "soft signs" is troublesome. For example, "questionable dystonia" assessed by one neurologist may not be clinically obvious, bringing in the risk of inter-rater variability (178, 179). Hence, a "soft sign" for one examiner may be a "no sign" for another examiner or a separate and distinct disorder for another examiner. This uncertainty about the presence and relevance of such "soft" signs makes the classification challenging. Therefore, in the absence of reliable objective biomarkers, an accurate clinical distinction between ET and ET plus, only on the basis of these subtle/questionable signs may not be possible. While it needs to be confirmed by additional studies, a recent post-mortem study that compared certain pathological changes in the cerebellum of ET and ET plus patients did not find any significant difference between the two conditions (180). The introduction of ET plus group will have substantial impact on epidemiological studies. Indeed, since the publication of the Consensus statement, many studies have demonstrated that ET Plus is more prevalent than ET (6–10). In such scenarios, the significance of the previous clinical and epidemiological studies in which a large proportion of ET plus patients were categorized as ET, is going to be relatively uncertain (8). Additionally, as ET plus is a time-sensitive diagnostic placeholder, counseling the patients about the diagnosis and the expected clinical course is going to be challenging.

ET- a "Disease" or "Syndrome?"

Before the introduction of the new tremor classification by the IPMDS, ET has been regarded as a "disease" or a "family of diseases" (181, 182). However, the new classification describes ET as a tremor "syndrome." This change has stimulated scientific debates as to whether ET should be regarded as a "disease" or a "syndrome" or whether the various variants of ET should be simply considered subtypes, such as ET-PD, ET-dystonia, ET-ataxia, and other, since one may with time evolve into another (10, 183–185). A recent study using multimodal investigations, including objective gait assessment, neuropsychological assessment, and optical coherence tomography (OCT) for retinal thickness measurement, provided objective evidence for the existence of two ET subtypes (186). Using cluster analysis one subtype, characterized by midline tremor, cognitive decline and thin retinal inner layer, suggests that this subtype of ET is more likely to be associated with neurodegeneration. Hence, additional studies exploring and confirming the existence of such ET subtypes would provide more scientific insight to this "disease vs. syndrome" controversy.

FUTURE PERSPECTIVES

While there has been a substantial progress in the research on pathophysiology of ET, the exact neural correlate still remains elusive. Majority of the studies, as mentioned above, indicate structural and functional abnormalities in the cerebellum (especially in the Purkinje cell) and in the cerebello-thalamo-cortical circuit. However, these studies have not yielded any objective biomarkers for ET that can supplement the clinical diagnosis at an individual level. Therefore, future studies should explore more data-driven approach to utilize multi-modal imaging and electrophysiology to supplement the clinical diagnosis of ET.

The introduction of the term "ET plus" by the "consensus statement on the classification of tremors" (1) generated much controversy and numerous publications. When applied in clinical practice many (perhaps most) patients with prior diagnosis of ET now have to be reclassified as "ET-plus." Furthermore, when followed prospectively many patients with ET evolve into "ET plus." Hence, longitudinal studies of patients with isolated ("pure") ET are needed to determine which characteristics of the tremor, or associated "soft signs," predispose some patients to transition to "ET plus."

Future research should also address other issues related to the diagnosis and classification of tremor syndromes. For example, two common features of ET, the presence of family history of ET and alcohol responsiveness, were not included in the diagnostic criteria of ET in the new classification of tremor (1). It would be interesting to see if these two features are predictive of future outcome or a particular subtype of ET. Thus, the entity of isolated ET should be considered a time-sensitive diagnostic placeholder.

PWT should be another fruitful area of research in the future. It has been debated for long time whether it is a distinct entity or a variant of ET or dystonic tremor. As discussed above, a recent study has provided compelling evidence in support of important dystonic component to this form of tremor (82). If confirmed through additional multimodal diagnostic interventions, terms such as "dystonic writing tremor" or "writers' dystonic tremor" would more accurately reflect the underlying dystonia. As cerebellar abnormalities have been reported in studies on PWT (91), the concept that PWT is dystonic in origin would pave the way for additional research on the role of cerebellum in the pathogenesis of dystonia and dystonic tremor (187, 188).

One of the tremor syndromes which needs more clarity and consensus on the nomenclature is "palatal tremor." Although currently described as "tremor," it clearly does not fit into all

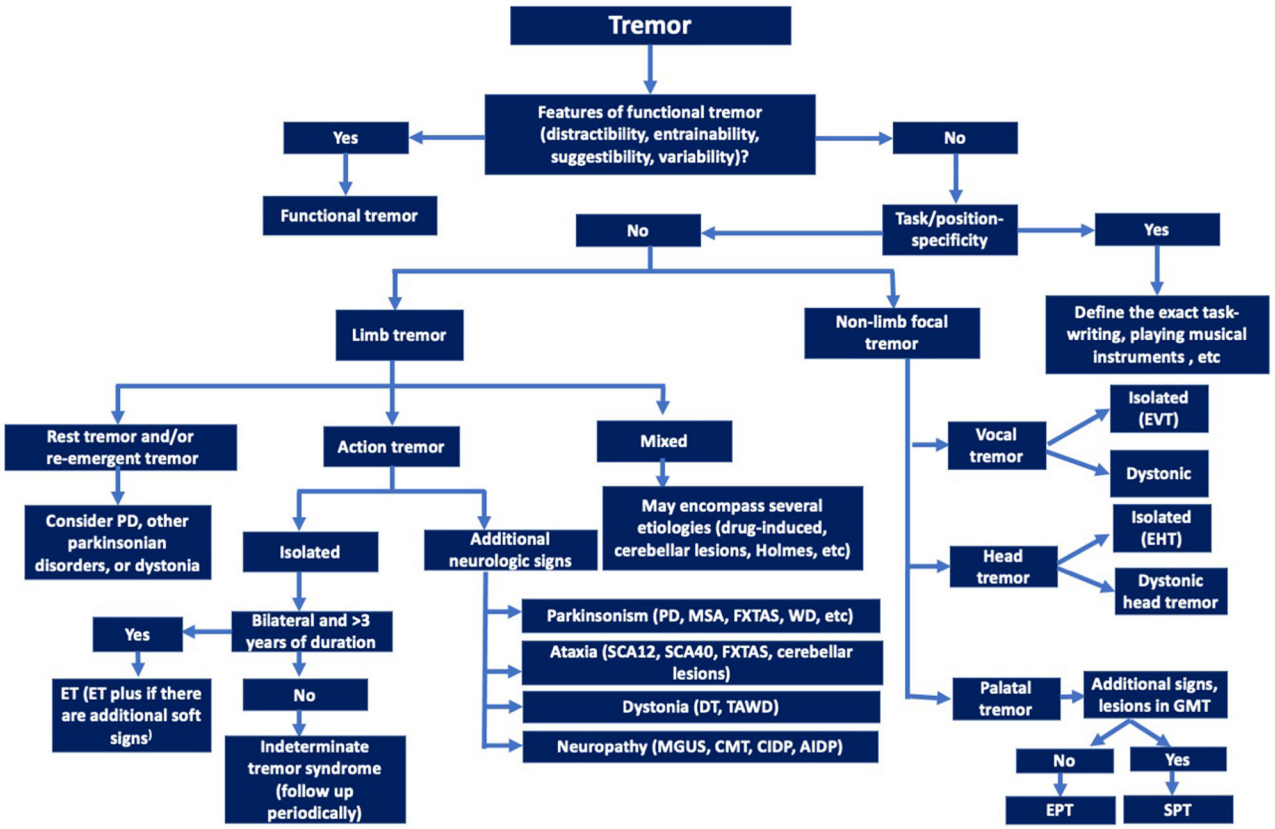

FIGURE 2 | Decision tree for clinical identification of the major tremor syndromes (Axis-2 etiologies should be explored for all the tremor syndromes). EVT, Essential vocal tremor; EHT, Essential Head tremor; EPT, Essential palatal tremor; SPT, Symptomatic palatal tremor; ET, Essential tremor; PD, Parkinson's disease; DT, Dystonic tremor; TAWD, Tremor associated with dystonia; MSA, Multiple system atrophy; FXTAS, Fragile-X-tremor ataxia syndrome; CMT, Charcot-Marie-Tooth disease; MGUS, Monoclonal gammopathy of uncertain significance; AIDP, Acute inflammatory demyelinating polyradiculoneuropathy; CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy.

the characteristics of tremor and it phenomenologically overlaps with segmental myoclonus and myorthythmia.

Ultimately, better understanding of physiological, genetic, pathological and other biological mechanisms is critical for development of diagnostic biomarkers that would facilitate classification and subtyping of tremors (**Figure 2**) and eventually leading to pathogenesis-targeted therapies.

AUTHOR CONTRIBUTIONS

AL: design and conceptualization of the work, prepared the first draft of the manuscript. JJ: design and conceptualization of the work, critical review, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Habituation After Deep Brain Stimulation in Tremor Syndromes: Prevalence, Risk Factors and Long-Term Outcomes

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Deep brain stimulation (DBS) of the thalamus is an effective treatment for medically refractory essential, dystonic and Parkinson's tremor. It may also provide benefit in less common tremor syndromes including, post-traumatic, cerebellar, Holmes, neuropathic and orthostatic tremor. The long-term benefit of DBS in essential and dystonic tremor (ET/DT) often wanes over time, a phenomena referred to as stimulation "tolerance" or "habituation". While habituation is generally accepted to exist, it remains controversial. Attempts to quantify habituation have revealed conflicting reports. Placebo effects, loss of micro-lesional effect, disease related progression, suboptimal stimulation and stimulation related side-effects may all contribute to the loss of sustained long-term therapeutic effect. Habituation often presents as substantial loss of initial DBS benefit occurring as early as a few months after initial stimulation; a complex and feared issue when faced in the setting of optimal electrode placement. Simply increasing stimulation current tends only to propagate tremor severity and induce stimulation related side effects. The report by Paschen and colleagues of worsening tremor scores in the "On" vs. "Off" stimulation state over time, even after accounting for "rebound" tremor, supports the concept of habituation. However, these findings have not been consistent across all studies. Chronic high intensity stimulation has been hypothesized to induce detrimental plastic effects on tremor networks, with some lines of evidence that DT and ET may be more susceptible than Parkinson's tremor to habituation. However, Tsuboi and colleague's recent longitudinal follow-up in dystonic and "pure" essential tremor suggests otherwise. Alternatively, post-mortem findings support a biological adaption to stimulation. The prevalence and etiology of habituation is still not fully understood and management remains difficult. A recent study reported that alternating thalamic stimulation parameters at weekly intervals provided improved stability of tremor control consistent with reduced habituation. In this article the available evidence for habituation after DBS for tremor syndromes is reviewed; including its prevalence, time-course, possible mechanisms; along with expected long-term outcomes for tremor and factors that may assist in predicting, preventing and managing habituation.

Keywords: tremor, deep brain stimulation, habituation, dystonic tremor, essential tremor, Parkinosn's disease

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INTRODUCTION

Tremor is an involuntary, rhythmic, oscillatory movement of a body part (1), with an estimated prevalence of 14.5% in the general adult population (2). The spectrum of tremor extends from the enhanced physiological postural tremor, often only noticeable during states of fatigue and heightened anxiety, to persistent pathological syndromes including essential tremor (ET), where currently available medications are moderately effective at best. For the severe end of the spectrum of tremor syndromes, functional neurosurgical techniques and neuroradiological procedures exists. These have evolved since Cooper (3) made the unintentional observation nearly 70 years ago, that destruction of a portion of the globus pallidus suppressed tremor of a patient with Parkinson's Disease (PD). Stereotactic lesional surgery mainly targeting the ventrolateral thalamus and posterior subthalamic white matter was used since the 1950's. During this period it was discovered that intraoperative high frequency electrical stimulation would suppress tremor and was used to verify the target region prior to thermal abalation (4, 5). These pioneering stereotactic interventions paved the way for the first cases of deep brain stimulation (DBS) performed by Cooper et al. (6). Motivated by a desire to avoid the frequent dysarthria observed following bilateral radiofrequency thalamotomy, DBS of the thalamic ventral intermediate nucleus (VIM) was revisited by Benabid in 1987 for second-side treatment of tremor and popularized following their 1991 publication of a series of 26 PD and six essential tremor (ET) patients treated with VIM DBS who reported to have a sustained tremor response over a 13-month median follow-up period (7). Subsequently large studies confirmed the effectiveness of VIM DBS for ET and PD (8, 9).

DBS remains the most common surgical procedure for medication-refractory tremor. However, the long-term benefits of therapy, particularly in ET, are often observed to wane over time, in a variable, unpredictable pattern. A phenomenon of "tolerance" was first described by Benabid et al. in a series of 80 tremor-dominant PD and 20 ET patients, with either uni- or bi-lateral VIM stimulation (10). Regular increase in stimulation to alleviate tremor was required to a final threshold that could no longer be increased due to the induction of side effects. "Tolerance" was associated with eventual loss of functional benefit and was more commonly observed with those with action tremor, in severe syndromes, with higher stimulation intensity, and where continuous 24-h stimulation had been adopted (10). The phenomenon of "tolerance" has continued to be observed in clinical practice and is now usually referred to as "habituation" (11). Attempts to characterize and quantity habituation have revealed conflicting reports in the medical literature and remain the subject of debate.

In this narrative review article, the available evidence for habituation after DBS for tremor syndromes is reviewed to reappraise perceptions of expected long term outcomes and factors that may assist in predicting this phenomenon. We also provide some information on possible pathophysiological mechanisms underlying 'habituation' and approaches to its management.

HABITUATION DEFINITION

Habituation in the context of benefit from DBS was first mentioned in the medical literature by Benabid et al. and described as "tolerance". It was hypothesized a progressively decreased biological response (habituation) of the neuronal network to be a possible mechanism for the phenomena of "tolerance" (10). Recently the term habituation has been proposed to replace "tolerance", defined by Fasano and Helmich to be the rapid vanishing of DBS efficacy after programming (11). This definition of habituation can be expanded to include delayed, progressive loss of therapeutic benefit for tremor after DBS, in line with the original concept of "tolerance" due to *"decreased biological response (habituation) of the neuronal network"* as described by Benabid et al. (10).

Authors have attempted to study habituation in the context of progressive loss of DBS benefit with particular attention given to differentiating progression from the natural history of disease. We agree in theory that comparing the tremor severity in the "off" state at two different time points, after allowing for rebound, represent disease progression; whereas tremor severity in the "on" state is determined by both disease progression and the stimulation effect. The difference (delta) between the on-off state, when compared over time, has been assumed by authors to be a measure of changing stimulation over time and attributed to habituation (12, 13). This is based on the premise that over time, other variables, specifically lead location and optimization of programming remain constant; but further, alternative mechanisms are not contributing or causing the phenomena that has been labeled habituation. Given these provisions, we will proceed on the operational hypothesis, reflected by the change in delta over time, from the definition of habituation known previously as "tolerance"; to be the loss of benefit from electrode reprogramming over time in the setting of optimal electrode placement and programming not explained by disease progression of the tremor syndrome. Habituation should not be explained by loss of micro-lesional implant effect or expected progression due to the natural history of the tremor syndrome. In line with the concept of "rapid vanishing of effect" habituation also refers to temporary improvement in tremor severity following increasing electrical field strength or contact adjustment, followed by subsequent paradoxical worsening.

Although this definition is useful conceptually, determining if an individual patient is experiencing habituation after tremor DBS remains very difficult because of the following; Firstly, there is no absolute agreed definition of what constitutes optimal lead placement; more troubling though, is the fact not all DBS leads placed within the optimal 2 mm radius of the intended target have a concordant clinical response (14). Secondly, optimal DBS programming is highly operator dependent as evidenced by significant clinical improvements achieved after expert reprogramming (15). Lastly, progression of the underlying tremor syndrome as part of the natural history of the disease must be subtracted from any apportionment of habituation, in itself a very difficult distinction, highlighting the inherent complexity and uncertainties surrounding this topic.

DOES "HABITUATION" REALLY EXIST?

Loss of Benefit Over Time

Habituation has most commonly been associated with ET, possibly reflecting the experience of clinicians in practice. Over 20 studies have been published looking at the long-term clinical efficacy of DBS in this condition; most commonly involving uni- or bilateral VIM stimulation (12, 13, 15–32). When looking at studies with a greater than 3-year follow-up, the long-term effect compared to baseline, ranges from 31.2–88.4% improvement (11, 13). The less traditional target, posterior subthalamic area (PSA)/caudal zona incerta (cZi), in comparison has relatively few follow-up studies; but with a similar range of effect size from baseline: 33–76% improvement (30, 33, 34). Some studies have suggested that the PSA/cZI may be less prone to habituation; however, no superiority has ever been clearly established (33–35). Despite this persistent improvement from DBS in the long-term, the majority of studies have shown that the effect diminishes over time.

A recent systematic review and meta-analysis by Lu et al., included 26 studies with 439 patients, looked at potential outcome predictors following VIM DBS in ET. The pooled treatment effect was 60.3% improvement in objective Tremor Rating Scale (TRS) scores at 20 months (+/– 17.3). Correlation with outcome was seen only with pre-operative TRS scores and follow-up time; both negatively correlated with the clinical outcome (36). It had previously been reported that pre-operative cerebellar dysfunction was a risk factor for the development of early "tolerance" (37). Natural disease progression and habituation have been proposed as the most plausible factors contributing to VIM-DBS treatment declining overtime (17, 23, 27, 31, 33). Despite the absence of consensus guide lines, electrode placement beyond a 2–3 mm radius of an intended target have been associated with suboptimal tremor control and can be a correctable cause of DBS "failure" (37, 38). Further, in cases of suboptimal clinical benefit, DBS lead adjustment of only a few millimeters can have a meaningful benefit (39). Other possible co-contributing factors include incorrect pre-operative diagnosis (14), loss of microthalamotomy (9) and increased impedance of brain tissue over time (10) (**Figure 1**). However, effects of varying tissue impedance are minimized by constant current DBS systems now more widely used.

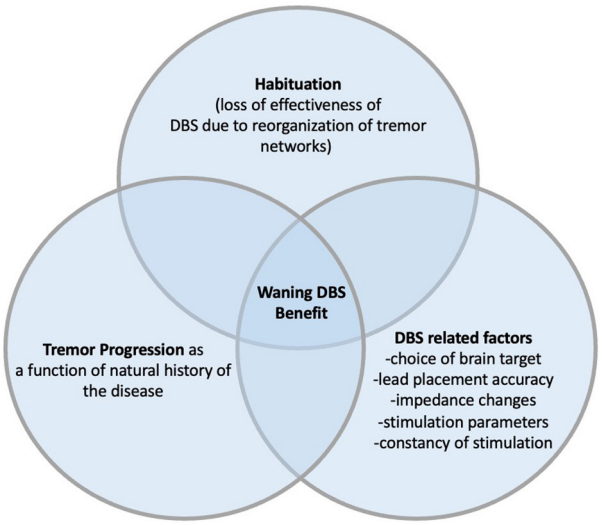

FIGURE 1 | Factors contributing to decline in clinical benefit of tremor after DBS.

Short-Term Habituation

Continuous increase in DBS stimulation parameters, followed by a temporary improvement in tremor severity but an ultimate paradoxical worsening is the hallmark clinical observation in habituation. This was first demonstrated in the short-term by Barbe et al. in patients treated with VIM DBS for ET. After optimization of stimulation parameters, patients were followed and reassessed at 10-weeks. Statistically significant improvement in TRS hemi-body scores compared to baseline was observed after optimization; but at 10-weeks this stimulation effect was remarkable weaker, abolishing the immediate effect compared to baseline (40). Furthermore, of the 21 patients who agreed to follow-up after initial stimulation changes, only 16 completed the 10-week assessment, with two patients dropping out due to unacceptable worsening of the tremor syndrome. Adaption of the pathological tremor networks to the new DBS interface was proposed, clinically seen as paradoxical worsening of tremor, referred to as "habitation" by the authors.

Long Term Habituation or Disease Progression?

Separating natural disease progression and habituation in the context of gradual loss of DBS benefit overtime is difficult. In theory, comparing the "off" stimulation tremor severity at two different time points should only represent progression secondary to disease. While tremor severity in the "on" stimulation state over similar time points should reflect both disease progression and the stimulation effect (12, 13). Delta, the difference between the "off" and "on" state, when compared overtime, appears our best measure of any changing stimulation effect, and possible habituation. Of all the long-term DBS follow-up studies in ET, only seven (12, 17–19, 29, 32, 33) have "off/on" data at more than one defined time point, that allows the analysis of change in delta overtime, and the possible detection of habituation (**Table 1**). Further, the most recent study by Paschen et al. have calculated the difference in TRS score in both "off/on" states compared to baseline, allowing for statistical separation of disease progression and habituation (13).

In the seven long-term DBS studies in ET that data is available to determine the percentage of delta change over time, loss of stimulation benefit was seen in all but one study (17). The effect lost over time, as a percentage of the stimulation effect on the first assessment compared to the last assessment, ranged from 4–42% (**Table 1**). However, owing to the design of the studies, the statistical significance of these changes remains unclear in all but one study, where subgroup analysis revealed the loss of effect to be not significant ($p > 0.05$). The target of DBS

TABLE 1 | The change in deep brain stimulation effect in long term studies of Essential Tremor.

Reference, Study type	Patients	Syndrome	Mean follow-up	DBS target	Uni/bilateral stimulation	Off assessment time^	Outcome*	Exclusion & other
Rehncrona et al. (17), prospective	*N* = 25 Exclusion = 14	ET and PD	ET: 6.5 yrs PD: 6.6 yrs	VIM	ET: 17/2 PD: 19/0	2-year: 4-hours 6–7 years: 1-hour	ET 2-year delta: 49% 6–7-year delta: 47% Loss of benefit: 4% PD 2-year delta: 77% 6–7-year delta: 54.5% Loss of benefit: 29%	ET *N* = 6 (3 dead, 1 refused, 1 lost, 1 battery life end) PD *N* = 8 (4 dead, 2 refused, 2 lost)
Sydow et al. (18), prospective	*N* = 19 Exclusion = 7	ET	6.54 yrs	VIM	Baseline: 15/4 6-years: 12/7	UN	1-year delta: 45.6% 6-year delta: 46.3% Gain of benefit: 1%	*N* = 7 (1 stopped due to SE, 3 dead, 1 refused, 1 lost, 1 battery life end)
Blomstedt et al. (21), prospective	*N* = 19 Exclusion = 8	ET	7.17 yrs	VIM	UN	UN	Initial (mean 13 months): delta: 52% Final (86 months) delta: 30% Loss of benefit: 42%	*N* = 8 (3 diagnosis revised, 4 died, 1 lost)
Favilla et al. (12), retrospective	*N* = 28 Controls = 21 Excluded = 41	ET	>36 months	VIM	19/9	30 mins	Unilateral 6 months delta: 27% 36 months delta: 26% Loss of benefit: 4% Bilateral 6 months delta: 63% 36 months delta: 37% Loss of benefit: 41%	*N* = 41 (10 prior DBS outside facility, 4 stimulator revision, 13 lost, 11 follow-up <24months)
Fytagoridis et al. (33), prospective	*N* = 18	ET	4.04 yrs	cZI	16/2	DBS deactivated overnight	1-year delta: 54.5% 3-5-year delta: 51.4% Loss of benefit: 6%	-
Cury et al. (29), retrospective	*N* = 98	ET, PD & DT	ET: 8.1 yrs PD: 10.2 yrs DT: 10.8 yrs	VIM	ET = 35/3 PD = 24/30 DT = 2/4	60 mins	PD Bilateral 1-year delta:73% 11–15 year delta: 69% 16–21 years delta: 60% Loss of benefit: 18% Unilateral 1-year delta: 67% 11–16 years delta: 58% 16–21 years delta: 63% Loss of benefit: 6% ET year delta: 66% >10 years delta: 48% Loss of benefit: 27% DT Delta: UN	DT 4/6 received GPi DBS after VIM DBS, 3 due to lack of efficacy and intolerable side effects
Tsubio et al. (32), retrospective	*N* = 124 Exclusion = 40	ET & DT	ET: 3.5 yrs DT: 3.4 yrs	VIM	ET: 72/25 DT: 17/9	At least 30 mins	ET 6-month delta: 50% 1–year delta: 42% 2–3 year delta: 37% 4–5 year delta: 38% 6year delta: 34% Loss of benefit: 32% DT 6-month delta: 42% 1–year delta: 45% 2–3 year delta: 41% 4–5 year delta: 8% 6–year delta: 42% No loss or gain of benefit	*N* = 40 (24 alternative diagnosis and 16 lack of assessments)

cZI, caudal zona incerta; DBS, deep brain stimulation; DT, dystonic tremor; ET, essential tremor; GPi, globus pallidus internus; N, number; PD, Parkinson Disease; PSA, posterior subthalamic area; SE, side effect; UN, unknown; VIM, ventralis intermedis nucleus of thalamus.

^Time after DBS was switched off.

**Statistical significance of delta at each time point or change in delta overtime (loss or gain of benefit) were not able to be verified.*

stimulation was the VIM in six (12, 17–19, 29, 33) and the PSA in one (32) of these studies. In five of the studies the exclusion and drop-out rate ranged from 24–59%, with drop-outs often including patients with progressive tremor severity, unacceptable side-effects or even stimulation revision. This could possibly lead to an underestimation of the loss of stimulation benefit over time. During follow-up, stimulation parameters increased across three studies, remained unchanged or statistical insignificant across two studies and were not reported in two.

Limitations beyond the high drop-out rate exists across all these studies. Only one group look at the relationship between lead location and tremor response, despite it being a known cause for chronic loss of DBS benefit over time. Cury et al. reported that stimulation to the caudal part of the right VIM was associated with a worse tremor result at 1-year but how this related to the change in delta overtime and habituation is unknown (29). Favilla et al. who concluded that disease progression is the most likely explanation for worsening tremor after DBS (12), failed to assess the change in response to stimulation over time in patients whose tremor was either stable or improved in the "off" state. Assessment including this cohort reveals a 4 and 41% loss of stimulation benefit between 6 and 36 months in the unilateral and bilateral stimulated groups respectively. Paschen et al. attributed 13% of the worsening "stim-on" to habituation (13). However, overestimation to disease progression is likely to have occurred after the mean monthly worsening of the TRS scores in the "off" and "on" state were calculated from different time points. In which, part of the decline in the "off" state is likely due to the loss of microthalamotomy that is not reflected in the TRS stim-on scores. In the most recent study by Tsuboi et al. delta values need to be interpreted with caution as not all patients were assessed in the "off" state at each separate time point (33).

Emerging Ataxia and Rebound Tremor as Biomarkers for Habituation?

The relationship between stimulation-induced ataxia and habituation is unclear. The two entities are often addressed independently despite the clinical observation that some patients develop a progressive ataxic cerebellar syndrome after bilateral VIM DBS for tremor when the stimulation intensity is increased (41, 42). This syndrome may be characterized by dysarthria, gait unsteadiness, limb incoordination and tremor of a different quality to the original tremor syndrome and often worse (43). DBS induced ataxia is not rare occurring in a third of patients in one large series (44). The cerebellar signs may dissipate if DBS is stopped and allowed to wash-out over several days, usually revealing the original tremor syndrome which may be more manageable than the DBS induced ataxic syndrome (43, 45). Induction and reversibility of the cerebellar dysfunction in these patients implies long-term aberrant plasticity within cerebellar networks. This clinical observation has been supported by functional imaging that has demonstrated stimulation induced hypermetabolism in the cerebellar nodule, exclusive to those with this syndrome, associated with stimulation particularly in the sub-thalamic white matter, the effect linked to antidromic stimulation of cerebello-thalamic fibers (45). Furthermore, a post-mortem study identified preservation of climbing and parallel cerebellum input fibers exclusive to those who had undergone DBS (46). Intriguingly, VIM DBS has also been shown to improve gait and limb ataxia in ET patients, independent of tremor-suppressing effects, provided the stimulation intensity is not excessive, at which point ataxia is worsened (41, 42). These data point to dual contribution of both stimulation proximity to cerebellar outflow tracts and intensity on the development of ataxia after VIM DBS.

Another phenomenon is rebound tremor where tremor severity is much worse than the pre-operative baseline immediately after DBS is switched off (10, 42, 45). This phenomenon has been strongly associated with the stimulation induced ataxic cerebellar syndrome, in which less tremor suppression benefit from stimulation was also observed (45). However, there has not been a clear association between rebound tremor and habituation. Nevertheless, switching the DBS off is a regular occurrence and many DBS groups advise patients to switch their device off at night in an effort to avoid habituation; although controlled studies to confirm this hypothesis are so far lacking. Not infrequently patients with waning tremor benefit and habituation describe more marked rebound tremor with the device off, such that some may become incapable of switching their device off at night owing to unacceptable worsening of tremor (43, 47).

Deep Brain Stimulation and Dystonia–An Insight for Habituation?

DBS of the globus pallidus internus (GPi) is an effective treatment for primary dystonia (48). However, unlike other neurological conditions, maximal clinical benefit can take weeks to months (49). This often occurs with similar stimulation parameters, in the absence of an abrupt but monotonic improvement in dystonia (50). Longitudinal neurophysiological examinations have provided mechanistic insights into excessive muscle activity and overflow characteristics. After GPi DBS a quick absence of enhance per-operative plasticity is seen but the normalization of cortical inhibition takes months to achieve, following a similar time course to the clinical response (51). Further, these physiological changes do not immediately ablate after stopping the stimulation (52). The long-term effects on the cortical circuitry in dystonia are positive, but negative examples, in the form of emergent dystonia, after lesional and DBS surgery of the thalamus have been reported (53). Conceptually, habituation is likely a form of neural reorganization in a negative sense, with many similarities to the changes we observe after GPi DBS for dystonia.

HABITUATION AND OTHER TREMOR SYNDROMES

Parkinson's Disease Tremor

DBS for the management of PD is a well-established treatment (54–60). It has been shown to be superior to medical therapy in the early (54) through to advanced disease stages (60). The subthalamic nucleus (STN), GPi and VIM have all been shown

to be effective DBS targets for tremor suppression (61, 62). Despite the initial reports of habituation involving a cohort predominantly of PD patients (10); little has been published in the literature since. Rechrona et al. demonstrated a 29% loss of effect with VIM stimulation over a 4–5-year follow-up period (17). More recently, Cury et al. showed up to an 18% loss of benefit with the same target over a duration of 16–21 years (29). However, other long-term follow-up studies have not demonstrated a similar waning benefit of DBS commonly associated with ET (61–65). In early-stage PD, STN DBS has been shown to slow the progression of rest tremor and provide long-term symptomatic benefit compared to standard medical care (54). Collectively these data may suggest that habituation is less likely to occur in PD tremor and less likely with DBS targets other than VIM.

Dystonic Tremor

In comparison to ET and PD the long-term effectiveness of DBS for dystonic tremor is not as well established (66). Many studies have reported on the effectiveness of GPi DBS for dystonia without reporting on tremor outcomes (67). The thalamus, commonly the VIM, is the predominant target in DT but alternative or tandem targets (GPi or STN) are often used when dystonic symptoms are more problematic (68). In a systematic review, improvement in TRS motor scores from baseline was approximately 40–50% (66). Recent studies by Tsuboi et al. and Cury et al. reported tremor suppression benefit was not significant at greater than 5–6 years after implantation (29, 32). Moreover, four of six patients in the study by Cury et al. received additional GPi stimulation due to lack of efficacy or intolerable side effects (29). Others have report the similar need to proceed to an alternative DBS target to manage persistent or emergent dystonia and/or tremor after an initial single target DBS implantation (68, 69). The delta change over time could only be assessed in the Tsuboi et al. (32) cohort, where a loss of benefit was seen at the majority of time points (**Table 1**). The outlying result at greater than 6 years was considered non-significant by the authors (32). It has been hypothesized that these observations represent habituation (32). There is growing evidence dystonia results from widespread multi-level network dysfunction (70), involving the basal ganglia, cerebellum and excessive motor cortical plasticity, with evidence long-term network modification after GPi DBS (71), however the long-term effects of thalamic DBS on these networks in dystonia is unknown.

Uncommon Tremor Syndromes

Apart from one randomized clinical trial in multiple sclerosis (MS)-associated tremor (72), experience with uncommon tremor syndromes; Holmes' tremor (HT) (73), orthostatic tremor (OT) (74), neuropathy-associated tremor and fragile X-associated tremor/ataxia syndrome (75); come from case reports and small case series. Habituation has been reported in neuropathic tremor from demyelinating neuropathy treated with VIM DBS, worse than a comparison ET group (76). Bi-or-unilateral VIM stimulation is the commonest modality of treatment used irrespective of tremor syndrome. Other targets of stimulation used independently or as an adjacent to the VIM included: cZi, GPi, PSA, STN, Ventro-lateral (VL), Ventralis oralis anterior or Ventralis oralis posterior nuclei (VOA/VOP) (75). Data suggests that DBS might be useful for these uncommon syndromes; but both the rarity of these conditions and heterogeneity makes the nature and magnitude of any effect uncertain (75). Furthermore, the same must be said for the development of unwanted events to stimulation including habituation.

FACTORS THAT MAY PREDISPOSE TO HABITUATION

Does Habituation Differ Between Tremor Subtypes?

Attempting to identify factors that predisposed to habituation, a phenomenon hard to define and even more difficult to study, should be done with caution. However, the underlying disease seems to be an important factor in predicting long-term outcomes (29, 32). DT appears to be the tremor syndrome least responsive to DBS in the long-term and potentially the most susceptible to habituation (29, 32). Although Tsubio et al. reported comparable long-term tremor suppression results between DT and ET in VIM DBS, loss of stimulation benefit at greater than 6-years was only present in the DT cohort. Furthermore, improvement in activities of daily living tended to be greater in the ET cohort (32). Cury et al. have demonstrated a similar loss of tremor suppression benefit in DT compared with both ET and PD (29). This may reflect disease progression or emergent dystonia (10, 53) rather than habituation (32). Combined VIM and GPi DBS (77) could potentially alleviate some of these issues but long-term follow-up studies are required.

There is evidence to suggest habituation is less common in PD tremor treated with DBS. In the long-term comparison study of thalamic DBS in PD, ET and DT; greatest stimulation benefit was seen with PD tremor (**Table 1**) (29). In non-comparative studies of VIM, STN and GPi DBS; more stable consistent response to stimulation have been demonstrate (61–65). In some of these studies up to 50% of the cohort experience complete absence of rest tremor (62–65). One interesting observation after both VIM and STN DBS, tremor in the off-medication-off-stimulation condition is often less severe than the off-medication baseline state. This is surprising despite the knowledge that PD tremor doesn't necessarily get worse over time. Structural or neurochemical change leading to the improvement of tremor has been suggested; a persistent micro-thalamotomy effect or residual effect from electrical stimulation have not been excluded (64). This evidence would argue against habituation in PD tremor.

Does Habituation Depend on DBS Target?

The DBS target for tremor suppression is of particular interest in view of the progressive loss of tremor benefit seen with VIM DBS in ET (36). Given the important role the cerebellothalamic tract plays in tremor, the PSA/cZI has been used as an alternative DBS target. A randomized trial comparing the two targets in the treatment of ET, although not statistically significant, favored lower amplitude stimulation of the PSA for tremor control. Owing to the short follow-up duration, any

implication on the development of habituation could not be assessed (78). A comparative study comparing the cZI and VIM targets in ET, demonstrated both to be beneficial for tremor suppression; but a potential long-term advantage with applying VIM stimulation due to the gradual worsening of tremor scores in patients stimulated in the cZI region (30). However, other studies have demonstrated persistent long-term benefit with PSA/cZI stimulation and an absence of habituation (33–35). Available evidence suggests PSA/cZI to be equivalent to VIM in effectiveness for tremor suppression but with lower stimulation energy requirements, likely reflecting closer electrode proximity to the dentatorubrothalamic tract. Lower energy requirements for chronic stimulation using the PSA/cZI target could confer some advantage in reducing the risk of habituation but does not appear to eliminate the problem altogether.

PD tremor cohort comparison between VIM-STN and STN-GPi stimulation has occurred with differing strengths of evidence. In a meta-analysis of five randomized control trials, STN and GPi DBS were shown to reduced tremor symptoms without significant differences between the two stimulation targets. STN DBS appeared to reduced tremor severity with a larger effect size in the short-term, while GPi DBS appears to have a steadier and more stable tremor effect in the long-term (62). Further comparison of these two targets, specifically in relationship to action and rest tremor; suggested the initial STN superiority might be due to effective action tremor suppression in the early post-operative period (79). VIM and STN DBS have been compared in a small retrospective analysis, no significant difference in degree of improvement in rest, action or postural tremor was observed (62).

Is Habituation Different With Unilateral vs. Bilateral VIM DBS?

Despite bilateral VIM DBS leading to a greater overall reduction in tremor severity (80) often owing to the bilateral and midline benefits (18), unilateral VIM DBS has been associated with more persistent tremor benefit from stimulation in ET (12). Favilla et al. (12) demonstrated the benefit from stimulation compared with baseline was consistent through 36-months for both unilateral and bilateral stimulation. However, the loss of delta overtime was 4% in the unilateral compared to 41% in the bilateral group (**Table 1**). A similar finding was seen in the Cury et al. PD cohort who had undergone VIM DBS, tremor suppression was maintain in both unilateral and bilateral groups through 16–21 years of follow-up, but the loss of delta over time was more pronounced in the bilaterally treated group (29) (**Table 1**). Both observations may reflect a possible propensity for habituation with bilateral stimulation despite the tremor syndrome. Conceptually, bilateral stimulation could exert greater plastic force on cerebellar networks to adopt abnormal configurations, with less potential for compensation from an untreated side. Other factors that should be considered when counseling patients regarding the possible development of habituation include asymmetry of the tremor syndrome, stimulation intensity and continuous vs. interrupted stimulation.

PREVENTION AND MANAGEMENT OF HABITUATION TO DBS FOR TREMOR

The accuracy of lead placement is critical to avoid early loss of benefit after VIM or PSA/cZI DBS however this problem, by definition, is distinct from true habituation. For patients with well-placed DBS leads possible preventative strategies for habituation include conservative parameter setting to avoid overstimulation and instructing the patient to switch the device off at night (8). Patients may also be advised to only use stimulation the day when needed rather than continuously, in an on-demand fashion, which may reduce the risk of habituation (81). In clinical practice when patients return in long term follow up and report declining tremor benefit, there is a temptation to reprogram usually with increased stimulation current, which often improves tremor but only temporarily. Such increases when performed repeatedly over time may result in chronic DBS-induced ataxic syndrome. An alternate strategy is to refrain from increasing the DBS, clinical worsening is mild and provided patients remain significantly improved compared with the pre-operative baseline.

There are a few studies evaluating varying stimulation programs in an attempt to reduce the occurrence of habitation. Seier and colleagues found reduce benefit decay in patients varying between two equally effective stimulation programs weekly after 12 weeks compared with those receiving unvarying programs (82). However, another study using daily variation of stimulation programs found no superiority to unvarying stimulation at 10 weeks (83). In clinical practice, with limited options available, installing different effective programming groups for patients to vary between is feasible (84), and may reduce habituation, although weekly changes appear more effective than daily. Cycling of stimulation between ON and OFF in blocks of 1–30 s was reported as helpful in reducing habituation and rebound tremor in three PD tremor patients (85).

For patients with established benefit decay and habituation, particularly those with stimulation induced ataxia, reduction of stimulation current may be helpful, and can be more achievable if performed gradually and predominantly unilaterally. Cessation of stimulation for a few days can be attempted, preferably supervised in hospital, and after initial rebound tremor passes, dissipation of DBS induced cerebellar ataxia is expected with a return to the baseline tremor syndrome, and potential functional improvement if ataxia has become the predominant driver for disability. Cessation of stimulation provides an opportunity to reappraise DBS effectiveness in the On vs. Off stimulation condition. Some patients will experience improvement in DBS effectiveness after a period of complete DBS cessation, so-called "stimulation holiday", however such improvements are usually unsustained but can be repeated in an attempt to recapture benefits lost to habituation (47).

Related to prevention of habituation should be an attempt to stratify the risk of its occurrence in tremor patients being considered for DBS. The tremor subtype is relevant with PD patients less likely to develop habituation than those with ET or DT. Tremor phenomenology may also be useful in predicting

risk of habituation, with patients with more action-predominant tremor (7) and those with signs of cerebellar ataxia at greater risk (37).

Surgical approaches to habitation may include reimplantation of DBS with a repositioned electrode optimized to closer proximity to the dentatorubrothalamic tract (as imaged by diffusion tensor tractography MRI) which may achieve superior tremor control with less habituation (86). Moreover, there is growing evidence that closer targeting of MRI-visualized dentatorubrothalamic tract (DRT) provides more effective and efficient tremor control (87, 88) and it remains to be seen whether this approach of targeting DRT deliberately will confer lower rates of habituation in the longer term. Additional "rescue" leads have been implanted in targets including VIM, PSA/cZI, VOA and STN with moderate additional benefit (89, 90). Thalamotomy has been performed after failed VIM DBS including cases with waning benefit and habituation, with modest additional benefit (91).

The advent of more advanced DBS hardware and programming capabilities including independent, constant current directional leads, implanted pulse generators allowing shorter pulse widths $<60\ \mu s$ and sensing of local field potential (LFP) spectra hold promise to assist in the prevention and long-term management of habituation after tremor DBS. Directional leads allow shaped stimulation fields to maximize benefit with fewer side effects, widening the therapeutic window (92, 93). Similarly shorter pulse widths allow greater stimulation current to be delivered without provoking side effects (94, 95). DBS devices allowing real-time recording of LFPs foreshadow closed loop stimulation; the first study demonstrating successful ambulatory recording of VIM and cZI LFPs corresponding to voluntary movements and tremor with highly effective tremor suppression when DBS was delivered closed-loop triggered by LFP activity (96). Of relevance to closed-loop approaches is the important discovery that delivery of DBS stimuli in specific relation to the phase of tremor (phase-locked stimulation) is more effective and efficient with fewer side effects (97).

CONCLUSIONS

Habituation is a real phenomenon after DBS for tremor and is a contributory factor to waning clinical benefit after tremor DBS. The other major contributor to waning benefit is disease progression of the underlying tremor syndrome. Instances of more dramatic loss of clinical benefit over shorter timeframes (short term habituation) may occur and induction of progressive ataxic cerebellar symptoms suggesting aberrant plasticity within cerebellar networks targeted by VIM and PSA DBS. Our current mechanistic understanding of habituation is incomplete and further neurophysiological and imaging studies will be required to elucidate the pathophysiology. In clinical practice, habituation after DBS for tremor remains a feared complication, with available preventative strategies limited to interrupted stimulation regimens (typically switching off at night), minimizing stimulation current or varying programs. It remains to be seen whether technological innovations in DBS such as deliberate MRI-guided targeting of the DRT, directional leads, lower pulse widths or advanced stimulation methods such as phase dependent or on demand DBS will reduce the problem of habituation. In the meantime, it is important that habituation and disease progression of tremor be explained to patients prior to DBS as factors that may result in reduction in clinical benefit over time.

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REVIEW
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A Review on Wearable Technologies for Tremor Suppression

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Tremor is defined as a rhythmic, involuntary oscillatory movement of a body part. Although everyone exhibits a certain degree of tremor, some pathologies lead to very disabling tremors. These pathological tremors constitute the most prevalent movement disorder, and they imply severe difficulties in performing activities of daily living. Although tremors are currently managed through pharmacotherapy or surgery, these treatments present significant associated drawbacks: drugs often induce side effects and show decreased effectiveness over years of use, while surgery is a hazardous procedure for a very low percentage of eligible patients. In this context, recent research demonstrated the feasibility of managing upper limb tremors through wearable technologies that suppress tremors by modifying limb biomechanics or applying counteracting forces. Furthermore, recent experiments with transcutaneous afferent stimulation showed significant tremor attenuation. In this regard, this article reviews the devices developed following these tremor management paradigms, such as robotic exoskeletons, soft robotic exoskeletons, and transcutaneous neurostimulators. These works are presented, and their effectiveness is discussed. The article also evaluates the different metrics used for the validation of these devices and the lack of a standard validation procedure that allows the comparison among them.

Keywords: neurorehabiliation, pathological tremor, essential tremor, Parkinson's disease, wearable device, assistive technology

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INTRODUCTION

Tremor is defined as a rhythmic, involuntary oscillatory movement of a body part (1). Although physiological tremor is present in everyone, this small degree of tremor is not enough to affect daily activities. However, some pathologies lead to very disabling tremor. Pathological tremor—simply referred to as tremors in the remainder of the document—is one of the most common prevalent movement disorders, affecting over 0.4% of the general population (2), strongly increasing its incidence and prevalence with aging (3). Tremors arise due to various conditions (4), and their exact underlying mechanisms have not been elucidated; thus, none of them is wholly understood (1).

Although there are several causes for tremor disorders, the most prevalent and incident types of tremor arise from two neurodegenerative disorders: Parkinson's disease (PD) and essential tremor (ET) (5–7). ET is the most prevalent pathological tremor (8), affecting 5% of the population over

65 years old (9), while PD has an estimated prevalence of 1% for people over 60 years (10, 11). Other causes for atypical tremors could be multiple sclerosis (12, 13), head trauma (14), and psychogenic tremor (15), among others. Although tremor could not be considered inherently dangerous, more than 65% of the population suffering from upper limb tremor report severe difficulties in performing their activities of daily living (ADL), significantly decreasing their independence and health-related quality of life (16, 17). These patients often present psychological effects due to their condition, such as physical disability (18), leading to social exclusion (19) and depression (20–22). Almost a quarter of patients who go to treatment centers are forced to quit their profession, and 60% decide not to apply for jobs or promotions because of disabling symptoms (23). The exact causes of most of the tremors remain unknown (24, 25), and as they are not curable, the main purpose of the treatments is to alleviate their symptoms (26). Therefore, improving tremor management could drastically reduce direct and indirect costs related to tremor and improve the quality of life and independence of both patients and caregivers.

The treatments for tremor are mainly surgical or pharmacological. In ET, propranolol or primidone is the first-line therapy against tremor, reducing hand tremor by 50% during clinical tests (27, 28). Despite this, up to 30% of patients do not respond to this treatment or experience intolerable second effects (29). Moreover, up to 56% eventually give up their use (30) because of these secondary effects or the lack of efficacy. Regarding PD, levodopa is considered the most effective drug in managing its motor symptoms (31). However, motor fluctuation and dyskinesia seem to be related to levodopa treatment (32); in addition, its effect seems to decrease over the years (33).

Surgical alternatives to pharmacological treatments are stereotactic thalatomy or deep brain stimulation (DBS), which are invasive procedures with an associated high risk. Although both interventions show similar results in managing tremor, DBS is associated with a lower complication rate (34, 35). However, DBS is related to a higher risk of intracranial hemorrhage (4% of patients) (36) and secondary psychiatric effects (37), and, besides, the eligible patient rate is extremely low (1.6–4.5% in PD) (38). High-intensity focused ultrasound (HIFU) has recently emerged as an alternative treatment for medically refractory ET (39). A recent study supports that this noninvasive procedure reduces tremor by 55% after 6 months (40). However, some studies reported tremor recurrence (41) and mild adverse secondary effects such as the alteration in sensation (42) or paresthesia and gait disturbances (41).

Alternative research avenues were explored lately; some studies evaluated the possibility to suppress tremor by modulating afferent feedback to the spinal cord (43), motivated by the noninvasiveness, reversibility, and adaptability of this strategy. However, results were variable within and across subjects (43, 44). This variability is likely due to the complexity of the neural circuits targeted when treatments aim to suppress tremors peripherally in specific muscles (44). Recent works support the idea the stimulation of the afferent pathways through spinal cord stimulation (SCS) may alleviate the symptoms of tremors, probably by disruption of low-frequency synchronization in the corticobasal ganglion circuits (45, 46). Some case reports of SCS treatment for ET (47) and PD (48, 49) have shown its effectiveness in reducing tremor in these patients. These results suggest that this is an exciting area for future research, although its mechanisms remain unknown and it needs to be extensively validated.

In summary, surgery, DBS, and focused ultrasound are effective second-line treatments (50–52). However, they tend to lose effectiveness with time and are invasive procedures that cause nonreversible brain lesions (27). Despite all this variety of treatments, tremor is not effectively handled in 25% of cases (53). In this context, this paper presents the findings of several research works focused on tremor suppression through wearable technologies (exoskeletons and neuroprosthetics devices). These works demonstrated the feasibility of managing upper limb tremors with biomechanical loading, applied through either robotic exoskeletons or transcutaneous neurostimulation. This approach, on the contrary to pharmacotherapy or surgery, suppresses tremors by modifying the limb biomechanics, not targeting their site of origin. This article also evaluates research focused on suppressing tremor by triggering a response either in the central nervous system (CNS) or in the peripheral nervous system (PNS) as a consequence of afferent stimulation.

The paper is organized as follows. First, we describe and classify the different devices that suppress tremor through wearable technologies. Robotic exoskeletons are presented describing classical wearable robotic devices as well as recent soft robotic exoskeletons. Then, we present the use of functional electrical stimulation (FES) to emulate the exoskeleton's effect by using human muscles as actuators of the system. Eventually, we introduce the latest developments for tremor suppression based on afferent neurostimulation. The concept, implementation, and experimental validation are reviewed for all approaches, and then the significant findings are discussed. The high variety of technological approaches that we found highlights the importance of tremor evaluation methods to compare their effectiveness in tremor management, so we dedicate a section to present the most common metrics and discuss their results. The article concludes by outlining current and future research in the field of tremor suppression using neuroprosthetic devices.

LITERATURE SEARCH METHODOLOGY

We conducted a literature search using three different databases: Scopus, Web of Science, and PubMed until March 2021. We used the following in the search query in the title, abstract, and keywords: (tremor) AND (suppress* OR manag* OR reduc*) AND {[(robot* OR activ* OR soft) AND (exoskeleton OR orthos* OR neuroprosth*)] OR [stimul* AND (electric* OR afferent* OR mechanic* OR vibrat*)]}. Besides, we excluded those papers that included the following terms in the title: "surg*" OR "deep brain stim*" OR "ultrasound" OR "spinal cord stim*." The literature search was limited to papers published in the last 15 years.

Inclusion criteria for this review were as follows:

1. English full-text journal articles or conference proceedings.

2. Studies related to devices for suppressing tremor through different wearable approaches or technologies.
3. Description of the experimental validation and the yielded suppression through quantifiable scales.

Exclusion criteria included the following:

1. Documents that only described the mechanical structure of the device or the design of actuators or new materials intended for tremor suppression.
2. Treatments based on drugs, surgical interventions (like DBS), or noninvasive treatments that do not fulfill the wearability criteria (like transcranial magnetic stimulation or transcranial direct current stimulation).
3. Documents that lacked complete methods, results, or discussion sections.

In those cases that we identified both a conference proceeding version and a full-text journal article of the same study, we only included the complete journal version since it contained further details.

The initial number of papers (1,089) was reduced to 761 after looking for duplicated documents. After checking the title and abstract, we discarded 664 papers. Finally, 97 were selected for full-text reading. Based on the authors' experience and the bibliography of the reviewed articles, six documents that were not included in the initial search were also selected for full-text reading. As a result, we identified 36 documents out of 1,089 initial records to be considered for this review. **Figure 1** shows the flow diagram of the literature search and document selection procedure.

We analyzed several aspects of the selected documents: (i) working principle and hypothesis that supported the tremor management approach for each device; (ii) the experimental setup for device validation; (iii) subject sample size, tremor pathology, and metrics used to quantify the tremor reduction; and (iv) the efficacy of the tremor suppression reported by each approach.

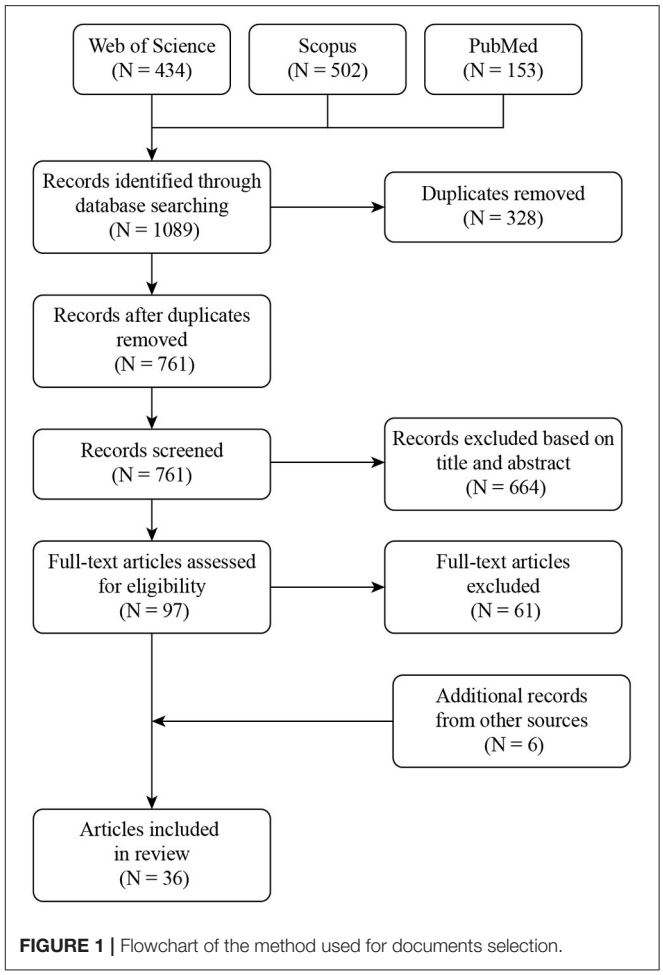


FIGURE 1 | Flowchart of the method used for documents selection.

RESULTS

Our literature search led to 36 documents to be considered for this review. **Table 1** summarizes the working principle of the reviewed devices, as well as their validation methods and tremor suppression results. In the next subsections, we deepen into the different suppression technologies and their effectiveness as well as the metrics and experimental setups used to evaluate each one of them. **Figure 2** represents the devices included in this review, showing their effectiveness in tremor reduction, the metrics, and the number of subjects used during the experimental validation.

Wearable Technology for Tremor Suppression

In this section, we present and describe the devices that claim to manage tremor through wearable technology. We have classified them according to their working principles into robotic exoskeletons, soft robotic exoskeletons, FES neuroprosthesis, and afferent neuroprosthesis. Robotic exoskeletons, or active orthoses, include such robotic devices composed of rigid frames, while soft exoskeletons are composed of flexible elements such as cables or straps. Both kinds of devices base their action on force application and biomechanical loading. Regarding neuroprostheses, FES devices are based on electrical stimulation that produces muscle contraction for biomechanical loading, while afferent neuroprostheses use sensory stimulation to generate a response in the nervous system through the afferent pathways. The intensity of the stimulation in FES devices is always over the motor threshold, while the stimulation in an afferent neuroprosthesis can be low-intensity electrical stimulation (under the motor threshold) or mechanical stimulation. **Figure 3** represents the distribution of reviewed papers according to this classification.

Robotic Exoskeletons for Tremor Suppression

Biomechanical loading is a classical solution for tremor suppression (16). In 1974, Joyce and Rack (89) reported the first results of adding force and inertia to physiological tremor. These results were posteriorly replicated in pathological tremor by adding inertial loads (90–94) or applying forces (95–100) to the affected limb using different kinds of orthoses. Afterward, active orthoses were proposed to achieve these same goals by

TABLE 1 | Overview of wearable devices that suppress pathological tremor.

#	Device	Suppression strategy	Validation method	Results
Active orthoses				
1	*WOTAS* (54)	Joint impedance control through DC motors	10 tremor-related patients	70% average PSD tremor reduction
		Force application opposed to tremor component using DC motors	10 tremor-related patients	81.2% average PSD tremor reduction
2	*Voluntary-driven elbow orthosis* (55)	Motor controller enabled voluntary movements	Replication of 1 ET patient tremor by a mechanical system	99.8% PSD tremor against 1% voluntary movement reduction
3	*Electromyogram-controlled exoskeleton* (56)	Motor controller enabled voluntary movements recognized by EMG data	Manual trigger of tremor recognition by 1 ET patient	50–80% tremor amplitude reduction
4	*Pneumatic actuation orthosis* (57)	Tremor torque counteracted by pneumatic cylinder	Robotic platform simulating tremor and volitional movements of 10 patients	98.1% tremor suppression at the fundamental frequency (74.3% at second-harmonic) 2.08% error tracking voluntary movement
5	*Wearable tremor suppression glove* (58)	Forces application through nonstretchable cables	Robotic platform simulating tremor and volitional movements of 7 PD patients	12.4% average error in volitional movement reconstruction
Soft robotic exoskeletons				
6	*WTSG* (59)	Force application through cable-enabled power transmission	Tremor simulator with seven recorded patient datasets	85 ± 8.1% amplitude reduction, and power reduction for the 1, 2, and 3 harmonics of 87.9 ± 13.6, 92 ± 7.4, and 81.7 ± 13%, respectively
7	*SETS* (60)	Force application opposed to tremor movement using magnetic fluid-based flexible semi active actuators	Five healthy subjects simulating tremor	61,82% mean absolute value (MAV) acceleration decreases 58.85% MAV angular velocity decreases 61.89% RMS acceleration decreases 56.22% RMS angular velocity decreases
8	*Soft exoskeletal glove* (61)	Force application opposed to tremor movement using PAMs	1 ET patient	75% tremor amplitude reduction and 70% frequency amplitude reduction
9	*Soft glove with layer jamming actuator* (62)	Joint rigidity controlled by jamming actuators	Tremor simulator with 15 recorded patient datasets	Maximum amplitude reduction of 74.79 ± 4.23%
FES neuroprostheses				
10	*Prochazka et al. FES device* (63, 64)	Activation of tremorogenic muscles out-of-phase	3 ET patients; 4 PD patients; six multiple sclerosis patients	58.1 ± 20.5% tremor attenuation ($N = 12$, tremor unaffected in one patient)
11	*Gillard et al. FES device* (65)	Activation of tremorogenic muscles out-of-phase	3 PD patients	84.5 ± 2.2% average tremor cancellation
12	*Popović et al. Multiple stimulation channels FES platform* (66)	Selective stimulation of multiple muscles out-of-phase	3 ET patients; 4 PD patients	67 ± 13 average tremor amplitude reduction ($N = 6$, tremor unaffected in one patient)
13	*Widjaja et al. EMG and FES platform* (67)	Activation of tremorogenic muscles out-of-phase	1 ET patient	57% suppression in tremor amplitude
14	*Dosen et al. Tremor predictor based on IHT of EMG and FES platform* (68)	Activation of tremorogenic muscles out-of-phase	2 ET patients; 4 PD patients	60 ± 14% average PSD tremor suppression ($N = 5$, tremor unaffected in one ET)

(Continued)

TABLE 1 | Continued

#	Device	Suppression strategy	Validation method	Results
15	*Tremor Neuroprosthesis* (69)	Adaptive cocontraction	2 PD patients; 4 ET patients	52.33 ± 25.48% tremor amplitude reduction ($N = 26$ trials, tremor was exacerbated in 4 trials)
16	*Grimaldi et al. FES platform* (70)	Cocontraction	1 ET patient; 1 PD patient; 1 paraneoplastic cerebellar syndrome	50% tremor reduction only in the ET patient
17	*Bó et al. FES device* (71)	Isometric cocontraction of the pair of antagonist muscles	10 ET patients	66.9 ± 21.7% tremor RMS reduction ($N = 8$, tremor unaffected and exacerbated in one patient)
18	*Tremor's glove* (72, 73)	Constant cocontraction of the pair of antagonist muscles	34 PD patients (72)	43.8 ± 33.2% tremor RMS reduction (61.8% of patients showed at least 30% reduction)
			15 PD patients (and 15 PD patients as sham group) (73)	56.86 ± 37.97% tremor RMS reduction; significantly different from sham group
Afferent neuroprostheses				
19	*Dosen et al. Tremor predictor based on IHT of EMG and FES platform* (68)	Electrical stimulation under motor threshold	2 ET patients; 4 PD patients	42 ± 5% average PSD tremor suppression (N=5, tremor unaffected in one ET)
20	*Multichannel electrode for afferent stimulation* (74, 75)	Out-of-phase sensory electrical stimulation	1 PD patient (74)	58% average reduction in wrist tremor angle
			9 ET patients (75)	32% average reduction in wrist tremor; surface stimulation led to lower reduction
21	*Heo et al. electrical afferent platform* (76–79)	Continuous electrical afferent stimulation	18 ET patients, stretched arm task (76)	40% RMS tremor reduction in wrist joint. 60% in MP joint
			18 ET patients, spiral drawing task (77)	12% RMS tremor reduction in MP joint
			14 PD patients (78)	RMS tremor reduction: 67.7 ± 23.6 in finger ($N = 64\%$); 62.1 ± 20.0 in hand ($N = 50\%$); 53.1 ± 22.9 in forearm ($N = 71\%$)
			9 SWEDDs patients (79)	No significant tremor reduction
22	*Shanghai Jiao Tong University electrical afferent platform* (80, 81)	Continuous electrical afferent stimulation	2 PD patients (80)	Significant tremor reduction (no data)
			8 PD patients (81)	61.7 ± 8.9% tremor movements reduction 47.9 ± 25.8% EMG reduction
23	*Dideriksen et al. electrical afferent platform* (44)	Out-of-phase electrical afferent stimulation	5 PD patients; 4 ET patients	52% average reduction ($N = 6$, tremor unaffected in three patients)
24	*Cala Health neuromodulation device* (82–85)	Transcutaneous afferent patterned stimulation of median and radial nerves	23 ET patients ($N = 10$ in treatment group; $N = 13$ in sham group) (82)	60 ± 8.4% tremor reduction in TETRAS scale (spiral drawing)
			77 ET patients ($N = 40$ in treatment group; $N = 37$ in sham group) (83)	Subject-rated Bain and Findley ADL score improvements were greater in the treatment group (49%) than in the sham group (27%). 42% tremor reduction in TETRAS scale

(Continued)

TABLE 1 | Continued

#	Device	Suppression strategy	Validation method	Results
Afferent neuroprostheses				
			205 ET patients in three month home therapy (84)	Improvements in TETRAS (62% patients) and BF-ADL (68% patients) scores Wrist tremor reduction in 92% patients (54% patients' improvements greater than 50%)
			15 ET patients (85)	80% of patients showed tremor improvement 60min after the stimulation
25	*Kim et al. electrical afferent platform* (86)	Transcutaneous afferent patterned stimulation of radial nerve	9 ET patients	42.17 ± 3.09% PSD reduction
26	*Essential platform* (87)	Continuous mechanical afferent stimulation	18 ET patients	Not conclusive
27	*Kyushu University Mechanical Vibration Stimulation platform* (88)	TVR movement induction to counteract tremor movement	5 healthy subject	Successful induction of movement through vibrating stimulation

using actuators; an overview of this technological approach is represented in **Figure 4**.

One of the first devices that followed this approach was the WOTAS (wearable orthosis for tremor assessment and suppression) exoskeleton reported by Rocon et al. (54). This device was a robotic exoskeleton with three degrees of freedom (elbow flexion–extension, forearm pronation–supination, and wrist flexion–extension) that was able to apply forces to the patient's upper limb joints. This exoskeleton identified the tremor and volitional components of motion with small phase lag by using a two-stage method (101). Once the tremor was identified, WOTAS was able to use two different strategies to counteract tremorous movements: simulating the application of viscosity and inertia to change the impedance of the limb and suppress high-frequency movements (passive control mode) or applying forces opposed to the tremor component of the movement to counteract it (active control mode). Both strategies were tested on 10 tremor-related patients, leading to 70 and 81.2% average power spectral density (PSD) tremor reduction for passive and active control modes, respectively (54).

Alternatively, the paradigm followed by the active elbow orthosis presented by Herrnstadt and Menon (55) was based on reducing tremor by estimating the voluntary movement of the user. The controlled motor of the orthosis only enabled the volitional action, while the tremor movement was rejected. They developed a mechanical system that replicated the movement from an ET patient record to test this device. Using this simulation platform, they reduced the PSD of tremor by 99.8%, while the voluntary movement was reduced to less than 1%.

The same strategy was followed by the exoskeleton developed by the team of Fujie to assist ET patients while eating (56). Their objectives were to identify volitional movement using electromyography (EMG) signals of ET patients in real time and enable only voluntary actions. However, although they were working on it, using an algorithm based on short-time Fourier transformation and time delay neural networks (102), they did not integrate this intention recognition with the robotic exoskeleton. Instead, they tested the tremor suppression simulating this recognition with a switch triggered by an ET patient (56), obtaining that the tremor was reduced by 50–80% compared to not wearing the exoskeleton.

By contrast, instead of generating the volitional movements of the patient, Taheri et al. (57) estimated and canceled the muscle torque responsible for tremor movements. This torque was canceled by generating an equal torque with opposite sense using a pneumatic cylinder. They validated the algorithm with data recorded from 10 patients with severe tremor that was simulated by an artificial wrist joint. Experimental results showed that they were able to suppress tremor movement with an average reduction of 98.1% at the fundamental frequency and 74.3% at the second-harmonic frequency. The average position error on the voluntary movement was 2.08%.

The main limitation of these devices is their poor wearability due to their size and rigid structure (54). Despite attaining a systematic attenuation of moderate and severe tremors, active orthoses were not helpful in daily life as users were reluctant to use them because of their bulky appearance (53).

Soft Exoskeletons for Tremor Management

New technologies developed in the context of soft robotics enable engineers to create devices more appealing than robotic exoskeletons to reduce pathological tremor while also fulfilling usability requirements for the final users; a conceptual representation of this technology is shown in **Figure 5**. In this context, Zhou et al. proposed a wearable tremor suppression glove (WTSG) that applied forces to the tremorous hand through nonstretchable cables acting as tendons do (58, 59). These cables were attached to the index finger, thumb, and wrist to

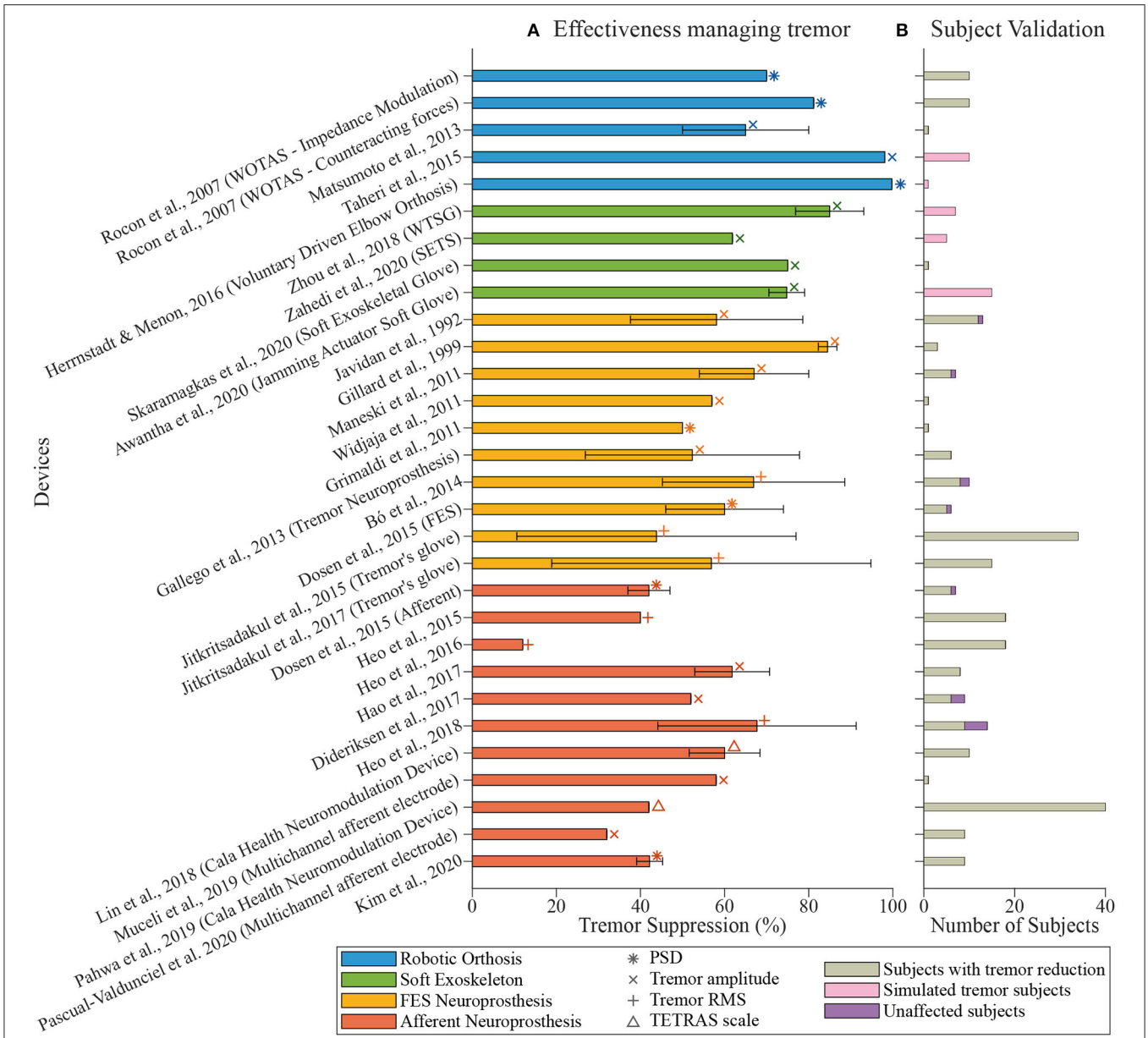


FIGURE 2 | Overview of tremor management devices. **(A)** shows the tremor reduction reported by each paper (percentage, mean ± standard deviation). The color of the bars indicates the technological approach followed by the authors: robotic exoskeletons in blue, soft exoskeletons in green, FES neuroprosthesis in yellow, and afferent neuroprosthesis in orange. Symbols indicate the metric used during the validation of the device. **(B)** shows the number of subjects involved in the validation. Colors point out if the tremor was successfully managed (in gray), if it remained unaffected (in purple), or if tremorous movements were simulated (in pink).

suppress tremor in the index finger metacarpophalangeal (MP) joint, thumb MP joint, and wrist joint in the flexion–extension direction. Inertial measurement units were used to sense the system and acquire tremorous and volitional movement, while DC motors coupled with rotary to linear converters were responsible for the actuation of the device.

Primarily, to test this prototype, the authors built a platform to simulate the tremor and volitional movements of seven PD patient. They calculated offline the voluntary action by using a Kalman filter for parkinsonian tremor estimation (103) and used it as the input for their system. They were able to reconstruct the volitional movement of the patients with an average root mean square (RMS) error of 12.4%, with the subsequent tremor suppression. In a second validation, the tremor simulator was also fed with seven PD tremor datasets. The authors evaluated the tremor suppression provided by the WTSG and the device's performance when following voluntary motion (59). The experiments showed an overall tremor amplitude reduction of 85 ± 8.1% and a power reduction for the first, second, and third harmonics of 87.9 ± 13, 92 ± 7.4, and 81.7

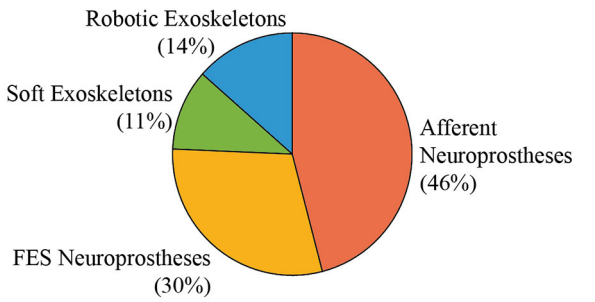


FIGURE 3 | Distribution of the reviewed devices according to their actuation principle. Percentages indicate the proportion of reviewed papers that use each technology.

± 13%, respectively. The voluntary motion showed a RMS error for the volitional movement reconstruction of 14.2 ± 2.5% and a correlation coefficient of 0.96 ± 0.01.

Another soft exoskeleton for tremor suppression (SETS) was proposed by Zahedi et al. (60). This device was equipped with a controllable flexible semi active actuator based on magnetic fluid and two hyper elastic blades. The combined action of these two was able to suppress wrist tremor with minimum restrictions on the voluntary motion during flexion/extension, abduction/adduction, and supination/pronation. Five healthy subjects simulated tremor movements in the wrist flexo/extension direction while wearing the device to test this device. These subjects also wore a blindfold, and the authors asked them to keep the movement as constant as possible. After comparing the movement while the system was turned on and off, the results showed that the RMS value of the movement acceleration decreased by 61.89%, and the RMS value of the angular velocity decreased almost 56.22% when SETS was active.

A different approach for a soft device was proposed by Skaramagkas et al. (61), who used pneumatic artificial muscles (PAMs) for suppressing hand tremor of ET patients due to the similar properties of these actuators with those of organic muscles. This device consisted of a PAM linked to target points through tendons, a soft glove that provided attachment points between the PAM and the target points, and a force sensor placed in the contact point to provide feedback of the exerted resistive force.

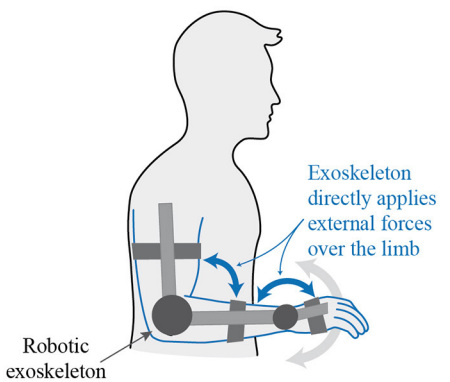
They tested two prototypes with different application points for the force: the index finger and the metacarpal region. Using the prototypes under open-loop control, the authors obtained the force that provided the maximal decrease in tremor amplitude (89%) and frequency (70%) for one ET patient. By using this force as the set point for a closed-loop controller, both prototypes obtained a maximal reduction of 75% in amplitude and 70% in frequency (61). Although the metacarpal solution provided slightly fewer reductions during closed-loop control, it had the advantage of allowing the free movement of the finger.

Finally, jamming actuators were also proposed as a solution for tremor management. Awantha et al. developed a soft glove for hand tremor suppression based on jamming actuators that stiffened the joint when vacuum was supplied and created resistance to the tremor motion (62). A prosthetic hand simulating finger tremor of 15 tremor patients was used to evaluate this device, while two different combinations of jamming elements and actuator placements were tested. The maximum tremor reduction was obtained for the placement of the actuator in the palmar side, and it yielded to an amplitude reduction of 74.79 ± 4.23%.

The main drawback of this technology is that it is still poorly validated. Except for one of the reviewed works (61), the rest of them only presented experimental validations with healthy subjects or artificial platforms. Thus, there is no objective evidence of the effectiveness of this technology in suppressing tremor.

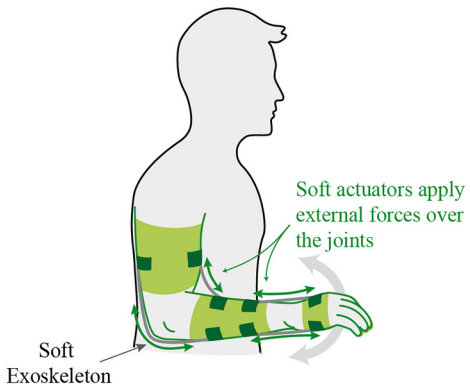
Tremor Suppression Based on Electrical Stimulation Over the Motor Threshold

Looking for the same biomechanical loading effect provided by active orthosis and soft exoskeletons, some studies have proposed electrical stimulation to reduce and suppress tremor because



Number of Studies	5
Number of subjects (Simulated Subjects)	7±5.20 (5.5±6.36)
Tremor Reduction (Simulated Subjects)	72.07±8.30% (98.95±1.20%)
Metric	PSD (n=3) TremorAmplitude (n=2)
Pros	High Suppression capability
Cons	Not useful in daily activities (noisy and bulky aspect)

FIGURE 4 | Conceptual representation of a robotic exoskeleton that manages tremor by applying forces over the limb of the subject.



Number of Studies	4
Number of subjects (Simulated Subjects)	1 (9±5.29)
Tremor Reduction (Simulated Subjects)	75±0% (73.89±11.58%)
Metric	TremorAmplitude (n=4)
Pros	Wearability potential
Cons	Lack of proper experimental validations

FIGURE 5 | Conceptual approach for soft exoskeletons that manage tremor by applying forces.

they enabled smaller and more discreet solutions compared with robotic exoskeletons. FES can activate tremorgenic and/or antagonist muscles to modify the dynamic behavior of the limb or apply forces to counteract the tremorous movements. A conceptual representation is shown in **Figure 6**. Concretely, the strategies that we detail in this section have the common characteristic that the pulse intensity of the electrical stimulation was high enough to activate muscle fibers and generate a muscle contraction.

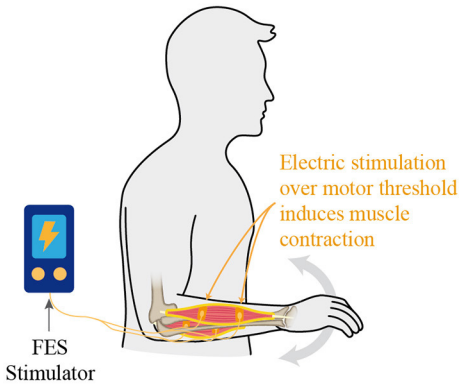
Two main strategies have been adopted to yield tremor suppression: cocontraction stimulation and out-of-phase stimulation (44). The cocontraction strategy was based on the stimulation of the pair of antagonist muscles of the affected joint, so the impedance presented by the joint was increased to counteract tremor. On the other hand, out-of-phase strategies applied electrical stimulation to the antagonist of the muscle responsible for the tremorous movement. The amplitude of this stimulation was enough to apply forces that were opposite to those that generated tremor.

One of the first approximations that used FES was the one proposed by Prochazka et al. (63, 64). Their work was based on the out-of-phase activation of the tremorgenic muscles using closed-loop FES to cancel tremorous movements. Their approach was based on that the neuronal activation of tremorgenic muscles generated by the nervous system could be considered as a disturbance that was rejected by the closed loop. However, only the high-frequency tremor-related movements needed to be suppressed, so low-frequency voluntary movements remained unaffected. By properly designing a feedback filter, it was possible to attenuate tremor-related frequencies (2–5 Hz) and minimally affect the frequency range of voluntary movements (0–1 Hz). The device was tested on three patients with ET, four patients with PD, and six patients with cerebellar tremor who presented disabling tremor in the wrist (ET and PD patients) and/or the elbow (in cerebellar tremor). Although tremor in one patient did not decreased, the device achieved an average suppression of 58.1 ± 20.5% (in a range between 91 and 10%) in the rest of the patients.

This same strategy was replicated by Gillard et al. (65), but they used a digital filter instead of analogic circuitry to define the stimulation to be applied to the wrist or finger flexor and extensor muscles. They tested their approach on three PD patients, obtaining an average tremor cancellation of 84.5 ± 2.2%. Afterward, Popović et al. enhanced this approach by developing a FES platform that was able to control multiple stimulation channels for tremor management in multiple joints (66). Their multichannel platform was able to selectively stimulate several single muscles following also an out-of-phase strategy with tunable stimulation properties. This system was tested on seven patients (three ET and four PD); although one of them did not respond to the stimulation, the remaining six showed an average tremor suppression of 67.0 ± 13.0%.

Widjaja et al. proposed a stimulation strategy based on surface EMG and accelerometer information to reduce the delay between tremor detection and stimulation, justifying the inclusion of muscle activation signals because of its earlier generation compared to kinematics information (67). Based on both sensory information, two extended Kalman filters and a phase equalizer algorithm differentiated between volitional and tremor-related components of the movements by calculating the electromechanical delay. They tested this strategy with an ET patient whose tremor was recorded by the accelerometer. The obtained results showed a decrease of 57% in wrist flexion–extension tremor amplitude.

Dosen et al. presented a tremor suppression strategy also based on out-of-phase stimulation of antagonist muscles (68). However, they used the iterative Hilbert transform (IHT) to detect and predict tremor bursts using EMG signals of the muscles involved in tremor generation. The strategy consisted of two consecutive phases: during the first, the system recorded and analyzed EMG signals to detect and predict the timing of tremorgenic bursts. During the second phase, and according to that timing, the stimulation was delivered to the antagonist muscles when the appearance of tremor was predicted on the agonist muscle. They tested this strategy on six patients who presented wrist flexion–extension tremor (four patients due to PD and two patients diagnosed as ET). Although one of the



Number of Studies	10
Number of subjects (Unaffected Subjects)	9.10±9.83 (0.50±0.71)
Tremor Reduction	59.65±11.25
Metric	Tremor amplitude (N=5) PSD (n=2) RMS (n=3)
Pros	Increased wearability
Cons	Less effective than exoskeletons Not effective in all subjects

FIGURE 6 | Electrical stimulation for managing tremor by inducing contraction of involved muscles.

ET patients did not respond positively to this strategy, results showed a tremor suppression rate of 60.0 ± 14.0% for the rest of them when their basal tremor was compared to tremor during out-of-phase stimulation.

A different approach was pursued by Gallego et al. (69), who designed a neuroprosthesis to generate mechanical loads in a pair of antagonist muscles in such a way that the impedance of the joint was properly manipulated artificially, cocontracting the muscles involved in the tremorous movement. As the dynamic response of the muscles to the tremor movement is analog to a low pass filter, by artificially increasing the stiffness and viscosity of the joint, the cutoff frequency would be decreased. Consequently, if this frequency is over the tremor frequency, tremorous movements would be filtered out. The system identified the tremorous and voluntary components of the movement and adapted the level of elicited cocontraction to the instantaneous frequency and amplitude of the tremor. This neuroprosthesis was validated within two PD patients and four ET patients, who reported a reduction of 52.3 ± 25.5% in 26 out of 30 trials compared to trials where the neuroprosthesis was not active.

Grimaldi et al. (70) also evaluated this same strategy in one PD patient, one ET patient, and one paraneoplastic cerebellar syndrome. However, they only reported a successful tremor reduction in the ET patient, whose tremor decreased 50% during the stimulation. Bó et al. also developed a neuroprosthesis based on the cocontraction strategy (71). They stimulated in an open-loop configuration, turning it on and off while subjects performed a static motor task, and validated this strategy in 10 ET patients. Although one of these patients did not clearly enhance his tremor amplitude and other even increased it, the other eight patients returned positive results, reducing the tremor amplitude by 66.9 ± 21.7%. However, these patients showed different behaviors when stimulation was applied, presenting in some cases an adaptation phase before the tremor was effectively managed.

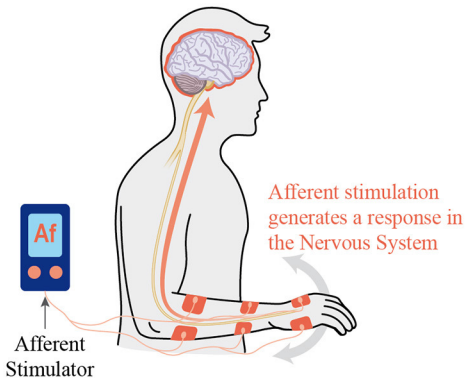
Jitkritsadakul et al. (72, 73) also delivered constant electrical stimulation over the motor threshold on hand muscles to suppress tremor, and they also considered the hypothesis of interfering with the cerebello-thalamo-cortical circuit through afferent stimulation. During their first approach (72), they compared the tremor angular velocity before and during stimulation in 34 PD patients, and their results showed an average improvement of 49.6 ± 38.89% in the peak amplitude and an average reduction of 43.8 ± 33.2% in the RMS value of tremor. However, just 70.6 and 61.8% of patients showed at least 30% tremor suppression in the peak amplitude and RMS value, respectively. Later, they developed and validated the Tremor's glove device to detect and suppress tremor based on this same strategy (73). They compared the tremor evolution in 30 PD patients wearing the Tremor's glove device ($N = 15$) or a sham replica ($N = 15$). Their results pointed out that the device significantly managed tremor in the glove group compared to the sham group according to the reduction in the RMS and peak value of the angular velocity (56.86 ± 37.97% X-axis and 49.64 ± 71.48% Y-axis, respectively) and the Unified Parkinson's Disease Rating Scales (UPDRS; 1.47 ± 0.74).

Despite these promising results, there are several drawbacks inherent to this technology. Timing of the control and selectivity of muscle stimulation are crucial aspects for tremor management (76). Besides, muscle fatigue due to induced contraction also decreases the effectiveness of these devices (66).

Stimulation of Afferent Pathways for Tremor Management

Several studies have found relationships between tremor generation and sensory activity to circumvent the limitations of FES-based tremor suppression. For example, providing proprioceptive input through passive joint movements can modulate tremor in PD patients (104). Similarly, low-level electrical stimulation applied at the wrist joint modulated the tremor frequency (105). In this way, sensory or afferent stimulation generates a response in the CNS that can modify tremor in patients. **Figure 7** schematically illustrates this approach.

Based on these studies, Dosen et al. presented the hypothesis that tremor could be reduced by stimulating sensory pathways



Number of Studies (with comparable data)	17 (11)
Number of subjects (Unaffected Subjects)	12.18±10.46 (0.82±1.66)
Tremor Reduction	46.33±15.90%
Metric	RMS (n=3) Amplitud (n=4) PSD (n=2) Tetras (n=2)
Pros	Less invasive and more tolerable than FES approaches
Cons	Less effective than FES Not effective in all subjects

FIGURE 7 | Afferent neuroprosthesis manages tremor by inducing a response in the nervous system of the subject.

instead of activating muscle fibers (68). Their work compared the effect of stimulation above and under the motor threshold on the tremor of four PD and two ET patients. Results for motor stimulation are presented in the previous section of this document, achieving an average tremor reduction of 60 ± 14%. They performed the same protocol with the same patients to test the sensory stimulation but using lower stimulation levels that did not generate muscular activity. Sensory stimulation resulted in an average tremor suppression of 42.0 ± 5.0%; although lower than that yielded with motor stimulation, it was postulated as a feasible alternative for tremor management (68).

In (44), Dideriksen et al. tested both surface and intramuscular stimulation and analyzed the most convenient stimulation settings (pulse amplitude and timing) to reduce the tremor amplitude. They recruited five PD and four ET patients who were stimulated according to the algorithm proposed by Dosen et al. (68) and received the stimulation through one of the tested electrode interfaces. For each patient, the different stimulation parameters (intensity and burst duration) were varied systematically. Although most patients (66.67%) showed a significant tremor reduction, with an average magnitude of 52% in the best case for each patient, the optimum conditions for tremor reduction varied between patients, pointing out the potential utility of patient-specific stimulation protocols.

As a second step, these same authors developed a multichannel electrode for muscle recording and stimulation (74). They tested this electrode using the same protocol as in (68) in one PD patient following the out-of-phase electrical sensory stimulation strategy. The patient showed an average tremor angle reduction of 58%, in the same attenuation range reported in their previous study. This technique was also assessed during a broader study (75) that involved nine ET patients. Results from this study pointed out that the use of this intramuscular electrode for out-of-phase electrical afferent stimulation led to a 32% average acute tremor reduction, significantly higher than the reduction achieved by surface electrodes.

A similar approach was followed by Heo et al., who studied the effects of electrical afferent stimulation in ET patients (76, 77). Sensory electrical stimulation was delivered to 18 ET patients on four upper limb muscles (flexor carpi radialis, extensor carpi radialis, biceps brachii, and triceps brachii) while the velocity of MP and wrist joints were measured. Two experimental setups were considered at three different phases (prestimulation, during stimulation, and 5 min poststimulation): (1) arms stretched forward during 15 s (76) and (2) Archimedes spiral drawing (77). By comparing the angular velocity before and during stimulation, electrical sensory stimulation resulted in a reduction ratio of RMS angular velocity for MP (60%) and wrist joints (40%) during the arm stretching task (76) and for MP joint (12%) during the spiral drawing task (77). These reductions were also measurable 5 min after the stimulation was applied in both experimental setups.

These same authors also tested their approach in 14 PD patients (78) and nine patients with scans without evidence of dopaminergic deficit (SWEDDs) (79). The tremor of these patients was evaluated during resting tasks before, during, and 5 min after the sensory stimulation by using the RMS of the angular displacement of the index finger, hand, and forearm. Although their strategy did not significantly reduce the tremor in SWEDDs patients (79), a variable percentage of PD patients (between 50 and 71% depending on the segment) reported a reduction in tremor amplitude ranging from 53 to 68% during stimulation (78). Five minutes after the stimulation, this suppression effect was still measurable in some patients (between 57 and 71% depending on the segment) with a reduction ratio ranging from 56 to 60%.

Based on a similar principle, Hao et al. hypothesized that electrical afferent stimulation could affect the transmission of tremorgenic signals, inhibiting tremor in PD patients as a consequence (80, 81). To test this hypothesis, they applied surface electrical stimulation on the dorsal skin of the hand, near the MP joint of the index finger. A preliminary study significantly reduced wrist and elbow flexion tremor and forearm pronation tremor in two PD patients (80). Lately, in a broader study, eight PD patients with tremor dominant symptoms were stimulated using an amplitude fixed from 1.5 to 1.75 times the radiating threshold (the stimulus amplitude that produces a radiating sensation from the dorsal skin to the fingers). Although tremulous movements and EMG signals seemed to be increased

in some trials due to the stimulation, both metrics decreased their severity in most cases, resulting in an average peak spectral amplitude reduction of 61.6 ± 8.9% and an average EMG activity reduction of 47.9 ± 25.8%.

A different approach was followed by the team led by Pahwa (82–84): they applied bursts of noninvasive electrical stimulation alternately to the median and radial nerves of the wrist at a frequency tuned to the tremor frequency of the wearer. They hypothesized that this stimulation would modulate the ventral intermediate nucleus and, therefore, would reduce the tremor in ET patients. These authors conducted three different studies to assess the effect of this strategy after 40 min of stimulation in ET patients. Twenty-three patients participated in a study that showed a 60 ± 80.4% tremor reduction in the spiral drawing Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) score for the treatment group ($N = 10$) compared to the sham group ($N = 13$) (82).

In the same way, in (83), the treatment group ($N = 40$) reported more significant improvements in the subject-rated Bain and Findley Activities of the Daily Life (BF-ADL) score (49%) than the sham group (27%, $N = 37$). The authors also evaluated the effects of this stimulation during a 3-month therapy in (84). A total of 205 ET patients were instructed to use the therapeutic device twice daily at home, and most of them (92%) improved their tremor according to accelerometer measurements at the wrist, with 54% experiencing an improvement greater than or equal to 50%. In addition, the clinician-rated TETRAS score was improved in 62% of patients, and the patient-rated BF-ADL was also improved in 68% of patients. Finally, the authors analyzed the duration of the effect of this stimulation in (85). They followed the same stimulation treatment as in previous studies with 15 ET patients and found that for 80% of them, the suppressive effect of the treatment lasted for 60 min at least.

Radial nerve stimulation to manage tremor in ET patients was also used by Kim et al., who developed a wearable device that assessed tremor in real time and tuned the stimulation parameters according to open-loop or closed-loop paradigms (86). This device was tested with nine ET patients who showed an overall tremor power reduction of 42.17 ± 3.09%. However, not all trials showed significant tremor reduction. Besides, they noticed that different stimulation parameters affected the attained reduction, so they should be properly tuned to manage tremor successfully.

Based on the results obtained by these electrical afferent stimulation devices, Lora-Millan et al. (87) evaluated a new hypothesis to suppress tremorous movements in ET patients by using mechanical afferent stimulation instead of low-level electrical stimulation. Their work was based on the hypothesis that sensory responses from Pacinian corpuscles could provide a pathway to modulate the circuits that mediate tremor in ET. These authors used piezoelectric actuators to stimulate the fingertips, palm of the hand, and anterior forearm with mechanical vibration at different frequencies. They tested this hypothesis over 18 ET patients who performed the same postural task to trigger the tremor, keeping their most affected arm on a support, with the forearm, hand, and fingers outstretched against gravity. Although the dominant trend in tremor response was to increase, the high variability observed in tremor severity, even without stimulation, made it difficult to interpret the results and, therefore, to reach conclusions.

Another mechanical stimulation approach was also proposed by Liu et al. (88), although they aimed to induce movements to the tremorous limb to counteract the tremor. They applied mechanical vibration over the pronator teres and supinator muscles to induce sustained muscle contraction, referred to as tonic vibration reflex (TVR). In this work, they proposed to use TVR to induce a movement that would counteract the tremorous movement in ET patients. To validate this approach, they induced a periodic pronation–supination movement in five healthy patients by using mechanical vibration. However, they did not present a proper validation counteracting tremorous movement in real patients.

Although these works present promising results, not all patients respond successfully to the afferent strategy for suppressing tremor, and the mechanisms that mediate their effects are not fully understood. In addition, as the physiopathological hypothesis that supports each device is different (106), it is difficult to compare their effectiveness.

Metrics in Tremor Assessment

Assessing tremor and its possible reduction is crucial to evaluate the effectiveness of the systems for tremor management. In clinical practice, motor symptoms and motor complications are most commonly appraised during clinic visits by rating the performance on clinical scales (e.g., UPDRS, TETRAS, Fahn-Tolosa-Marin). This clinical assessment is subject to bias from placebo effects, anxiety, or the opposite "white coat syndrome," where patients apply an extra effort, resulting in a performance that does not fully reflect patients' abilities (107, 108). To address this issue, handwriting and drawing patterns are often used to quantify tremor from a clinical perspective (109). Recording such patterns using a digitizing tablet has been introduced as one way to provide precise quantification (110). An example of this approach is the metric developed by the Tremor Research Group to quantify the severity of ETs and their impact on ADL and TETRAS (111). This scale was developed to merge clinical and technical quantification of tremor. It has excellent face validity, interrater reliability, and sensitivity to change. It was adopted in the studies proposed by Cala Health to evaluate the performance of their tremor suppression neuromodulation device (82–85).

From the point of view of tremor quantification, the two most important factors are frequency and amplitude. In this regard, the advances of wearable sensing technologies, in particular inertial measurement units (112), enable the development of different metrics to quantify tremor and assess the electiveness of the technologies proposed. These are the different metrics proposed to evaluate the tremor suppression achieved by the systems considered:

Tremor amplitude: This metric is the most used by the works reported in this review; it compares the maximum tremor amplitude before, during, and after the treatment. Of the 30 reviewed articles, 14 adopted the reduction of the tremor amplitude as a metric.

RMS: The RMS value is the most relevant measure of the amplitude of a tremor signal because it considers its history and provides a value directly related to its energy content. Therefore, this metric's evolution is directly related to the ability of the device to reduce tremor. Moreover, this measure allows taking data, both positive and negative, and obtaining a more exact metric. Of 30 articles, six adopted this metric.

PSD: Tremor is well suited to spectral analysis, the most popular method of tremor quantification, because of its oscillatory characteristics (113). It is used to calculate the PSD function indicating the signal power at different frequencies across the spectrum. The dominant frequency of tremor is evident as a peak in the PSD, while the average tremor amplitude can be determined from the area under the peak (114). In the tremor analysis, it refers to the magnitude of the most recurrent frequencies at the time of measurement, allowing observation of a decrease in tremor. Of the 30 studies, seven used this metric to evaluate.

A significant limitation we encountered in most of the studies was that the effectiveness of tremor suppression based on the metrics mentioned above was mainly based on trials with a short duration of time. For example, the experimental trial duration in (76) was only 15 s, or if longer trials were used as in (44, 68), the authors divided them into epochs. This methodology tried to cope with the high intrinsic variability of tremor (44, 54, 68, 76), but this may not be effective if several minute trials were considered (87). This is a relevant issue to face during the experimental validation of these technologies because of the high fluctuations in tremorous movements (44, 87), which even could be caused by subjective factors such as anxiety, distraction, or surprise (44, 112, 115, 116).

DISCUSSION AND CONCLUSIONS

This paper reviewed and discussed the concept of tremor suppression using wearable technology (summarized in **Table 1**). We identified four groups of technological approaches for tremor management: (1) active orthosis or robotic exoskeletons, (2) soft robotic exoskeletons, (3) FES neuroprosthesis, and (4) afferent neuroprosthesis. Although all reviewed works claimed to manage tremor effectively, there are different degrees of effectiveness, as illustrated in **Figure 2**.

The technology that achieved the most significant reduction corresponds to active orthosis (exoskeletons). However, several limitations in wearability and comfort have yet to be addressed. Despite their effectiveness, users considered that they hampered their social relationships because of their bulky aspect, noise, and size. In addition, load transmission from the exoskeleton to the human musculoskeletal system was highly inefficient and was an issue to face (53). In summary, robotics-based solutions have shown clinical evidence of the approach based on human limb impedance control. However, it resulted in bulky and noncosmetic solutions for which patients were especially reluctant.

New approaches based on soft actuators are postulated as the next step in the development of this kind of device. These soft technologies could potentially increase the wearability of the resulting device and therefore increase its usability and reduce user rejection. However, further research is required to develop new soft actuator technologies in terms of cosmetic and aesthetic (low weight, compact to be worn beneath the clothes) and functional requirements (torque and bandwidth). As a result, there is yet a lack of proper validation of these actuators as a feasible solution for tremor management. In fact, only the soft exoskeletal glove presented by Skaramagkas et al. (61) presented a validation involving one actual ET patient.

Despite the large variety of robotic devices, their efficacy largely relies on their actuation mechanisms; however, this is not the only factor that interferes with the performance of a robotic exoskeleton. Sensory systems, control strategies, and human factors are also determinants of the efficacy of robotic exoskeletons. Human factors such as adaptation of the user to the orthoses structure, concrete characteristics of the tremor, or individual biomechanical properties condition the performance of these devices.

Some researchers, also focusing on increasing the wearability of these devices based on biomechanical loading, evaluated the use of electrical stimulation over the motor threshold to induce muscular contractions and generate forces or modify the biomechanics of the tremorous limbs. These devices have proven to be effective in suppressing tremor, although their effectiveness was lower than for robotic exoskeletons. Despite the promising results, several drawbacks are challenging to address. Regarding its control, electrical stimulation over the motor threshold requires precise real-time synchronization for reliable performance. The synchronization of the muscle activation timing with the tremor is crucial for proper tremor management. Possible time delays due to the control loop could reduce or avoid the effect of FES stimulation (76). Besides, the dependency between the control algorithm and the properties of the musculoskeletal system could lead to instability or undetermined states because of changes in muscle conditions. Selectivity of muscle stimulation is also an aspect that requires additional research for a proper operation of the systems.

Recent works support the idea that stimulation of the afferent pathways may alleviate the symptoms of tremors. Several groups developed neuroprosthesis focused on this concept, aiming to be less invasive and more tolerable by users than FES devices. However, their effectiveness was lower, and some patients did not respond to this treatment. Another drawback that hampered a direct comparison between tremor management results is the fact that each of the different devices described in the literature was based on a different physiopathological hypothesis (106). More profound studies are required to properly characterize the interaction between the afferent pathways and the neural structures involved in tremor generation. A complete understanding of these interactions would lead to a more efficient tuning of the stimulation strategies to the concrete characteristics of each pathology.

Another critical limitation that hampers a proper evaluation of these alternative treatments is the high variability in the metrics to quantify tremor reduction. There is an evident lack of a standard procedure to evaluate tremor management with

wearable technologies, making it difficult to compare results from different works. Differences in several aspects like the postural task, duration of the trial, or variation in the experimental conditions hamper extracting conclusions when comparing devices that followed different experimental procedures. This is particularly important because of the high intrinsic fluctuations of tremor movements (44, 87). For instance, several works used static tasks to trigger tremor and assess tremor management. However, this procedure could not represent daily living activities (117), and therefore, the experimental validation could not be useful to evaluate the effect on assisting the patient in daily life. In this sense, only the Cala Health neuromodulation device reported its effect over the performance of activities of the daily life (82–85).

Clinical validations of these technologies are still in the early stages, as the clinical evidence for their effectiveness is mainly based on a limited number of patients. Except for the Cala Health neuromodulation device, which reported experimental validation with 40 (83) and 205 (84) ET patients, and the Tremor's glove, which reported a validation with 34 PD patients, the rest of the reported devices are validated with less than 20 patients. Therefore, there is still a lack of large clinical trials to consider these technologies as a clinical alternative for tremor management.

Further, also the Cala Health's device and the Tremor's glove are the only two devices that reported experimental validations with a control group that used a sham version of the device (73, 82, 83). Since the validation process also needs to face the problem of high tremor variability (44, 87, 112, 115), further research that compares the action of these devices with sham controls would ensure the effectiveness of these devices.

In summary, this paper reviews the different approaches based on wearable technologies to suppress pathological tremors. We analyzed the complete spectrum of recent developments, from bulky active orthoses, which provide high suppression rates but are not feasible in real life, to new approaches such as (1) soft robotic exoskeletons, (2) FES, or (3) afferent neuroprosthesis. These current developments aim to attain more discrete and wearable solutions, although their effectiveness is usually lower when compared to exoskeletons.

Promising results derived from these devices illustrate their ability to suppress tremor, although they lack the functionality to represent an alternative treatment for tremor. There is no research focused on using these devices in combination with pharmacological or surgical tremor treatments. Researchers should evaluate the ability of these technologies to complement traditional tremor treatments. They have the potential to reduce medication intake or to prolong the effectiveness of surgical tremor treatments.

Further research is required to transform these devices in a real stand-alone alternative treatment for tremor. (1) Although soft actuators seem to be an alternative for wearable solutions, their tremor-suppressing potential needs to be validated with real patients. (2) FES or afferent neuroprosthesis should be extensively validated on larger samples of patients, including control and sham populations, before being considered a clinical alternative for tremor suppression. (3) A standard benchmark for testing and validating these devices, including metrics that account for tremor fluctuations, should be defined and developed. These developments would help researchers to compare different alternatives and find the best technological approach for tremor suppression for each patient.

AUTHOR CONTRIBUTIONS

JL-M designed and performed the main literature review, collected the information about the different devices, and drafted and wrote the manuscript. GD-O collected the information about the different devices and drafted and wrote the manuscript. JB-L revised the manuscript. ER designed the review, revised the draft, and made substantial comments. All authors approved the final manuscript.

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REVIEW
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Transcranial Magnetic Stimulation in Tremor Syndromes: Pathophysiologic Insights and Therapeutic Role

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Transcranial magnetic stimulation (TMS) is a painless, non-invasive, and established brain stimulation technique to investigate human brain function. Over the last three decades, TMS has shed insight into the pathophysiology of many neurological disorders. Tremor is an involuntary, rhythmic oscillatory movement disorder commonly related to pathological oscillations propagated *via* the cerebello-thalamo-cortical pathway. Although tremor is the most common movement disorder and recent imaging studies have enhanced our understanding of the critical pathogenic networks, the underlying pathophysiology of different tremor syndromes is complex and still not fully understood. TMS has been used as a tool to further our understanding of tremor pathophysiology. In addition, repetitive TMS (rTMS) that can modulate brain functions through plasticity effects has been targeted to the tremor network to gain potential therapeutic benefits. However, evidence is available for only a few studies that included small patient samples with limited clinical follow-up. This review aims to discuss the role of TMS in advancing the pathophysiological understanding as well as emerging applications of rTMS for treating individual tremor syndromes. The review will focus on essential tremor, Parkinson's disease tremor, dystonic tremor syndrome, orthostatic tremor, and functional tremor.

Keywords: transcranial magnetic stimulation, tremor syndromes, essential tremor, dystonic tremor, Parkinson's disease, functional tremor, orthostatic tremor, theta burst stimulation

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INTRODUCTION

Tremor is the most common movement disorder, defined as an "involuntary, rhythmic, oscillatory movement of a body part" (1). The phenomenology, pathophysiology, and treatment of the various tremor syndromes are highly nuanced and complex. Some features of tremor disorders may be difficult to distinguish from each other. Transcranial magnetic stimulation (TMS) is a painless and non-invasive technique used to study human brain function. TMS produces a magnetic field that induces a transient focal electric field in the targeted brain region. It can identify brain circuits involved in motor control and motor disorders and is an appealing technique for studying pathological tremors. It has shown promise as a potential treatment for tremors due to its ability to modulate the underlying pathological circuitry and brain functions. The current narrative review will discuss the role of TMS in understanding the pathophysiology and treatment for essential tremor (ET), Parkinson's disease (PD) tremor, dystonic tremor syndrome (DTS), and the less common or rare tremor syndromes such as orthostatic tremor (OT) and functional tremor.

PATHOPHYSIOLOGY OF TREMOR

Many models have been proposed to explain the pathophysiology of tremor. One important model relevant to all tremor syndromes is the oscillator hypothesis, which posits that a system can produce abnormal oscillatory activity under certain conditions that manifests clinically as tremor (2). There are four potential mechanisms that can lead to generation of these oscillations. These include mechanical properties of the body part, stretch reflexes in the extremity, oscillatory properties of neurons in certain brain regions, and oscillatory activity that occurs when feed forward or feedback systems involving the cerebellum become unstable (2, 3). With regards to the central oscillators, abnormal rhythmic activity generated within specific brain regions is propagated through networks critical for tremor; for instance, the cerebello-thalamo-cortical (CTC) network (2, 3). Brain regions with neurochemical disturbances are particularly susceptible to the generation of oscillations. For example, loss of cerebellar Purkinje cells in conjunction with GABAergic receptor abnormalities have been found to lead to tremor oscillations along the CTC pathway (4). Some studies have found loss of dopaminergic, serotonergic, and noradrenergic neurons in the brainstem lead to abnormal basal ganglia or thalamic oscillations (5).

Electromyography (EMG), electroencephalography (EEG), and neuroimaging such as functional magnetic resonance imaging (fMRI) are multiple pieces of the puzzle that have advanced our understanding of the brain circuitries and physiology involved in tremor syndromes. TMS is another important puzzle piece that has contributed to understanding the central mechanisms underlying the pathophysiology of tremor syndromes.

TMS TECHNIQUES: BASIC CONCEPTS

TMS examines brain circuitries by using a magnetic field to induce changes in neuronal excitability (**Figure 1A**). TMS includes single-pulse paradigms, paired-pulse paradigms, and repetitive-pulse paradigms. A single-pulse paradigm delivers a single pulse of TMS to specific brain regions in order to understand brain function. When a single pulse of TMS is delivered to the primary motor cortex (M1), this pulse subsequently generates a corresponding motor evoked potential (MEP) in the contralateral peripheral muscle, measured with an EMG recording (**Figure 1B**). MEP is a measure of corticospinal excitability. Single pulse TMS delivered during voluntary muscle contraction produces a period of EMG suppression known as the silent period (SP) (**Figure 1C**) (6). The SP evoked in the muscles of the upper limb originates largely from activation of cortical inhibitory interneurons with spinal contributions for the early part. SP is thought to represent motor cortex excitability involving the GABAergic receptors. When the SP is shortened, it reflects a dysfunctional inhibition. The resting motor threshold (RMT) is defined as the lowest stimulation intensity required to cause a muscle twitch in a target muscle for 5/10 pulses delivered (7). The active motor threshold (AMT), in contrast, is the motor threshold evoked by stimulation during a voluntary contraction of the peripheral muscle (7). These motor thresholds reflect the excitability of the motor cortex.

In paired-pulse paradigms, a conditioning stimulus (CS) is followed by a test stimulus (TS) with various interstimulus intervals (ISI) in order to generate MEPs that provide information about cortical excitability. The ratio of MEP amplitudes produced by a subthreshold CS and a suprathreshold TS when the ISI is short (1–4 ms) is known as short-interval intracortical inhibition (SICI) (**Figure 1D**). The ratio of MEP amplitudes produced by a suprathreshold CS and TS when the ISI is long (50–200 ms) is known as long-interval intracortical inhibition (LICI) (**Figure 1E**) (8). Intracortical facilitation (ICF) is an excitatory phenomenon whereby the MEP response is facilitated following a subthreshold CS paired with suprathreshold TS at an interstimulus interval of 10–15 ms (**Figure 1F**). A particular type of paired-pulse paradigm utilizes a CS targeted at the cerebellum and a TS at the motor cortex. When the ISI between these two pulses is 5–7 ms, the cerebellar cortex activated by the TMS pulse is observed to inhibit the contralateral motor cortex, a concept known as cerebellar-brain inhibition (CBI) (9). CBI paradigms can be used to study the cerebellar contribution, specifically involvement of the CTC pathway, in the pathophysiology of different tremor syndromes. In general, these paired pulse TMS paradigms can provide insights into the role of the motor cortex and the cerebellum, respectively, in tremor pathophysiology.

In contrast to single- and paired-pulse TMS, which can detect changes in cortical excitability, repetitive TMS (rTMS) can be used to modulate the cortical excitability. When rTMS is delivered to specific cortical targets in the brain, specific aspects of brain activity can be influenced with the goal of translating these effects to clinical improvement (**Figure 2**). Low frequency ($\leq$1 Hz) rTMS mimics long-term depression, resulting in inhibitory effects in the cortex (**Figure 2A**). In contrast, high frequency ($>$5 Hz) rTMS mimics long-term potentiation, resulting in excitatory changes (**Figure 2B**) (10). A specific type of rTMS known as theta-burst stimulation (TBS) uses triplet bursts of stimulation to deliver more pulses in a shorter time (3-pulse 50 Hz burst). When these triplet bursts are given continuously, known as cTBS, it exerts an inhibitory effect on the cortex similar to low frequency rTMS (**Figure 2C**). In contrast, when the triplet bursts are given intermittently, known as iTBS, it exerts an excitatory effect on the cortex similar to high frequency rTMS (**Figure 2D**) (9, 10). These neuromodulatory effects of rTMS, when targeted to the motor cortex and the cerebellum, can be leveraged to treat tremor syndromes. Following application of a rTMS paradigm, single- and paired-pulse TMS can detect differences in corticospinal excitability for clinical correlation.

A few studies have employed TMS techniques in healthy subject cohorts to understand tremor pathogenesis. Topka et al. examined the contributory role of the oscillations within the central brain circuits (11). rTMS delivered to the left motor cortex at a rate of 20 Hz, and an intensity of 120 % AMT was observed to transiently lead to the generation of tremor that correlated with an increase in frequency and stimulus intensity. In contrast, peripheral stimulation was unable to produce similar findings (11). The investigators concluded that the circuitry for

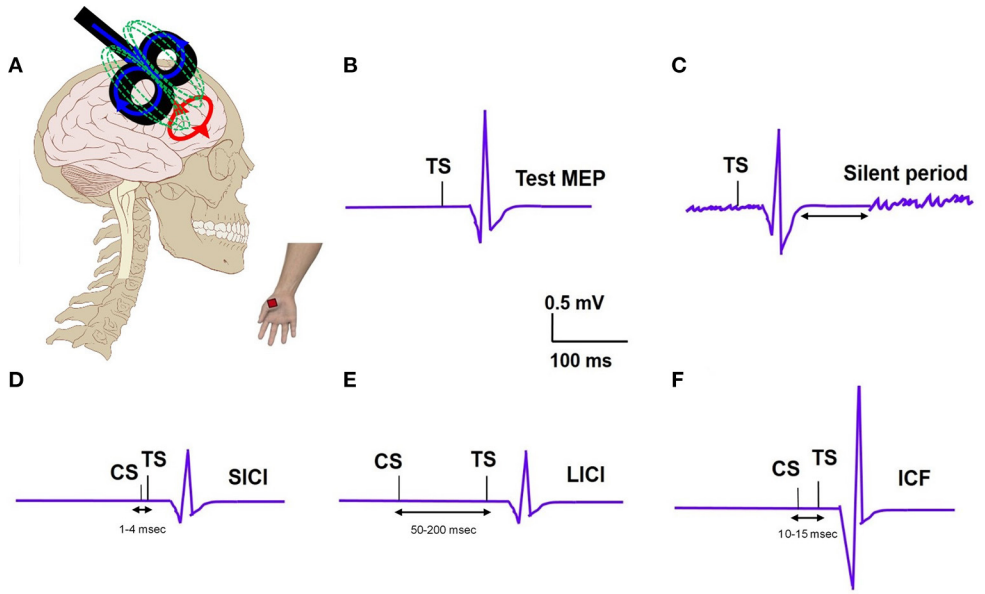

FIGURE 1 | (A) TMS set up: TMS coil applied to the motor cortex and motor evoked potential (MEP) recording from the distal hand muscle; electric field (blue); magnetic field (green); induced electric field (red). **(B)** Test MEP: MEP elicited with a test stimulus (TS). **(C)** Silent period: Recording of EMG silence that occurs after the MEP when a suprathreshold TMS pulse is delivered during active muscle contraction. **(D)** Short interval intracortical inhibition (SICI); MEP elicited with TS is inhibited when preceded by a subthreshold conditioning stimulus (CS) at a short interval of 2–3 ms. **(E)** Long interval intracortical inhibition (LICI); MEP elicited with TS is inhibited when preceded by a suprathreshold CS at a long interval (100 ms). **(F)** Intracortical facilitation (ICF); MEP elicited with TS is increased when preceded by a subthreshold CS at an interval of 10–15 ms.

tremor is mainly central. In another study with healthy subjects, a visuomotor task was used to induce an action tremor. When 6 Hz rTMS was applied to the M1, there was an increase in the action tremor, indicating that the modulation of tremors occurs centrally (11, 12).

In the following sections, we will discuss the role of TMS for each of the individual tremor syndromes. A summary of the TMS studies used to assess tremor pathophysiology (**Table 1**) and therapeutic role in individual tremor syndromes (**Table 2**) is provided.

ESSENTIAL TREMOR

ET is the most common tremor syndrome, occurring in 4% of adults over the age of 40 years (54, 55). The clinical manifestation of ET typically includes a combination of postural and action tremors of the arms. In some patients the head, voice, legs, and trunk may also be involved (56). Propranolol and primidone are mainstay pharmacological therapies; however, many patients discontinue medical treatments given an average of 50% improvement in symptoms and a relatively high incidence of medication-related side effects. Surgical techniques, including deep brain stimulation (DBS) and focused ultrasound, can be considered in severe, medication-refractory cases (54), but they have limitations such as side effects and costs. Therefore, rTMS in ET has gained interest as a potential alternative option for treating tremor.

ET is generally accepted to result from pathologic oscillations within the CTC pathway. Prior kinematic studies have demonstrated that rhythmic finger movements in patients with ET had higher variability than healthy controls, supporting cerebellar dysfunction as an underlying factor (26). Lesions in the cerebellum and the motor cortex have been observed to sometimes lead to the disappearance of symptoms (2, 3). Imaging studies have shown increased activity in the cerebellum and the motor cortex (57). Some pathological studies have found degenerative changes in the cerebellum; for example, the loss of Purkinje cells and focal axonal swelling that likely leads to abnormal GABAergic output and generation of pathological oscillations (55). Despite a growing understanding of the CTC pathway's involvement, whether the main tremor oscillator resides in the cerebellar cortex or is further downstream in the thalamus or motor cortex, and whether cerebellar involvement is related to decoupling remains an important physiologic question (5).

Pathophysiological Insights From TMS

Except for one study that found decreased RMT and AMT (32), the vast majority of studies have demonstrated that the baseline excitability in patients with ET is not significantly different from matched, healthy controls (17, 20, 21, 23, 24, 28). Resetting tremor with a TMS pulse applied to the cortical brain has further facilitated understanding of the pathophysiology. Resetting studies assume that if the tremor rhythm is disrupted or reset by the TMS pulse, the area stimulated must be involved

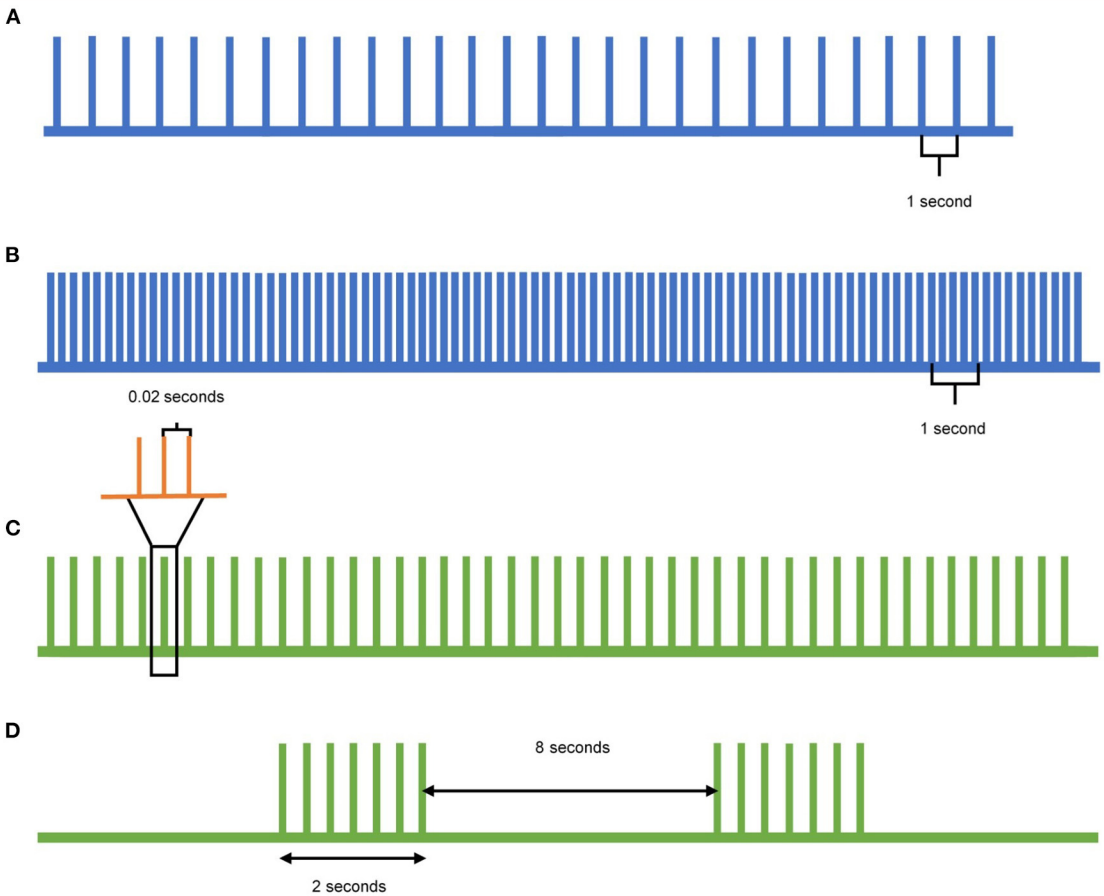

FIGURE 2 | Pulse patterns of different rTMS protocols. **(A)** Low-frequency TMS is delivered at a rate of 1 Hz or lower and acts as inhibitory stimulation. **(B)** High-frequency TMS is delivered at a rate of 5 Hz or higher and acts as excitatory stimulation. **(C)** Continuous theta-burst stimulation (cTBS) delivers a triplet burst of pulses continuously, and acts as inhibitory stimulation. Each green pulse represents three pulses given at 50 Hz (orange), whereas each green pulse is delivered at 5 Hz. **(D)** Intermittent theta-burst stimulation (iTBS) delivers a triplet burst of pulses intermittently, acting as excitatory stimulation. Each triplet burst (green) is delivered at 5 Hz over 2 s with an 8 s pause between.

in the tremor circuit (58). A single pulse of TMS targeted at the motor cortex was observed to reset tremor in ET (13, 14, 20, 29), however, it somewhat surprisingly did not reset when delivered to the cerebellum (20, 29). The authors speculated that the distal thalamo-cortical part of the CTC pathway might have a more prominent contribution to tremor generation than the proximal cerebello-thalamic part, which is why a single pulse of TMS to the primary motor cortex reset ET, but the cerebellum did not (29). Paired-pulse TMS studies investigating CBI have found variable results, with one study demonstrating no difference in CBI (20), and another study demonstrating reduced CBI in ET compared to healthy controls (30). The precise target within the cerebellum and the number of study participants differed between the two studies, which may be why there was a difference in their results (58).

TMS studies have also investigated the role of the cerebellum in ET generation by implementing an inhibitory cTBS protocol directed at the cerebellum. In one study, there was normalization of touch duration and temporal variability of ET with the cTBS protocol (26). In another study, cTBS targeted at the cerebellum led to a reduction in MEP amplitude in healthy controls, which could not be replicated in patients with ET. The authors interpreted this lack of response observed in the ET group to indicate dysfunction of the CTC pathway (39). Similarly, when inhibitory rTMS was targeted to the motor cortex, there was evidence of prolonged SP and reduced SICI in healthy controls, but no changes in ET, suggesting impaired plasticity and less modifiable motor cortical circuits (28).

Therapeutic Use of rTMS

Since the thalamus in the CTC pathway is too deep to reach with conventional TMS pulses, the cerebellum and the motor cortex remain the two best potential candidates for clinical efficacy. Most studies to date have targeted the cerebellum (58). In one study, low frequency rTMS to the cerebellum led to a significant decrease in clinical tremors immediately

TABLE 1 | TMS studies for understanding the pathophysiology of tremor syndromes.

References	Participants	TMS protocol	Results
Britton et al. (13)	10 PD vs. 12 ET vs. 10 HC	Single pulse TMS over M1 at 110% RMT	Tremor reset occurred for both ET and PD groups; latency to tremor return was prolonged, period of tremor was shortened in PD compared to ET or HC
Pascual-Leone et al. (14)	9 ET vs. 12 PD (postural tremor)	Single and paired pulse TMS over M1	Tremor reset occurred equally for both ET and PD groups and correlated with stimulus intensity and duration of SP; tremor reset bilaterally even with unilateral stimulation
Mills and Nithi (15)	5 OT	Single pulse TMS over the contralateral leg motor cortex while patients were standing	OT was not reset by cortical stimulation
Tsai et al. (16)	2 OT	Single pulse TMS over the contralateral leg motor cortex at 110% RMT while patients were standing	OT reset by cortical stimulation
Romeo et al. (17)	10 ET vs. 8 HC	Single and paired pulse TMS over M1 with ISIs of 3, 5, 20, 100, 150, and 200 ms; stimulation delivered at 80% RMT for short ISI and 150% for long ISI	No significant difference in RMT, SP, or SICI between ET and HC
Manto et al. (18)	3 OT with pancerebellar atrophy	Single pulse TMS over the contralateral leg motor cortex at 120% RMT with delays from time of EMG recording of the quadriceps femoris to TMS pulse delivery ranging from 25 to 60% while patients were standing	OT reset by motor cortex stimulation, which may suggest primary OT and OT associated with cerebellar atrophy have distinct pathophysiological mechanisms
Wu et al. (19)	6 OT	Single pulse TMS over the contralateral arm motor cortex while patients were standing	OT was not reset by motor cortex stimulation
Pinto et al. (20)	9 ET vs. 10 HC; medications discontinued 24 h prior to study	Conditioning stimulus delivered to right cerebellum and test stimulus delivered to left motor cortex with ISI values of 3, 9, and 15 ms	No significant difference in MEP or CBI between ET and HC; tremor was reset with stimulation over M1 but not over the cerebellum
Shukla et al. (21)	24 ET vs. 24 HC	Single pulse TMS over M1	No significant difference in SP between ET and HC
Spiegel et al. (22)	7 OT	Single pulse TMS over contralateral and ipsilateral cortical leg motor cortex at 110% RMT vs. lumbar magnetic stimulation vs. peripheral nerve stimulation	Tremor was reset in the bilateral legs with unilateral cortical stimulation, but was not reset with lumbar or peripheral nerve stimulation
Molnar et al. (23)	7 ET with DBS of the VIM in the dominant hemisphere vs. 11 HC with TMS; not on medications at time of study	Single pulse TMS over M1 at 100–150% of RMT; DBS conditions included ON, HALF, and OFF stimulation	No difference in SICI, LICI, or active ICF between ET and HC; significantly higher MEP with DBS ON compared to HC at high but not low TMS intensity, suggesting VIM DBS activates the target area
Lo et al. (24)	20 ET vs. 20 HC; not on medications at time of study	Single pulse TMS over M1 at 110% RMT in 3 s intervals at rest and during a motor imagery task 2 s before the TMS pulse	MEP amplitude increased following motor imagery in HC, but not in ET; no significant difference in RMT between ET and HC at baseline; no correlation between motor imagery scores and ET frequency or severity
Mazzochio et al. (25)	10 PD vs.16 ET vs.10 HC vs. 8 PT; not on medication prior to the study	Single-pulse TMS over the M1 combined with changes in shoulder position to influence motor cortical outflow	MEP amplitude decreased in HC and ET under resting conditions but increased under active conditions; no difference in MEP amplitude in PD at rest but decreased during activation
Avanzino et al. (26)	15 ET vs. 11 HC; medication stopped 72 h before study	Single session of 600 pulses of 1 Hz rTMS over the right lateral cerebellum at 90% RMT	At baseline, patients with ET had longer touch duration and temporal variability of movement compared to HC; following inhibitory rTMS, these parameters normalized
Ni et al. (27)	10 PD OFF medication vs. 10 HC	CBI paired pulse paradigm consisting of TMS pulse to the cerebellum followed by TMS pulse to the M1 with ISI ranging from 3 to 8 ms; CBI was tested at rest and with arm extension	Rest tremor reset by M1 but not cerebellar stimulation; postural tremor reset by both M1 and cerebellar stimulation; CBI abnormal in both rest and postural tremor and correlated with the degree of reset caused by cerebellar stimulation
Rogasch et al. (12)	26 HC with action tremor induced by a visuomotor task	Single session o 600 pulses of 6 Hz rTMS over the M1 at 80% AMT Active vs. sham	Peak power and tremor frequency increased following active rTMS; decreased corticospinal excitability but increased amplitude following active rTMS

(Continued)

TABLE 1 | Continued

References	Participants	TMS protocol	Results
Chuang et al. (28)	13 ET vs. 18 HC	Single pulse TMS to the M1; Paired-pulse TMS with subthreshold conditioning stimulus 80% AMT and test pulse at 100% AMT at ISIs of 3 and 12 ms; 600 triplet bursts of cTBS targeted at either the M1 or premotor cortex at 80% AMT	No change in SICI or SP in ET but reduced SICI and prolonged SP following cTBS in HC; reduction in MEP amplitude in both ET and HC, but sustained longer in HC
Lu et al. (29)	10 PD vs. 10 ET; medication discontinued 24 h prior to study	Single pulse TMS over the M1; paired pulse TMS over M1, SMA, and cerebellum in random order	Tremor reset occurred for both M1 and SMA targets in both groups; tremor reset index was significantly higher for M1 as compared to SMA stimulation in PD group, but no difference in ET group; no tremor reset with cerebellar stimulation; no significant difference in MEP, LICI, or SP between PD or ET group
Hanajima et al. (30)	18 ET vs. 19 HC; medications stopped 18 h before study	CBI paradigm consisting of conditioning stimulus with insentiy at 95% of AMT directed at the cerebellum and test stimulus applied over the motor cortex with ISIs of 4, 5, 6, 7, 8, and 10 ms	Abnormal CBI in ET compared to HC
Pattamon et al. (31)	12 ET vs. 8 DT	CBI paradigm consisting of a conditioning stimulus delivered to the cerebellar cortex and a test stimulus delivered to the contralateral motor cortex with an ISI of 5 ms	M1 stimulation reset both ET and DT whereas cerebellar stimulation reset ET more so than DT
Khedr et al. (32)	21 ET vs. 20 HC; no medications 1 week before study	Single pulse TMS over M1 at intensities ranging from 110 to 150% RMT and AMT	RMT and AMT were significantly decreased compared to HC; no difference in SP between ET and HC
Panyakaew et al. (33)	21 ET vs. 22 DTS vs. 19 HC; not on medications prior to study	CBI paradigm consisting of a conditioning stimulus delivered to the cerebellar cortex and a test stimulus delivered to the contralateral motor cortex with an ISI of 5 ms	Correlation between CBI and tremor severity scale only in ET; CBI significantly reduced in DT but not in TAWD compared to ET or HC
Leodori et al. (34)	10 PD in the OFF medication state	Single-pulse TMS over M1 at 80% AMT	Both rest and re-emergent tremor were reset following stimulation of M1
Helmich et al. (35)	14 PD (rest and re-emergent tremor)	Single-pulse TMS over M1 and cerebellum	Both rest and re-emergent tremor were reset following stimulation of M1 but only re-emergent tremor was reset following stimulation of the cerebellum

AMT, active motor threshold; CBI, cerebellar-brain inhibition; CSP, cortical silent period; cTBS, continuous theta burst stimulation; DT, dystonic tremor; DTS, dystonic tremor syndrome; ET, essential tremor; HC, healthy controls; ICF, intracortical facilitation; LICI, long intracortical inhibition; M1, primary motor cortex; MEP, motor evoked potential; PD, Parkinson's disease; PT, physiologic tremor; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SICI, short intracortical inhibition; SMA, supplementary motor area; TAWD, tremor associated with dystonia; TMS, transcranial magnetic stimulation.

following the stimulation, correlating with accelerometer-based tremor improvement (36). However, this improvement did not persist 1 h following stimulation, which is likely attributable to a single stimulation session. Another study, which used a single session cTBS protocol to the cerebellum, did not demonstrate improvements measured clinically or with kinematic analysis (26, 39). Further studies expanded the number of total pulses provided to patients by repeating stimulation sessions over several days. An open-label low frequency paradigm that extended the number of sessions to 5 consecutive days found significant improvement in the clinical rating scale and tremor as measured by accelerometry (38). These improvements lasted up to 3 weeks following stimulation (38). This study also demonstrated restoration of CTC connectivity on the fMRI (38). However, two other low frequency rTMS studies with a similar 5-day paradigm found no significant difference between active and sham stimulation conditions (41, 42).

In addition to the cerebellum as a target, the M1, the premotor cortex (PMC), and the supplementary motor area (SMA) have been pursued as potential rTMS targets for the treatment of ET. In one study, 600 triplet bursts of cTBS to the M1 or PMC led to significant reduction in tremor amplitude with no change in tremor frequency (28). In another study with cTBS targeted at the M1, there was reduction of tremor measured with accelerometer studies; however there was no significant change in the clinical tremor rating scale, which may be due to the implementation of only a single stimulation session (37). Inhibitory low frequency rTMS was pursued in one study for 15 stimulation days and the investigators chose the pre-SMA as the target. The study found that compared to sham stimulation, there were sustained benefits at 8-week follow-up in the active stimulation group (40).

While multiple brain targets have been pursued, albeit with limited data, a recent meta-analysis evaluating non-invasive brain stimulation for ET found that there was tremor improvement regardless of the tremor rating scale used, the stimulation site, the number of sessions, or how long after stimulation outcome measures were assessed (54). However, based on methodological merits including randomization,

TABLE 2 | rTMS studies for therapeutic use in tremor syndromes.

References	Participants	Target	Stimulation parameters and study design	Number of pulses per session	Duration	Results
Essential tremor						
Gironell et al. (36)	10 ET; patients were allowed to continue medications during the study	Posterior cerebellum (2 cm inferior to the inion)	Thiry 10-s trains of 1 Hz rTMS at 100% RMT with 30 second intertrain intervals Crossover design of active and sham rTMS separated by 1 week	300	Single session	Significant decrease in tremor rating scale and improvement in accelerometry scores 5 min following active rTMS compared to sham rTMS, but no difference at 60 min after stimulation
Avanzino et al. (26)	15 ET and 11 HC; medications stopped at least 72 h before study	Right lateral cerebellum (3 cm lateral and 1 cm inferior to the inion)	One 10-min train of 1 Hz rTMS at 90% RMT	600	Single session	No change in frequency or intensity of tremor by clinical rating scales
Hellriegel et al. (37)	10 ET and 10 HC; patients were allowed to continue antitremor medications if started at least 4 weeks before the study	M1	Two 20-s trains of 50-Hz cTBS at 80% AMT with an intertrain interval of 60 s crossover design of active and sham rTMS separated by at least 1 week	600	Single session	Significant reduction in tremor as measured by accelerometry 45 min following active stimulation as compared to sham; no significant difference in the tremor rating scale or MEP amplitude
Popa et al. (38)	11 ET and 11 HC; patients were allowed to continue antitremor medication	Cerebellum (repeated over lobule VIII of each cerebellar hemisphere)	One 15-min train of 1 Hz rTMS at 90% RMT to each cerebellar hemisphere open label study	1,800 pulses per session (9,000 pulses total)	5 days	Significant reduction in tremor rating scale and improvement in tremor amplitude by accelerometry with sustained response up to 3 weeks; restoration of functional connectivity in the CTC network to a near normal level following stimulation
Chuang et al. (28)	13 ET and 18 HC	M1 or PMC	One 40-s train of 50-Hz cTBS at 80% AMT Crossover design of active vs. sham cTBS separated by at least 1 week	600	Single session	Significant reduction in tremor amplitude but no change in tremor frequency; no difference between motor vs. PMC
Bologna et al. (39)	16 ET and 11 HC	Cerebellum (right cerebellar hemisphere)	One 40-s train of 50 Hz cTBS at 80% AMT crossover design of active and sham cTBS separated by at least one week	600	Single session	No significant change in tremor rating scale or kinematic analysis of tremor following active stimulation; reduction of MEPs in the HC and not the ET patients, suggesting dysfunction of the CTC connectivity in patients with ET.
Badran et al. (40)	10 ET	Pre-SMA	20 min of 1 Hz rTMS at 110% RMT Randomized to active vs. sham	1,200 per session (18,000 pulses total)	15 days	Significant reduction in the tremor rating scale compared to baseline in both groups but sustained reduction at 4 and 8 week follow-up persisted only in the active group.
Shin et al. (41)	22 ET; patients were allowed to continue antitremor medications during study	Cerebellum (each cerebellar hemisphere, 3 cm lateral and 1 cm inferior to the in inon)	Twenty 30-s trains of 1 Hz rTMS with a 10 s intertrain interval at 90% RMT Randomized to active vs. sham	1,200 per session (6,000 pulses total)	5 days	No significant difference in tremor rating scale (immediately after rTMS: 33% reduction in active vs. 20% reduction in sham; 4 weeks following rTMS: 31% reduction in active vs. 17% reduction in sham)
Olfati et al. (42)	23 ET	Cerebellum (right then left cerebellar hemisphere, 1/3 distance from the inion to the mastoid process)	Two 15-min trains of 1-Hz rTMS at 90% RMT with a 5-min intertrain interval Crossover design of active vs. sham with a 2-month washout period	1,800 pulses per session (9,000 pulses total)	5 days	Significant reduction in tremor rating scale following active or sham rTMS but no significant differences between active or sham rTMS

(Continued)

TABLE 2 | Continued

References	Participants	Target	Stimulation parameters and study design	Number of pulses per session	Duration	Results
Parkinson's disease tremor						
Bologna et al. (39)	13 PD and 10 HC; patients discontinued antitremor medications the night before the study	Cerebellum (in the hemisphere ipsilateral to the tremulous side of the body, 3 cm lateral and 1 cm inferior to the inion)	One 40-s train of 50-Hz cTBS at 80% AMT Crossover design for active vs. sham during off medication state at least 1 week apart	600	Single session	No significant difference in tremor amplitude or frequency between active and sham stimulation by kinematic analysis; significant reduction in M1 excitability following active but not sham stimulation
Lefaivre et al. (43)	50 PD; patients continued antitremor medication during the study	Cerebellum (medial cerebellum defined as directly beneath the inion, or lateral cerebellum, defined as 3 cm lateral and 1 cm inferior to the inion)	One 15-mi train of 1 Hz rTMS at 120% RMT Active (medial or lateral) vs. sham during on medication state	900	Single session	Significant improvement in rest tremor rating score by Kinesia motion sensor following medial and lateral cerebellar stimulation compared to sham
Fricke et al. (44)	20 PD; patients discontinued antitremor medications the night before the study	M1 and dPMC	Forty 25-s trains of 1-Hz ADS-rTMS at 95% RMT with a 5-s intertrain interval Crossover design for active and sham during off medication state at least 1 week apart	1,000 (pairs of stimuli)	Single session	No significant difference in UPDRS, finger tapping, or tremor by kinematic analysis between active and sham stimulation
Dystonic tremor syndrome						
Murase et al. (45)	9 WC; one patient with tremor	M1, PMC, SMA	One 21-min train of 0.2 Hz rTMS at 85% RMT Crossover design to different rTMS target sites and sham; each target site separated by at least 1 week	250 pulses per session (750 pulses total)	single session per target site	Significant improvement in handwriting scores with PMC stimulation; no comment on tremor
Huang et al. (46)	18 WC; one patient listed as having tremor	dPMC	One 40-s train of 50-Hz cTBS at 80% AMT Randomized to active or sham stimulation	600 pulses per session (3,000 pulses total)	5 days	Subjective improvement in writing following active rTMS but no significant difference in writing speed or spiral between groups; no comment on tremor
Kimberley et al. (47)	17 FHD; 2 patients listed as having tremor	dPMC	One 30-min train of 1-Hz rTMS at 90% RMT Crossover design between active and sham rTMS separated by 10 days	1,800 pulses per session (9,000 pulses total)	5 days	No significant difference in clinical measures between active and sham stimulation; no comment on tremor
Pirio Richardson et al. (48)	8 CD; 3 listed as having dystonic tremor	ACC, dPMC, M1, SMA	One 15-min trains of 0.2-Hz rTMS at 85% RMT Crossover design to different rTMS target sites and sham with 2 day washout	180 pulses per target (540 pulses total)	single session per target site	Trend for improvement in TWSTRS score for the dPMC and M1 sites; no comment on tremor
de Oliveira Souza et al. (49)	Case report: 1 patient with FHD and associated tremor	PMC	One 20-min train of 1 Hz rTMS at 80% RMT	1,200 pulses per session (18,000 pulses total)	15 days	Significant improvement following stimulation but benefits not sustained at 3 month follow-up; no specific comment on tremor

(Continued)

TABLE 2 | Continued

References	Participants	Target	Stimulation parameters and study design	Number of pulses per session	Duration	Results
Orthostatic tremor						
Gallea et al. (50)	9 OT	Cerebellum (over lobule VIII of each cerebellar hemisphere)	Two 15-min trains of 1 Hz rTMS at 90% RMT over each cerebellar hemisphere Open label design	1,800 pulses per session (9,000 pulses total)	5 days	No significant difference in FABRS or standing duration following rTMS; significant reduction in tremor amplitude by EMG analysis following rTMS; functional connectivity between lateral cerebellum and SMA which was abnormally increased in patients with OT compared with HC was reduced following stimulation
Hu et al. (51)	10 OT; 9 HC; patients discontinued antitremor medication at least 12 h before study	Cerebellum (3 cm lateral to the inion on the line joining the inion and the external auditory meatus)	One 15-min train of 1 Hz rTMS at 90% RMT Crossover design for active and sham rTMS separated by 1 day	900	Single session	Significant improvement in FABRS and standing duration immediately following active rTMS as compared to sham rTMS, but no sustained difference 1 h after rTMS; CBI significant increased at baseline compared to HC and normalized following active rTMS
Functional tremor						
Dafotakis et al. (52)	11 FT	M1 (contralateral to the affected hand)	30 total pulses of 0.2 Hz rTMS at 120% (15 pulses) and 140% (15 pulses) of the RMT Open label study	30	Single session	Using kinematic motion analysis, there was a significant reduction in tremor following rTMS, with a sustained response in about half of patients
Taib et al. (53)	18 FT	M1 (contralateral to the affected limbs)	800 × 2 biphasic pulses of 1 Hz rTMS at 90% RMT Randomized to active vs. sham followed by an open-label phase in combination with hypnosis	800 pulses per session (4,000 pulses total during randomized phase)	Randomized phase: 1 session for 5 consecutive days; open-label phase: 1 session weekly for 3 consecutive weeks	Significant decrease in PMDRS following active rTMS with sustained benefit at 6 month follow-up and throughout the open-label phase

ACC, anterior cingulate cortex; ADS-rTMS, associative dual-site repetitive transcranial magnetic stimulation; AMT, active motor threshold; CBI, cerebellar-brain inhibition; CD, cervical dystonia; CSP, cortical silent period; cTBS, continuous theta burst stimulation; CTC, cerebello-thalamo-cortical; DT, dystonic tremor; dPMC, dorsal premotor cortex; DTS, dystonic tremor syndrome; ET, essential tremor; FABRS, Fullerton advanced balance rating scale; FHD, focal hand dystonia; FT, Functional tremor; HC, healthy controls; M1, primary motor cortex; MEP, motor evoked potential; OT, orthostatic tremor; PD, Parkinson's disease; PMC, premotor cortex; PMDRS, psychogenic movement disorder rating scale; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SICI, short intracortical inhibition; SMA, supplementary motor area; TAWD, tremor associated with dystonia; TMS, transcranial magnetic stimulation; TWSTRS, Toronto western spasmodic torticollis rating scale; UPDRS, unified parkinson's disease rating scale; VIM, ventral intermediate nucleus of the thalamus; WC, writer's cramp.

blinding, inclusion of sham-control, and duration of benefits, the overall evidence was deemed to be of moderate quality. Thus, studies involving multiple sessions and larger samples are needed to further clarify the role of rTMS in ET.

PARKINSON'S DISEASE TREMOR

PD is a neurodegenerative disorder characterized by motor symptoms including tremor, rigidity, bradykinesia, and postural instability (8). The most classical type of PD tremor is rest tremor, which is commonly asymmetric and/or unilateral at the time of onset (1). Rest tremor is defined as a tremor that occurs in a body part that is not voluntarily activated and is completely supported against gravity (ideally, resting on a couch). During postural elevation of arms, rest tremor typically subsides for a transient period, followed by delayed re-emergence, which is known as re-emergent tremor (1). In addition to rest and re-emergent tremors, some patients may also have a postural tremor, which is typically a higher frequency than rest tremor (59). In some circumstances, it can be difficult to clinically distinguish rest, re-emergent, and postural tremor. Rest tremor is commonly treated with dopaminergic and anticholinergic medications. In medication-refractory cases, DBS of the subthalamic nucleus or globus pallidus internus can be considered (8).

The underlying pathophysiology of PD tremor is complex and not fully understood. Tremor-predominant PD has more pronounced degeneration of the medial substantia nigra compared to akinetic-rigid PD (3). There is evidence to support

both the basal ganglia projecting to the motor cortex and the CTC pathway as possible primary oscillators for PD tremor (60). Neuroimaging studies have shown dopaminergic deficits primarily contributing to rest tremor (3). Recently a "dimmer-switch" model was proposed that posits that the basal ganglia activates the tremor ("light switch"), whereas the CTC pathway modulates the tremor amplitude ("light dimmer") (60). This model helps to explain a paradox that unlike the other motor symptoms, PD tremor does not necessarily correlate with the degree of basal ganglia disease (60). In addition, this model also provides a potential explanation for the varying responses of PD tremor to dopamine. Dopamine-resistant PD tremor may have a larger contribution from the cerebellum, whereas dopamine-responsive tremor may have a larger contribution from the thalamus or globus pallidus internus (5).

Pathophysiological Insights From TMS

Single-pulse TMS delivered to the M1 was found to reset the rest component (13, 14, 27, 29), whereas a single-pulse over the cerebellum reset the postural component of the PD tremor (27, 29). In one study, application of the cerebellar pulse reset the re-emergent subtype of postural tremor suggesting that the cerebellum is involved in the oscillatory mechanism controlling pure postural and re-emergent postural tremor (35). Ni et al. found that rest tremor was reset with M1 stimulation; however, postural tremor was reset by both M1 and cerebellar stimulation (27). Ni et al. also found that compared to the healthy controls, CBI was reduced in PD tremor, which correlated with the degree of postural tremor reset caused by the cerebellar stimulation (27). These findings imply that the motor cortex may have more consistent involvement in the pathogenesis of rest tremor whereas the cerebellum likely contributes to pure postural and re-emergent subtypes of postural tremor.

Therapeutic Use of rTMS

A multitude of studies have demonstrated motor symptom improvements with rTMS in PD. These studies employing either low or high frequency protocols have targeted the M1, SMA, and dorsolateral prefrontal cortex (8, 61–63). However, there is a paucity of data for PD tremor benefits directly related to rTMS. Bologna et al. used a cTBS protocol targeted at the cerebellum and found that motor cortex excitability was reduced following active stimulation, but there was no change in rest tremor assessed clinically or with kinematic analysis (64). The study authors concluded that the CTC pathway was not primarily driving the rest tremor. However, in another study by Lefaivre et al., rest tremor as rated by kinematic parameters was reduced by low-frequency rTMS targeted to the medial and lateral cerebellum (43). These two studies used different stimulation techniques and there were differences in clinical populations, which could explain the conflicting results. For example, Bologna et al. focused on rest tremor and evaluated tremor during the off-medication state, whereas Lefaivre et al. included patients with tremor-predominant and akinetic-rigid PD, and all assessments were performed during the on-medication state (43, 64).

A novel protocol known as associative dual-site rTMS was implemented by Fricke et al., who hypothesized that simultaneous targeting of the dorsal premotor cortex and the M1 in a coordinated fashion might lead to decoupling of pathogenic oscillatory tremor activity (44). However, the study found no clinical improvements, suggesting that the optimal target site for PD tremor is still not clear (44). Based on the data from pathophysiological studies, it is reasonable to postulate that the rest and postural tremors are likely amenable to different stimulation sites. More extensive studies involving multiple targets and multiple stimulation sessions will further clarify the role of rTMS in PD.

DYSTONIC TREMOR SYNDROME

Tremor is a part and parcel feature of dystonia. When the tremor is found in a body part affected by dystonia, it is labeled as dystonic tremor (DT) (1). On the other hand, if dystonia and tremor are seen in different body parts, it is referred to as tremor associated with dystonia (TAWD) (1). Prevalence rates for tremors in dystonia are higher when patients are diagnosed with adult-onset focal dystonia and in dystonia that begins to spread from the original affected body part (65). In most patients, tremor manifests during posture or voluntary movements, but some patients may have tremor at rest (65). Few studies in the literature have specifically addressed DTS treatment, with most being retrospective and non-randomized studies (66). The available literature has not found consistent improvements with oral pharmacological therapies; however the use of botulinum toxin injection therapy is promising (66). There is also evidence to support that medication-refractory DTS responds to DBS targeted to the globus pallidus internus or the thalamus (66, 67).

The pathophysiology of DTS is not well-characterized (2). Neuroimaging studies have demonstrated that both the cerebellum and connections to the basal ganglia are involved (5). In a recent functional MRI study, task-based connectivity of the cerebellum, globus pallidus internus and motor cortex was significantly more affected in DT than ET (57). It is unclear whether the oscillators within the CTC pathway or the basal ganglia projections are the primary drivers for DTS (5). Furthermore, DT and dystonia may have distinct pathophysiological substrates as they may respond to different medical and surgical treatments (68). For example, DT may respond to medications such as propranolol and primidone that are not usually employed for dystonia, and although DBS is typically targeted to the globus pallidus internus for dystonia patients, the thalamus may be a viable option for DT.

Pathophysiological Insights From TMS

Single-pulse TMS studies have demonstrated DT could be reset with stimulation over the motor cortex as well as the cerebellum (31). However, when comparing DT with ET, stimulation over the cerebellum was observed to have more robust effects. The role of the cerebellum was further explored in a follow-up study that used a CBI paradigm to distinguish the characteristics of DT from TAWD (33). CBI was reduced in DT but not in TAWD, indicating less inhibition in the CTC pathway (33). Compared to TAWD and ET, DT had higher variability and increased instability. During motor task (especially complex tasks) performance, DT

became more unstable likely due to abnormal interactions of the motor command with the central oscillator (33). The study also found that the characteristics of TAWD were closer to ET than DT.

Therapeutic Use of rTMS

There have been numerous studies evaluating rTMS for therapeutic benefit in dystonia. The rTMS studies that have assessed dystonia have tried to alleviate symptoms in focal hand dystonia (45–47, 69–75), cervical dystonia (48, 76, 77), blepharospasm (78–80), and generalized dystonia (81–83). However, these studies have not focused on DTS in particular. Only five studies reported inclusion of patients with DTS as part of the baseline characteristics. However, the tremor outcomes were not separately analyzed, making it difficult to draw conclusions about rTMS specifically in DTS (45, 47–49, 73). Future studies should include separate cohorts of DT and TAWD and compare DTS with dystonia in general to elucidate the therapeutic role of rTMS in this patient population.

ORTHOSTATIC TREMOR

OT is a rare disorder characterized by a high frequency (13–18 Hz) tremor recorded during EMG from the leg muscles (1). OT results in unsteadiness when standing, which improves with walking or sitting (1). OT is defined as primary when the tremor is the sole manifestation with no additional neurological features. "OT plus" refers to tremor in combination with other associated neurological features such as an ET-like arm tremor or parkinsonian features (84). Most OT cases are idiopathic; some patients reportedly have cerebellar degeneration, paraneoplastic syndromes, or other metabolic disturbances that may be contributory (85). Since OT is rare, evidence to support treatment is limited and also challenging to study systematically. The most commonly used medication is clonazepam, as it can moderately reduce tremors in about one-third of patients and may eliminate symptoms in some patients (85). Beta-blockers and anticonvulsants are other medications that have shown mild benefits in a small percentage of patients (86). Some studies have reported that DBS targeted to the thalamus is effective, but this requires further study (87–89).

OT is a unique tremor syndrome for many reasons: tremor is only induced in weight-bearing positions, frequency is high ($\geq$13 Hz) compared to frequencies of other pathological tremors (4–12 Hz) (3), and high coherence is observed between EMG signals recorded from muscles in the legs, arms, and face (90). Unlike the other tremor syndromes, the coherence pattern recorded from homologous muscles in both sides of the body does not change over extended periods. The oscillator for OT likely resides in the posterior fossa, most likely the cerebellum and its connections with the brainstem and spinal motor neurons (3, 85, 91).

Pathophysiological Insights From TMS

A few studies have used single-pulse TMS techniques with variable results. While some studies were unable to reset OT (15, 19), others targeting the leg area in the motor cortex found significant effects (16, 18, 22, 92), thus supporting the hypothesis of a supraspinal generator for the tremor (16, 22, 85). Evidence suggests that OT may be modulated along the CTC pathway and downstream to the spinal cord from the central tremor generator (88). In a recent study, CBI was found to be significantly increased in the OT group compared to healthy controls, further supporting the involvement of the cerebellum in the pathophysiology of OT (50).

Therapeutic Use of rTMS

Only two small clinical trials have studied rTMS for OT. Both studies targeted the cerebellum and used the same paradigm of 900 pulses of 1 Hz rTMS at 90% of the RMT (50, 51). While Gallea et al. employed multiple stimulation sessions, Hu et al. used a single session of active vs. sham in a crossover design (50, 51). Gallea et al. found no improvements in clinical assessment, but the accelerometer analysis revealed a decrease in tremor amplitude sustained up to 3 weeks (50). There was also a decrease in functional connectivity between the lateral cerebellum and SMA (50). Hu et al. found improvements in standing time with active stimulation that correlated with changes in CBI (51). Future randomized studies should employ large samples with multiple sessions to determine if these clinical improvements persist.

FUNCTIONAL TREMOR

Up to 20% of patients presenting to the movement disorder clinics are ultimately diagnosed with a functional movement disorder (FMD), which refer to various movement symptoms that are unexplained by organic disease or have features that are only partially explained by underlying organic disease (93). Recent studies have found a clear interplay between neurological and psychological components (53, 93). Treatment of FMDs is quite challenging, and patients may experience significant impairment in their quality of life. An integrated and transparent approach involving multiple disciplines is most helpful. Cognitive-behavioral therapy is a promising treatment option that helps identify how the thought processes may affect emotions or behaviors for these patients. Physical therapy employs motor retraining to treat predominant motor symptoms (94). Finally, identifying and treating comorbid anxiety and depression remains an important consideration.

The pathophysiology of functional tremor remains unclear. Some patients have tremor that is often distractible and in some co-contraction of antagonist muscles leads to an oscillatory movement similar to clonus, with tremor resolution when the co-contraction stops (3). Many neuroimaging studies have demonstrated hypoactivation of the SMA, which is involved in movement preparation (94). Studies in functional tremor have demonstrated an increased activity of the cingulate cortex, paracingulate gyrus, and left insula compared to healthy controls (95). Neuroimaging studies have also demonstrated decreased activity of the right middle temporal gyrus, which plays a vital role in self-agency and helps to detect discrepancies between internal motor intentions and external motor actions (95). cTBS targeted at the pre-SMA has been shown to reduce abnormal

sense of agency, which may be an underlying cause of FMDs in general (95). To date, no studies have implemented TMS paradigms to gain insight specifically into the pathophysiology of functional tremor, and this is an important area for future study.

Therapeutic Use of rTMS

TMS has been used in several small, open-label studies for patients presenting with functional paresis, aphonia, mixed phenomenology (including myoclonus, Parkinsonism, and dystonia), and tremor (93). TMS paradigms used in these studies have been highly variable, making a comparison across studies difficult. Many studies have found promising results, with some reporting sustained benefit at long-term follow-up; however there is inadequate quality of evidence as there is considerable heterogeneity in the population sampled, study design, TMS parameters, and outcome measures. These studies have not included a sham arm (93). In an open-label study ($n = 24$) of patients with FMD, a single 50 pulse session of 0.25 Hz rTMS was applied over the M1 contralateral to the affected limb and the clinical scores improved by 50–75% for almost 2 years (96). Another study in patients with FMD ($n = 33$) involved a crossover design of a single session of rTMS over the contralateral motor cortex and ipsilateral spinal roots (97). There were clinical improvements in both groups, suggesting that the effects of rTMS were more cognitive-behavioral, as opposed to true neuromodulation. Given the short washout period between stimulation for the two groups, a definitive conclusion could not be drawn (97). One study employed suggestibility in their treatment design (98). Participants were told there would be a high likelihood of benefit following 5 consecutive days of a single rTMS session delivered at 0.33 Hz. The study found rTMS to premotor cortex led to improvement in physical quality of life, but there was a reduction in the psychological quality of life. These dissociative findings were attributed to the complex pathophysiology of the FMDs (98).

Two additional studies specifically focused on the response of functional tremor to rTMS. An early open-label study implemented a single session of 0.2 Hz rTMS applied to the motor cortex that led to clinical improvements, but the benefits in many patients were transient (52). There was no sham arm to rule out a placebo effect. More recently, in a randomized, double blind, active vs. sham arm study, 1 Hz rTMS at 90% RMT was delivered to the motor cortex in patients presenting with functional tremor. The study found significant and sustained clinical improvements in the active stimulation group lasting for 12 months (53). These preliminary studies suggest that rTMS can improve functional tremor; however, future studies should target specific and individualized sites determined to be hypoactive or hyperactive with fMRI and measure brain functions with TMS to characterize the pathophysiological underpinnings of functional tremor.

CURRENT LIMITATIONS

Although TMS can be an important tool for understanding physiology and potentially treating clinical symptoms of tremor, there are several limitations to consider. There is high variability in the rTMS paradigms and study designs used to investigate tremor syndromes, including differences in sham application, washout periods in crossover designs, target location, number of pulses, number of stimulation sessions, and duration of the stimulation in total. Many studies implemented only a single stimulation session (26, 28, 36, 37, 39, 43, 44, 51, 52, 64, 73), whereas other studies included multiple sessions ranging anywhere from 5 consecutive days to 15 stimulation days (38, 40–42, 47, 49, 50), or more unique protocols in which 5 consecutive days of stimulation are followed with a weekly session of stimulation for 3 weeks (53). The number of stimulation sessions may play a role in the duration of benefit, and thus it is critical to not only assess benefit following stimulation but also to assess how long that benefit lasts. Protocols with fewer or only single stimulation sessions would be expected to have theoretically shorter-lasting benefits than paradigms that include multiple stimulation sessions. For example, one ET study found a significant improvement in tremor scores 5 min after stimulation, but this benefit was not seen 60 min following stimulation (36). In contrast, a study incorporating 5 days of stimulation found a sustained benefit in tremor scores up to 3 weeks following stimulation (38). The number of stimulation sessions is not the only TMS parameter that may influence the duration of benefit. In fact, it may be the total number of pulses delivered to the brain that has a bigger influence on the duration of benefit as opposed to the number of stimulation sessions. Indeed, number of stimulation sessions does not appear to be linearly related to improvement in tremor, suggesting that there may be a certain threshold of pulses or sessions after which optimal clinical improvement is seen (54). In addition, the stimulation intensity, typically reported as a percentage of RMT or AMT, as well as the rate of delivered pulses may influence the degree and duration of benefit. Given the heterogeneity of rTMS paradigms between studies, it is difficult to compare and contrast results from one study to another and the optimal stimulation parameters are not yet known.

Given that the pathophysiology of each of these tremor syndromes is different from one another, the ways in which they are treated is also different. This is reflected by the current standard of care treatments, which range from specific pharmacotherapy to specific DBS target sites based on the type of tremor syndrome. Therefore, it makes sense that different TMS stimulation parameters and target sites also be needed to have the greatest therapeutic benefit for each individual tremor syndrome. However, there is variability in the TMS study designs within the same type of tremor syndrome as well. Some studies chose to randomize two separate groups of patients in an active and sham protocol (40, 41, 43, 53, 73), whereas others used a crossover design to evaluate benefit (36, 37, 39, 42, 44, 47, 51, 64). There are a few limitations specific to crossover designs performed in rTMS studies. First, a real TMS coil emits a loud clicking noise with each pulse and also generates a tapping sensation along the patient's skull throughout the procedure. Therefore, it is important to have a sham condition which mimics this active condition as closely as possible. However, sham conditions are highly variable in these studies. These sham conditions include tilting an active coil away from the target (36, 41–43, 47, 48), delivering the

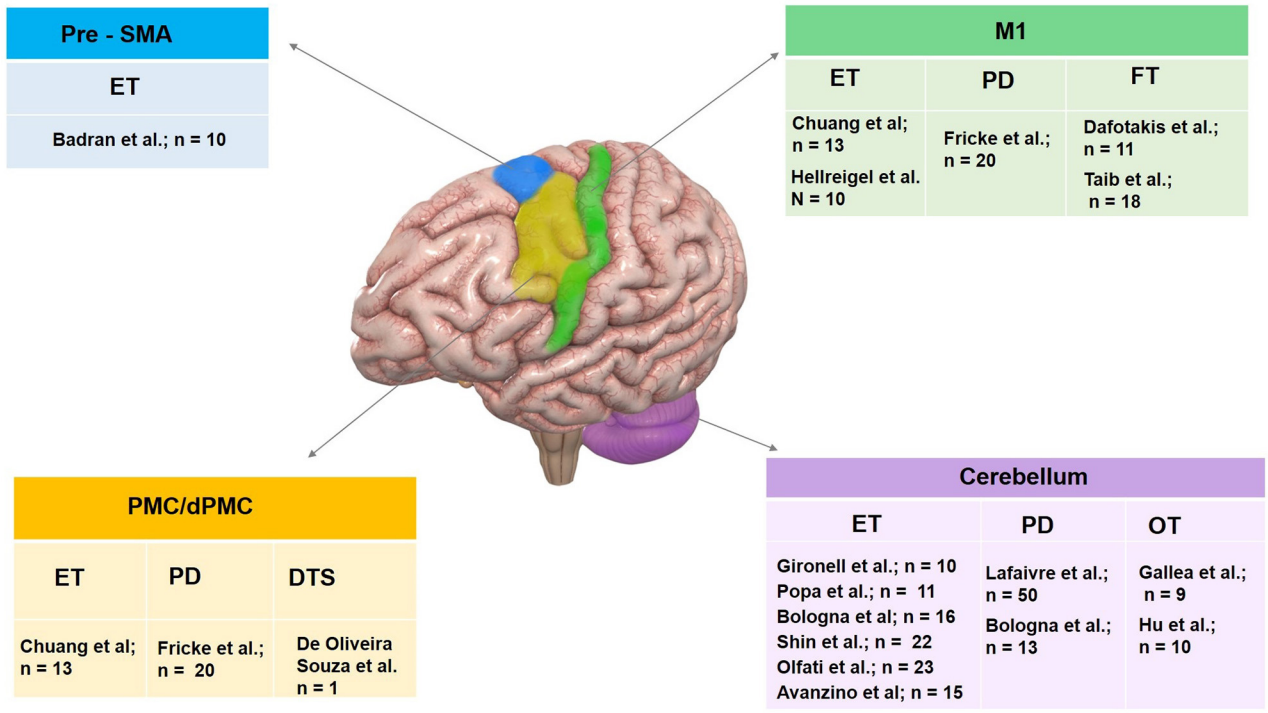

FIGURE 3 | Summary of therapeutic use of rTMS in tremor syndromes organized by target site. Pre-SMA, pre supplementary motor area; M1, primary motor cortex; PMC, premotor cortex and cerebellum have been targeted. Investigator group and sample size enrolled for individual tremor syndrome including essential tremor (ET), Parkinson's disease (PD) tremor, dystonic tremor syndrome (DTS), orthostatic tremor (OT) and functional tremor (FT) are illustrated.

stimulation at a lower intensity than would be expected to cause neuromodulatory changes (28, 37, 44, 73), stimulation of neck muscles instead of the cortex (39, 64), or using a sham coil that delivers a tapping sensation accompanied by a loud clicking noise without delivering any stimulation (40, 45, 51, 53). A sham coil offers the most reliable way of ensuring blinding without unintentional neurostimulation.

A second important design factor in rTMS crossover studies is the amount of time dedicated to "washout" between the active and sham stimulation sessions. This washout period varies widely between studies, with some waiting 1–2 days (48, 51), 1 week (28, 36, 37, 39, 44, 64), or weeks to months (42, 47). It is critical to choose a washout period that will allow for stimulation effects to wear off before starting the next session. Given that paradigms with a higher total number of sessions and the total number of pulses have led to cumulative effects or longer-lasting benefits, studies implementing these paradigms should include more extended washout periods between active and sham stimulation sessions. In addition, implementing several follow-up periods, ranging from immediately after rTMS, to hours after rTMS, to weeks after rTMS, will give us a better understanding of how long we should expect different rTMS paradigm benefits to last.

These limitations, some of which are inherent to rTMS study design, make it difficult to draw any overall conclusions about the efficacy of rTMS in tremor syndromes at this time. The majority of these studies have looked at small and often heterogenous populations. Given these known limitations of rTMS studies, it is important to design future studies that will more systematically assess the therapeutic use of rTMS for tremor syndromes.

CONCLUSION AND FUTURE DIRECTIONS

In summary, TMS is a valuable tool that can potentially enhance the pathophysiological understanding of movement disorders. Although tremor is the most common movement disorder and recent imaging studies have advanced the knowledge of the critical pathogenic networks, TMS has been underutilized overall. Single pulse TMS paradigms have been helpful in demonstrating the brain circuitry that is likely involved in the generation of tremor. Single pulse TMS targeted to the primary motor cortex has resulted in tremor reset for both ET and rest tremor in PD (13, 14, 20, 27, 29) as well as for re-emergent tremor in PD (34), suggesting similar circuitry involved in the generation of these two tremor syndromes. However, single pulse TMS directed at the cerebellum led to tremor reset in postural tremor in PD but not in rest tremor in PD or in essential tremor, suggesting that these tremor syndromes have different underlying pathophysiology or are modified by additional factors outside of these circuits (20, 27, 29). Similarly, single pulse TMS to M1 led to reset of both ET and DTS, whereas single pulse TMS to the cerebellum led to reset in ET more so than in DTS (31). These differences suggest that certain parts of the brain circuit are more involved with the generation of tremor whereas other

parts of the circuit are more involved with modulation of tremor. In addition, paired pulse TMS paradigms have demonstrated involvement of the cerebellum in ET, postural tremor of PD, and OT. TMS studies evaluating the pathophysiology of functional tremor are still needed. These pathophysiological insights are not only important for our understanding of tremor syndrome symptoms, but can also guide us into selecting appropriate rTMS parameters for treating these tremor syndromes clinically. Using knowledge of tremor pathophysiology to design rTMS studies is one important way of being more thoughtful when approaching the rTMS design for tremor syndrome studies. For example, using associative dual site TMS targeted at the M1 and dPMC was based on the assumption that each of these target sites was connected *via* different tracts to the subthalamic nucleus (STN), which is an important structure in the manifestation of tremor in PD (44). Therefore, simultaneous stimulation of these targets was hypothesized to lead to decoupling of the pathogenic oscillatory activity (44). Future pathophysiologic studies should focus on determining which brain circuits are the primary oscillator and which are more responsible for modulating existing tremor. Studies combining TMS with EEG and fMRI will be critical to answering these questions.

There is emerging evidence supporting the therapeutic potential of rTMS for treating tremor syndromes. rTMS paradigms inhibiting the cerebellum have shown promise at reducing ET, OT, and specific subtypes of PD tremor. Inhibitory paradigms targeted to the motor cortex, pre-SMA, or SMA have shown improvements in ET populations and those presenting with functional tremor (**Figure 3**). Although these early results are encouraging, studies involving multiple sessions, larger samples, blinded outcome assessments, and long-term follow-ups are warranted to confirm the therapeutic role of rTMS in tremors. It is crucial to include a sham-controlled arm to ensure that a placebo response does not drive clinical benefits. Future rTMS study designs would benefit from using both clinical scales and kinematic outcomes and correlating tremor improvement with underlying changes in the pathophysiology. In addition, it will be beneficial to determine if rTMS and standard pharmacological treatments have synergistic benefits. Future studies should combine TMS with imaging to identify individualized brain abnormalities and employ personalized rTMS protocols to provide robust, long-lasting benefits.

AUTHOR CONTRIBUTIONS

JF contributed to the writing of the first draft, conceptualization of the topic, data collection, and major revisions. CH was responsible for major revisions. MW and LK were responsible for data collection, figure illustration, and major revisions. AW was responsible for conceptualization of the topic and major revisions. All authors agree to be accountable for the content of the work.

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