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REVIEW

Linking Essential Tremor to the Cerebellum: Physiological Evidence

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Abstract Essential tremor (ET), clinically characterized by postural and kinetic tremors, predominantly in the upper extremities, originates from pathological activity in the dynamic oscillatory network comprising the majority of nodes in the central motor network. Evidence indicates dysfunction in the thalamus, the olivocerebellar loops, and intermittent cortical engagement. Pathology of the cerebellum, a structure with architecture intrinsically predisposed to oscillatory activity, has also been implicated in ET as shown by clinical, neuroimaging, and pathological studies. Despite electrophysiological studies assessing cerebellar impairment in ET being scarce, their impact is tangible, as summarized in this review. The electromyography–magnetoencephalography combination provided the first direct evidence of pathological alteration in cortico-subcortical communication, with a significant emphasis on the cerebellum. Furthermore, complex electromyography studies showed disruptions in the timing of agonist and antagonist muscle activation, a process generally attributed to the cerebellum. Evidence pointing to cerebellar engagement in ET has also been found in electrooculography measurements, cerebellar repetitive transcranial magnetic stimulation studies, and, indirectly, in complex analyses of the activity of the ventral intermediate thalamic nucleus (an area primarily receiving inputs from the cerebellum), which is also used in the advanced treatment of ET. In summary, further progress in therapy will require comprehensive electrophysiological and physiological analyses to elucidate the precise mechanisms leading to disease symptoms. The cerebellum, as a major node of this dynamic oscillatory network, requires further study to aid this endeavor.

Keywords Cerebellum · Essential tremor · Dynamic oscillatory network · Electrophysiology

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Abbreviations

ET	Essential tremor
EMG	Electromyography
MEG	Magnetoencephalography
EOG	Electrooculography
rTMS	Repetitive transcranial magnetic stimulation
Vim	Ventral intermediate nucleus of the thalamus

Introduction

Essential tremor (ET) is a slowly progressive disorder defined by postural and kinetic tremors predominantly in the forearms and hands, eventually spreading to the head and other body regions [1, 2]. ET is not a benign condition considering the disability during daily life activities and the negative impact

on a patient's quality of life [3] and even the increased mortality [4]. Moreover, ET is one of the most common movement disorders with a prevalence of approximately 3 % in those aged over 50 years [5]. However, it is assumed with reasonable confidence that the underlying pathology develops far in advance of clinical signs [6].

The mechanisms giving rise to this seemingly monosymptomatic disorder have been elusive, but several lines of converging evidence from animal models [7], functional imaging [8–10], and neuropathological studies [11] implicate dysfunction of the oscillatory network comprising the cerebello-thalamo-cortical loops. In addition, a potential role of cerebellar hyperactivity in ET pathophysiology has been highlighted by clinical observations [12, 13], but cortical motor regions seem to be entrained in the tremor rhythm only intermittently [14].

The aim of this review is to summarize the available neurophysiological and electrophysiological evidence of involvement of the cerebellum in the pathophysiology of ET.

Oscillatory Mechanisms of the Cerebellum and Its Network

Theoretically, the architecture and neuronal structure of the majority of the motor centers enable the production of oscillatory activity [15]. Particularly, the cerebellum has high potential for repetitive cyclic processes. The dendritic structure of cerebellar neurons, with a basic three-layer organization comprising a line of Purkinje cells between the outer molecular and deeper granular layers, is markedly dissimilar to that of pyramidal cells and cells found elsewhere in the motor network and allows for oscillatory modulations in the cerebellum [16]. Purkinje cell inhibitory GABAergic neurons exhibit tonic activity, with spontaneous discharges modulated by efferent motor action or incoming stimuli [17]. Input from climbing fibers arising from the inferior olivary nucleus appears to drive complex spikes, a large initial spike followed by a train of lower-amplitude potentials [18] and oscillations in the alpha range. Such complex spikes arise owing to the ability of climbing fibers to generate periodic synchronous discharges [19]. Furthermore, cerebellar granular cells generate oscillations of up to 25 Hz in low-frequency ranges synchronized with the cerebral cortex [20, 21]. Lastly, the architecture of parallel fibers, axons arising from granular cells, allows for the creation of synchrony between Purkinje neurons [16] (see Fig. 1 for a schematic drawing).

Invasive recordings of the human cerebellum are extremely rare [22], and largely functional hypotheses only have been proposed for cerebellar oscillatory activities. Local field potentials oscillating in the delta (1–4 Hz) and theta (4–9 Hz) bands, generated in the granular layer, have been attributed to learning-dependent timing [23], sensory state assessment, and intermittent motor control [24]. Generally, tremors with comparable frequencies are associated with oscillations in the cerebellum and motor cortex at the tremor frequency and its first harmonic [25]. The beta band (10–30 Hz) is associated with movements and sensorimotor processing [26, 27]. Thus, lower frequencies of cerebellar oscillations are closely related to activity in the cerebral cortex during specific stages of behavior [18], in accord with the posture-dependent clinical character of ET. Unfortunately, the function of frequencies above 30 Hz remains elusive, owing to vastly different neural architecture, and it is not clear to what extent cerebellar gamma activity is similar to that of the cerebral cortex [16].

In addition to the cerebellum, almost the entire physiological central motor network is involved in the generation of ET. The inferior olive in the brainstem and the thalamus play important roles, with multiple lines of evidence indicating a role of cortical motor centers as well [14, 25] (see Fig. 1). However, network activity is not stable over time and its components' participation may fluctuate and change. Specifically, cortical involvement in tremor generation is intermittent, and given that it is not essential for the persistence of ET symptoms [28], it must affect the cooperation of all other components in tremor generation, thus changing network composition in a complex and dynamic way [14]. It has been hypothesized that cortical inputs, not phase-locked to voluntary movement, can depolarize thalamic neurons and, even when not leading to active movement, may elevate tremor inputs from deep cerebellar nuclei above a specific threshold, thus enabling thalamic tremor-related activity [29]. Another hypothesis proposes activation of reverberating cerebello-thalamo-cortical circuits during posture as the foundation for posture-dependent thalamic oscillations [29, 30], leading to tremor activity generation during posture and movement but not at rest. However, the mechanisms for switching from a non-oscillatory pattern during rest to oscillatory patterns during tremor, in the context of significant resting cerebellar activity found in functional imaging studies [9], have yet to be determined. In both hypotheses, the thalamus is a key structure for oscillatory entrainment of subcortical and cortical nodes, with the highest percentage of tremor cells found in the ventral intermediate nucleus (Vim) [29]. Interestingly, the Vim primarily receives excitatory input from the cerebellum and projects to the primary motor cortex [31]. Indeed, the considerably higher mean spontaneous firing rate of Vim neurons in patients with ET [32], combined with the periodic activity of thalamic neurons coherent with electromyographic (EMG) findings during posture (but not rest) [29], suggests a close pathophysiological relationship between the thalamus and ET. Moreover, the position of this structure in the oscillatory network provides a possible explanation for the effectiveness of Vim neurosurgical lesions and microstimulation in ET treatment [33]. Indeed, ischemic lesions in any of the components of the proposed oscillatory network have been found to abolish ET in single

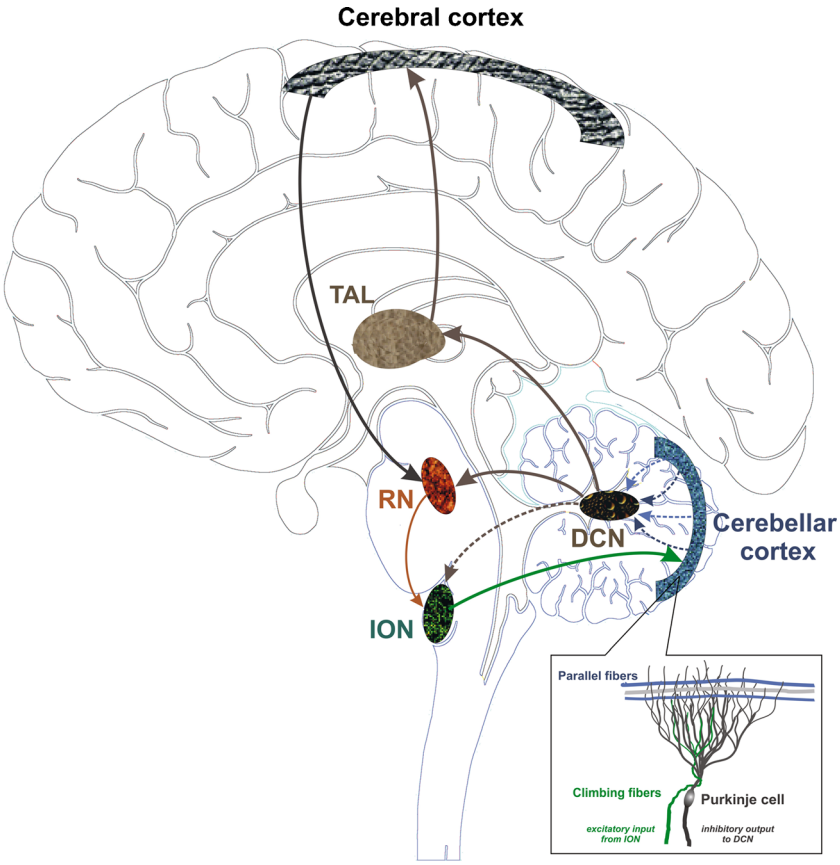

Fig. 1 Schematic drawing of cerebellar connections. Excitatory connections in *full line* and inhibitory connections in *dashed line*. *ION* inferior olivary nucleus, *DCN* deep cerebellar nuclei, *TAL* thalamus, *RN* red nucleus. The cerebral cortex and the olivocerebellar system are strongly connected via reverberating loops involved in sensorimotor processing

patients [34]. Last, the inferior olivary nucleus, a major source of input to the cerebellum, is hypothesized to be a possible source of oscillations, further transmitted via the cerebellum to the whole motor network and responsible for ET symptomatology [35]. The electrotonic coupling of neurons of the inferior olivary nucleus predisposes mammals to synchronous rhythmic discharges [36]. Peculiarly, the discharge pattern of this structure in healthy awake monkeys was shown to be just the opposite, aperiodic to the extent of being random [37]. The harmaline model of drug-induced continuous olivary oscillations with generalized 8–12-Hz tremor has been frequently compared with ET [7]. Interestingly, even direct functional correlates of the affected olivocerebellar circuit have been hypothesized with the character of associative learning dysfunction in the form of delayed eyeblink conditioning [38], which showed clear improvement to the conditioning rates within the range of controls after ventrolateral thalamus deep brain stimulation (DBS) [39]. Hence, different central network structures seem to be comparably effective in producing oscillations, implying that there might be no single driver. Rather, all network components may contribute in a specific way to the complex clinical picture of ET.

Functional Electrophysiology

The functional electrophysiology of the cerebellum remains poorly characterized compared with the cerebral cortex. Although intracranial EEG recordings from neurosurgery patients have greatly improved our understanding of the neurophysiology of the cerebral cortex and subcortical structures, clinical cerebellum surface recordings are performed less frequently. Indeed, reports detailing direct recordings from the cerebellum are extremely rare. EEG studies in ET have clearly demonstrated cortical activity coherent with ET [28, 40], but have not yet provided direct evidence concerning the cerebellar contribution to the pathophysiology of ET. Intrathalamic recordings have shown that the highest number of neurons with oscillatory properties is contained within the Vim. The close neuroanatomical link between cerebellar nuclei and Vim neurons provides compelling, although indirect, evidence for a cerebellar pathology [29], but there are no reports of intracranial recordings that have specifically targeted the cerebellum itself.

Thus, existing knowledge supporting a cerebellar role in the oscillatory network of ET originates mainly from neuroimaging studies [9], an intriguing magnetoencephalography (MEG) study reporting a core structure consistently linked to

brainstem and cerebellar activities in ET [25], transcranial magnetic stimulation (TMS) studies, indirect evidence based on complex EMG, and electrooculographic (EOG) studies showing signs of cerebellar dysfunction in ET (for summary, see Table 1).

Cerebellar TMS in ET

Repetitive TMS (rTMS) is a convenient method for studying human brain cortex and cerebellar physiology [41]. In general, fast rTMS at frequencies >5 Hz gives rise to increased cortical excitability, whereas low-frequency rTMS (1 Hz) has the opposite effect, as evidenced by decreased neuronal metabolic rate [42]. The physiological foundation of this phenomenon is yet to be determined. Thus, the extrapolation of the effects observed in motor cortex studies to the human cerebellum is plausible but not definitive. Nonetheless, interference of rTMS with the action of oscillatory cerebellar neurons affects populations of neurons entrained at a particular frequency, thus removing them from participation in their potentially pathologic function. As a proof of concept, an exploratory study using active rTMS produced a notable, albeit transient, tremor improvement in patients with ET [43]. Furthermore, single-pulse TMS of the cerebellum in patients with ET elicited no disruption in cerebello-thalamo-cortical pathways, suggesting the presence of abnormalities with cerebellar afferent input [44]. Therefore, even if the therapeutic utility of cerebellar rTMS in patients with ET is low, owing to the short-term anti-tremor effect compared with DBS of the Vim [33], the ability of rTMS to reduce tremors argues strongly for a critical role of the cerebellum in ET pathophysiology.

EMG

In addition to evidence of cortical involvement in simultaneous EEG-EMG recordings [40], and strong correlation of thalamic neuronal activity with forearm EMG signals in ET [45], complex EMG tests based on timing of activation of different muscles involved in movement have provided indirect evidence of cerebellar dysfunction in ET.

Fast limb movements are controlled by a triphasic pattern of EMG activity. The timing of burst discharges is under cerebellar control, in line with the major contribution of cerebellar circuitry in timing function [46]. The first agonist burst initiates movement and is followed by an antagonist burst, which provides decelerating torque. A second agonist burst attenuates oscillations induced by deceleration [47]. Movements performed by patients with ET have a normal duration and adequate peak velocities and peak accelerations. However, delayed onset of phasic activity of the second agonist muscle has been repeatedly reported [48, 49], allowing the antagonist to operate unopposed for longer periods of time. Consequently, the higher-than-normal peak deceleration leads to a series of dampened oscillations around the target point, possibly reflecting abnormalities in anticipatory muscle activity timing, a process generally attributed to the cerebellum [50–52]. Furthermore, the latency of the second agonist EMG burst correlates significantly with the tremor period [48] and the clinical presentation of ET. This was more pronounced in a group of patients with ET with additional intention tremor compared with patients with isolated postural tremor [49]. In agreement with the general interpretation of intention tremor as a hallmark for cerebellar dysfunction, patients with ET with this symptom have an additional delay of the antagonist burst, suggesting even more marked dysfunction of the cerebellum [49]. Hence, differences in the clinical presentation of ET may reflect various stages of disturbed

Table 1 Summary of electrophysiological studies providing evidence of cerebellar involvement in ET

Study	Method	Result	Interpretation
Gironell et al. [43]	rTMS of cerebellum	Transient tremor improvement	Possible abolition of pathologic cerebellar rhythms leading to ET
Pinto et al. [44]	Single-pulse TMS of cerebellum	No disruption in cerebello-thalamo-cortical pathways	Possible presence of abnormalities in the cerebellar afferent input
Britton et al. [48] and Köster et al. [49]	EMG	Delayed onset of second agonist muscle activity, correlating with the tremor period	Impairment in EMG bursts timing—a process generally attributed to the cerebellum
Schnitzler et al. [25]	EMG-MEG	Pathologically altered communication between contralateral primary motor cortex, premotor cortex, thalamus, brainstem, and ipsilateral cerebellum	The first direct evidence of pathologically altered communication in a network involving the cerebellum
Helmchen et al. [56]	EOG	Smooth pursuit initiation impairment and impaired vestibulocerebellar function	Impairment in complex visuomotor functions—processes generally attributed to the cerebellum

cerebellar timing function related to ET severity. Nonetheless, thalamic stimulation, even though providing a dramatic improvement of ET, does not lead to the reduction of the delayed antagonist muscle response [53]. Conversely, Elbe et al. found no differences in the latencies of the triphasic EMG burst complexes in ET, but highlighted the fact that the onset of the initial agonist muscle activation was in phase with a rhythmic tremorous burst in EMG of opposite momentum to the volitional movement, thus contributing to the impaired performance in fine motor tasks of the patients with ET [54].

Moreover, simultaneous EMG recordings made in an elegant MEG study of peripheral tremor activity [25] provided the first direct evidence of pathologically altered communication in a network involving the contralateral primary motor cortex, premotor cortex, thalamus, brainstem, and ipsilateral cerebellum. Additionally, the presence of oscillatory activity was related to the clinical presentation of ET. Despite the limited spatial resolution of this method in subcortical areas, this finding provides a reasonable foundation to exclude the possibility of oscillation entrainment within the network from one central driving oscillator to other nodes and further promotes the ET as a network disorder hypothesis. Even so, the activity of the network might be launched by a node within the loops.

EOG

The cerebellum is a crucial structure for many complex visuomotor functions, including saccade processing, smooth pursuits, adaptation of vestibulo-ocular reflex, and the optokinetic reflex [55]. Although no oculomotor deficits are detected in patients with ET during bedside clinical examination, a more subtle impairment, assumed to be of cerebellar origin, may nevertheless be found [56]. This is in the form of smooth pursuit initiation impairment with normal latency (thus not likely of cortical origin [57, 58]) and impaired vestibulocerebellar function in reducing the time constant of post-rotary vestibular nystagmus [59]. Moreover, the impairment of initial pursuit acceleration was found to correlate with clinically apparent intention tremor, possibly indicating a similar pathophysiological background [56]. The sole center participating in cerebellar visuomotor processing that could elicit both such deficits is the caudal vermis (nodulus and uvula) [60, 61]. Furthermore, the uvula receives climbing fiber afferents originating from the dorsolateral pontine nuclei and the inferior olive [62], an important node in the proposed oscillatory network in ET. Hence, cerebellar dysfunction in ET is not limited to clinically apparent control of arm and leg movements but extends to complex oculomotor and vestibular processes as well.

Conclusions

Although classically positioned as one of the most prominent brain structures associated with motor control, research indicates that the cerebellum may be a center for far more diverse processes [55]. Its pathology is now implicated in a wide range of neurological disorders [63–65], in addition to ET. Complex imaging techniques have provided evidence of functional alterations [8, 9] and morphological changes [10, 66] in the cerebellum in patients with ET, further supported by post-mortem studies showing signs of pathology not only in the cerebellum but also in the brainstem [11, 67]. However, there is still debate as to whether ET is primarily a degenerative cerebellar disorder emerging from genetic abnormalities with putative non-genetic factors [67].

Frequently, abnormal neuronal oscillations are regarded as a fundamental event in ET, leading to well-documented clinical cerebellar symptoms via interference of oscillations with the motor functions of the cerebellum [12, 13], and even secondary neuronal damage and neuroplastic changes, if allowed to persist [68]. Even improvement of tremor and cerebellar deficits associated with alcohol, a substance with typical toxic effects on the cerebellum [69], casts doubt on a primary cerebellar neurodegenerative affection categorization. However, the mechanism behind the effect of ethanol might be based on restoration of the function of glutamatergic pathways, as shown in the harmaline model [70], thus providing a plausible backing for the hypothesis supporting the neurodegenerative nature of the disease. Irrespective of the character of the dysfunction, these alterations argue strongly for cerebellar involvement in ET. Furthermore, direct involvement of cerebellar circuits in the initial stages of the disease has been hypothesized, with some data pointing to a pathogenic mechanism starting in the cerebellum, especially in Purkinje neurons, and disseminating secondarily to the entire motor circuitry [71].

The presence of dynamic oscillatory disturbance in ET is also supported by a wide spectrum of electrophysiological and physiological studies summarized in this review, including EMG, MEG, rTMS, and EOG studies, providing both direct and indirect evidence of cerebellar dysfunction. Furthermore, the architecture of the cerebellum encourages iterative cyclic processes with character close to oscillatory activity leading to tremor [14].

However, the intricate pathophysiological mechanisms and pathways giving rise to the clinical expression of ET are still undetermined. Simplistic models of individual centers or single loops, including the simple olivocerebellar drive, which partly replicate the clinical scenario, do not provide explanations consistent with the clinical expression of the disease. A 6–10-Hz tremor may also be generated in decerebrated preparations, caused by rhythmic activation of Purkinje cells synchronized with spinal motor neurons [72], and harmaline application leads to continuous olivary oscillations with clinical

presentation frequently compared with ET [6]. However, the continuous oscillatory drive generated by this circuit (and transmitted to the periphery without modulation by limb movement or position) would not produce postural and kinetic tremors with minimal symptoms at rest. In contrast, cerebellar efferent structures do not exhibit oscillatory behavior at rest, but show dramatic pattern changes during arm tremor that correlate with forearm EMG signals [29]. Thus, ET does not appear to emerge from a single node, but rather from a complex structure encompassing a significant part of the motor network, without one driver transmitting the oscillatory activity to other neural nodes and peripheral muscles. All of the network components provide important inputs, which dynamically entrain each other, that can induce the observed dynamic oscillatory disturbance. The cerebellum, while crucially important for ET pathophysiology, does not intrinsically possess the structural, physiological, or functional qualities needed to generate the entire ET symptomology.

In summary, notwithstanding the progress to date, we are far from a clear understanding of the precise underlying mechanisms of ET oscillatory activity and the cascade of events triggering such oscillations. Thus, currently, all available therapeutic approaches remain relatively unspecific and target symptoms rather than the primary cause of ET. Surgical lesions or DBS of Vim remain the only treatments which can abolish the symptoms of the disease [33, 73]. Our review underlines the need for further research in this area and for a particular focus on the cerebellum's role as one of the crucial components of the oscillatory network in ET.

Compliance with Ethical Standards

Conflict of Interest There are no potential conflict of interests regarding this paper and no financial or personal relationships that might bias this work.

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