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Tremor and Other Hyperkinetic Movements

Review

Essential Tremor, the Cerebellum, and Motor Timing: Towards Integrating Them into One Complex Entity

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Abstract

Essential tremor (ET) is the most common movement disorder in humans. It is characterized by a postural and kinetic tremor most commonly affecting the forearms and hands. Isolated head tremor has been found in 1–10% of patients, suggesting that ET may be a composite of several phenotypes. The exact pathophysiology of ET is still unknown. ET has been repeatedly shown as a disorder of mild cerebellar degeneration, particularly in postmortem studies. Clinical observations, electrophysiological, volumetric and functional imaging studies all reinforce the fact that the cerebellum is involved in the generation of ET. However, crucial debate exists as to whether ET is a neurodegenerative disease. Data suggesting that it is neurodegenerative include postmortem findings of pathological abnormalities in the brainstem and cerebellum, white matter changes on diffusion tensor imaging, and clinical studies demonstrating an association with cognitive and gait changes. There is also conflicting evidence against ET as a neurodegenerative disease: the improvement of gait abnormalities with ethanol administration, lack of gray matter volume loss on voxel-based morphometry, failure to confirm the prominent presence of Lewy bodies in the locus ceruleus, and other pathological findings. To clarify this issue, future research is needed to describe the mechanism of cellular changes in the ET brain and to understand the order in which they occur. The cerebellum has been shown to be involved in the timing of movement and sensation, acting as an internal timing system that provides the temporal representation of salient events spanning hundreds of milliseconds. It has been reported that cerebellar timing function is altered in patients with ET, showing an increased variability of rhythmic hand movements as well as diminished performance during predictive motor timing task. Based on current knowledge and observations, we argue that ET is essentially linked with cerebellar degeneration, or at least cerebellar dysfunction, together with disturbance of motor timing. We explain the context of our current understanding on this topic, highlighting possible clinical consequences for patients suffering from ET and future research directions.

Keywords: Cerebellum, essential tremor, motor timing, prediction, neurodegeneration

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Introduction

Essential tremor (ET) is the most common movement disorder in humans.[1–3] Although its prevalence is greater than that of epilepsy, stroke, and multiple sclerosis,[4] knowledge of this condition among the general population remains poor. ET is characterized by a postural and kinetic tremor most commonly affecting the forearms and hands. Isolated head tremor has been found in 1–10% of patients, suggesting that ET may be a composite of several phenotypes.[5] Tremor may also affect other regions of the body (such as the head, face, tongue, and legs), and it may occur in both the head and the arms in 34–53% of the patients. The exact pathophysiology of ET is still unknown.[6,7] ET has been repeatedly shown to be a disorder of mild cerebellar degeneration, particularly in postmortem studies. However, in recent years, an ardent and crucial debate has been taking place in the field regarding whether ET is a neurodegenerative disease.

The cerebellum contributes to the performance of a wide range of skilled behaviors, and it appears to be especially important for the neural representation of time.[8–11] The evidence for the role of the cerebellum in timing behavior comes from four main experimental paradigms in subjects with natural or experimentally induced lesions: 1) impaired time perception,[12,13] 2) time-dependent abnormalities in the acquisition of eye-blink conditioning,[14,15] 3) increased variability in performance during non-paced finger tapping tasks[10–12] and throwing tasks,[16] and 4) the prediction of sensory events.[17,18] Recently published data indicate that subjects with damage to the cerebellum have a fundamental problem with predictive motor timing and support the idea that the cerebellum plays an essential role in integrating incoming visual information with motor output when making predictions about upcoming actions.[19,20] These findings demonstrate that the cerebellum may have properties that would facilitate the processing or storage of internal models of motor behavior related to timing.[21]

In this review article, we address the issue of three previously inconsistently linked entities: ET, the cerebellum, and motor timing. Based on the current knowledge and observations we argue that ET is essentially linked with cerebellar degeneration, or at least cerebellar dysfunction together with disturbance of motor timing. We explain the context of our current understanding on this topic, highlighting possible clinical consequences for patients suffering from ET and future research directions.

Essential tremor: overview

ET is one of the most common disorders in the world. It often is called "benign". However, it frequently causes difficulties with everyday tasks such as writing, eating, and drinking, as well as tooth brushing and other hygiene-related tasks. ET is considered to be a heterogeneous condition with variable clinical expression. In addition to the above-mentioned postural and/or kinetic tremor in the frequency range of 4–12 Hz, tremor frequency generally decreases over time, while amplitude slowly increases. Alcohol transiently diminishes tremor amplitude. The location and amplitude of tremor varies among ET patients. Approximately 90% of patients have tremor in their upper extremities, 30% have a head tremor, 20% have a voice tremor, 10% have a face or jaw tremor, and 10% of ET patients may have a lower limb tremor.[22]

ET is commonly inherited by autosomal dominant transmission with incomplete penetration. Approximately 50% of ET patients have an affected first-degree relative,[22] and first-degree relatives of ET patients appear to be five times more likely to develop ET than control subjects.[23] A family history of ET appears to correlate with a younger reported age at tremor onset. Not all cases of ET have a genetic etiology, however, and the disease may occur sporadically.[24]

ET is more prevalent than Parkinson's disease or Alzheimer's disease.[3,24] The prevalence is estimated to be three to four per 1,000, and the incidence of ET increases with age.[24] Approximately 4% of adults over 40 years of age are affected by ET. ET has limited treatment options (propranolol is the only US Food and Drug Administration-approved drug), and the pathophysiology is still unknown, although there are discussions in the literature about a central oscillator originating in the myoclonic triangle located in the brainstem. Other areas of the brain that have been implicated in the pathogenesis of ET are the inferior olivary nucleus and the cerebellum.[25] The lack of ET research is even more striking if we consider that 30–50% of the patients with ET do not respond to medical therapy, and medication improves tremor magnitude by about 50%. In other words, even with the most effective treatment options available, the condition still interferes with the activities of daily living and causes social problems for the affected patients.

Over the last 12 years, there has been growing evidence to suggest that patients with ET may have significant non-motor features in addition to the known motor features. These non-motor features include mood and cognitive dysfunction, which appear to be more common in ET patients than in normal controls.[26,27] In addition to tremor, patients with ET have been reported to have 1) cognitive abnormalities characterized by mild frontal dysfunction that may have a functional impact, 2) an association with dementia (both prevalent and incident) among those with late-onset tremor (>65 years), 3) a higher prevalence of anxiety and an anxious and worrisome personality type, 4) depressive symptoms and even depression as a premotor symptom, 5) poor sleep quality, and 6) subjective hearing impairment.[28]

The cerebellum: some anatomical and physiological insights

The cerebellum was traditionally considered to be responsible primarily for the coordination of movement, balance, and motor speech.[29] However, the cerebellum is also activated by a large number of cognitive tasks that do not involve movement. More recent anatomical and functional studies showed that the cerebellum plays a wider role in many cognitive functions, such as language, executive functions, and spatial cognition.[30] Through indirect pathways, the cerebellum receives information from all sensory modalities (auditory, visual, somatosensory, and proprioceptive systems) as well as from the neocortex. In turn, the cerebellum sends the information indirectly throughout the brain.[30–32] Neuroanatomical studies convincingly showed cerebellar connectivity with associative areas of the cerebral cortex involved in higher cognitive functioning including limbic associative/neocortical systems and communicates with the basal ganglia and thalamus.[29–31] Deep cerebellar nuclei send information to prefrontal areas through dentatothalamic pathways, while the prefrontal cortex sends information back to the cerebellum via pontine nuclei.[31] More systematic neuropsychological research performed in patients with cerebellar lesions and the development of more sensitive neuropsychological tests allowed clinicians to identify significant cognitive and affective disturbances following cerebellar lesions.[29] We need to consider all cerebellar inputs/outputs and connections when studying its functions and links to previously overlooked cognitive and non-motor features. A connection was discovered between cerebellar dysfunction and a high number of neurologic and psychiatric conditions, including dystonia, multiple sclerosis, Parkinson's disease, ET, schizophrenia, autism, mood disorders, and depression.[32] Cerebellar cognitive affective syndrome (CCAS) has been described, extending the knowledge and current understanding of the cerebellar role in the nervous system beyond motor control.[33] In this concept, there maybe deficits in planning, set-shifting, verbal fluency, language abilities including grammatism and prosody, abstract reasoning and working memory, visuo-spatial organization and memory, personality structure with blunting of affect of disinhibited and inappropriate behavior, and an overall lowering of intelligence (for details on CCAS, see Schmahmann and Sherman[33]). It is becoming clear, based on observations which are revealing new insights into cerebellar function, that the cerebellum plays a more complex role in the brain than previously thought.[30]

Essential tremor and the cerebellum

Clinical observations,[34,35] electrophysiological,[36,37] and functional imaging studies including diffusion tension imaging, and voxel-based morphometry,[38–41] suggest that the cerebellum is involved in the generation of ET. Studies have demonstrated some similar abnormalities in patients with ET and cerebellar disease, such as intention tremor, slowness of goal-directed movements, overshoot of hand movements when reaching a target,[42] disturbed tandem gait,[43] eye movement abnormalities,[44,45] and balance and motor speech impairment, both clinical and subclinical.[46] Recent findings show high width variability during spiral drawing[47] and display new insights into the pathophysiological mechanisms of cognition in ET, suggesting a primary role of the cerebellum in mediating abnormal interactions between the executive control circuit and the default mode network.[48] The results of a deep brain stimulation (DBS) study in ET patients assessing gait ataxia showed the cerebellar movement disorder of ET is due to a typical cerebellar deficit. The authors hypothesize that DBS affects two major regulating circuits: the cortico-thalamo-cortical loop for tremor reduction and the cerebello-thalamo-cortical pathway for ataxia reduction and ataxia induction.[49]

Positron emission tomography and magnetic resonance imaging have documented the overactivity of deep cerebellar nuclei and the cerebellar cortex and their connections in patients with ET.[42,50–53] Evaluation of ET with multi-voxel magnetic resonance spectroscopy brought decreased N-acetylaspartate to creatine ratio (NAA/tCr) and N-acetylaspartate/Choline (NAA/Cho) ratios within the cerebellum which may represent an abnormality in neuronal function.[54] Another hypothesis is that ET may result from abnormal intrinsic oscillations originating in the inferior olive and spreading throughout the olivocerebellar network.[6,42] Consistent with this idea are results suggesting that CaV3.1 channels (low-threshold voltage-dependent Ca^{2+} channels) play a critical role in the onset of tremor-related rhythms and can be directly linked with ET. The potentiation of CaV3.1 T-type Ca^{2+} channels in the inferior olive contributes to the onset of tremor in a pharmacological model of ET in wild-type mice.[55] Further studies should be done to describe the specific role of the inferior olive rhythmicity modulated by CaV3.1 channels in higher motor functions.

Is essential tremor a neurodegenerative disorder?

Crucial debate exists as to whether ET is a neurodegenerative disease. ET has been repeatedly shown as a disorder of mild cerebellar degeneration. Recent neuropathological studies have shown that the majority of patients with ET presented discrete cerebellar degenerative changes.[56] Data suggesting that ET is neurodegenerative include postmortem findings of pathological abnormalities in the brainstem and cerebellum,[57] including Lewy bodies in the locus ceruleus, loss of Purkinje cells, and abnormalities of the dentate nucleus,[58,59] reduction in cerebellar cortical NAA/tCR,[60] white matter changes on diffusion tensor imaging,[61] and clinical studies demonstrating an association with cognitive[26,62,63] and gait changes. Recently, an increase in torpedo formation and a reduced number of Purkinje cells in ET subjects relative to control brains has been described.[60,64–67]

New observations have indicated memantine (N-Methyl-D-aspartate (NMDA) receptor antagonist) as a potential treatment for ET.[68] The association of ET with other neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease also supports the link between ET and neurodegeneration.[69]

Conflicting data argue against ET as a neurodegenerative disease. These data include improvement of gait abnormalities with ethanol administration,[70] lack of gray matter volume loss on voxel-based morphometry,[71] failure to confirm prominent presence of Lewy bodies in the locus ceruleus,[57] and other pathological findings.[72] Nevertheless, further research is needed to describe the mechanism of cellular changes in the ET brain, and also to understand the order in which these changes occur. More extensive discussion on this topic exceeds the subject of this paper; we recommend other relevant literature[73–75] (and other groups).

The cerebellum and motor timing

There is evidence that the cerebellum is involved in a wide variety of cognitive and perceptual activities, including temporal processing.[76–80]

Timing is a fundamental feature of human movement, perception, and cognition.[81] Time, as the fourth dimension, is central to both perception and action. Sensory events may have temporal lengths or they may define boundaries of "empty" temporal intervals. Likewise, moving targets possess temporal properties that need to be identified in order to assess their future trajectories.[82,83] In action, timing is essential when producing sequences (i.e., language) and when coordinating our movements with those of various moving objects in the external environment.[84,85] Given this multifaceted manifestation of time, uncovering the neural substrate of timing prediction is not a trivial task. Over the years, the cerebellum, the basal ganglia, and other cortical areas (i.e., the prefrontal and parietal regions) have emerged as important structures dealing with various aspects of timing.[86–91] However, there are still debates in the literature about the primacy of each of these structures, as well as about their specific roles in timing and prediction.[92–95] Holmes[96] suggested that the disturbance of voluntary movement in patients with lesions of the cerebellum was due to a "delay in cortico-spinal innervation"; in other words, the cerebellum might regulate motor timing. The cerebellum does not act alone but rather "primes" other brain areas in regulating the appropriate timing of muscular contraction.[96] This concept is theoretically supported by the idea that parallel fibers of the cerebellum provide delay lines for converting spatial patterns into temporal signals.[8,97] This framework has been developed and modified by many groups, but the exact role of the cerebellum in the timing process is still elusive.[98–101]

The cerebellum has been shown to be involved in the timing of movement and sensation,[102] acting as an internal timing system that provides the temporal representation of salient events spanning hundreds of milliseconds.[9–86] Cerebellar damage impairs event-based timing tasks,[103] especially when movements are not continuous.[11,104]

The coordination between cortico-striatal and cortico-cerebellar circuits is important for predicting the course of sensory perceptions (trajectory, speed, and duration of stimulus) and the timing of motor response, as required in the interception test.[20,92,93,105–107] The cerebellum is thought to be the brain area suitable for constructing sensory predictions and predictive control commands, which can be further processed by the cerebral cortex.[108,109] The ability to estimate, predict, and correctly time responses is essential for everyday life. Many everyday skills, such as playing sports and video games or operating motor vehicles or machinery, require precise timing.[110,111] Neurological disorders that disrupt motor timing lead to dysmetric or inaccurate movements.[96] Several time processing mechanisms, functioning on different levels of time scale, have evolved. The seconds or minutes level, which is essential for conscious, cognitively controlled time estimation and other conscious activities, is probably processed by cortico-striatal circuits. Intervals on the subsecond level, essential for motor and cognitive functions, are processed in the cerebellum.[112–115]

Recently published experimental data (*in vivo* recording) show that Purkinje cells do not only develop a change in responsiveness to conditioned stimulus. They also learn a particular temporal response profile where the timing is determined by the temporal interval between the conditioned and unconditioned stimuli.[116] The cerebellum and timing are essentially linked, and disorders of the cerebellum have a significant impact on timing: the resulting limitations need to be recognized by medical professionals.

Essential tremor, the cerebellum, and motor timing

There are a limited number of studies in the literature related to motor timing in ET. One of the studied areas is movement in ET patients; movements involve changes in muscle length over time, thus motor control and timing are inextricably related.[117] Britton et al.[118] studied ballistic wrist flexion movements towards 15-, 30-, and 60-degree visual targets in a group of 17 patients with ET. Compared with 16 age-matched normal subjects, the authors found three main kinematic differences: ET subjects overshot the target a little more; the kinematic profile of their movements was more "asymmetric" due to higher peak decelerations; and their movements initiated tremor. The onset latency of the antagonist electromyography (EMG) burst was also normal, but the onset of the second agonist EMG burst was delayed. The delay in the onset of the second agonist EMG activity resulted in unopposed action of the antagonist muscle in the second half of each movement. As a result, deceleration occurred too rapidly as the hand returned past the target leading to a series of damped oscillations around the point of aim. The onset latency of the second agonist EMG burst correlated significantly with the tremor period: the longer the period the later the burst. The authors concluded that the delay in the second agonist burst reflects an abnormality in the timing of anticipatory muscle activity in ET and that this may involve cerebellar mechanisms.[118] Another group found abnormal ballistic movements in ET subjects, too.[119] They studied kinematic parameters and the triphasic EMG components of ballistic flexion elbow movements in 17 ET subjects with postural tremor (ETPT), 15 ET subjects with an additional intention tremor (ETIT) component , and 14 healthy controls. The main findings were a delayed second agonist burst and a relatively shortened deceleration phase compared with acceleration in both the ET groups. These abnormalities were more pronounced in the ETIT group than in the ETPT group. ETIT and ETPT may represent two expressions within a continuous spectrum of cerebellar dysfunction in relation to the timing of muscle activation during voluntary movements.[119]

It has been reported that the cerebellar timing function is altered in patients with ET showing an increased variability of rhythmic hand movements.[120,121] Avanzino et al.[120] studied 15 patients with ET and 11 healthy controls using a sensor-engineered glove, and evaluated motor behavior during repetitive finger-tapping movements. The results showed longer touch duration (TD), a lower inter-tapping interval (ITI), and increased temporal variability of movement (coefficient of variation of ITI) in the performance of repetitive finger-tapping movements in patients with ET than in normal subjects. The longer TD could represent the result of an abnormal cerebellum feed-forward control; in turn, selection of an abnormal motor strategy (with a longer TD) induces a reduction of ITI and an increase in temporal variability of the movement. These results are consistent with previous results showing that the variability of rhythmic and alternating hand movements was significantly higher in patients with ET than in healthy controls.[121] These authors measured the variability and the maximum frequency of alternating hand and finger movements triggered by auditory stimulus in 34 patients with ET and demonstrated that ET patients are not able to synchronize repetitive movements to extrinsic timing. This deficit was present at both slow and fast movement rates, with disturbed regularity of repetitive movements on both sides. This suggests that cerebellar dysfunction in ET is bilaterally represented, and impairs event-based timekeeping and the transition between the slow and the fast working modes of rhythm production, causing a deterioration in the accuracy of more rapid repetitive movements.[121]

The results of an repetitive transcranial magnetic (rTMS) study which followed the behavioral study presented above[120] revealed that longer touch duration in patients with ET could be restored at normal values following 1 Hz rTMS applied over the lateral cerebellum. The authors concluded that the results of the behavioral and the rTMS studies support the idea that the cerebellum plays a central role in selecting motor strategy for rhythmic finger movements, particularly in terms of temporal organization of movement.[120] Another rTMS study[122] performed in 10 patients with ET induced a transient but notable reduction of tremor with 1 Hz rTMS over the lateral cerebellum; the authors concluded that the documented hyperactivity of cerebellar structures in patients with ET can be modified through the interference of rTMS with the synchronicity level of oscillatory cerebellar neurons.

In a recent study, Bares et al.[123] investigated predictive motor timing during a dynamic precise timing task that required mediated interception of a moving target in ET patients (with mild cerebellar damage). The task demanded that subjects integrate visual (sensory domain) prediction with a motor response (motor domain). The motor response was a simple finger press, thus avoiding the interpretative difficulties associated with whole limb movements. The authors investigated 16 patients with ET; given the heterogeneity of the familial ET clinical picture, the authors classified these subjects into two subgroups, based on the presence/absence of head tremor (eight ET patients presented with head tremor). The authors then analyzed and compared the results of these subgroups in terms of hit ratio, type of error, and trial-by-trial adjustment (the distribution of hits and early and late errors in the current trial as a function of the type of previous trial in each group (for details, see Bares et al.[123]). The authors excluded the effect of oculomotor difficulties on final results. The chi-square test showed that the arm ET and head and arm ET groups had a significantly different distribution of hits and early and late errors. In all cases, the head and arm ET group had significantly more late errors and fewer hits than the arm ET group. Taken together, these results suggested that the head and arm ET group has a significantly higher deficit, whereas the arm ET group had performances closer to healthy and Parkinson's disease subjects (which were studied as well). These results showed that the head and arm ET group had a significantly higher deficit at interception whereas the arm ET group was not affected in a predictive motor timing task and the head ET subgroup was significantly affected.[123] The authors concluded, in addition to their main result on motor timing, that the data strongly supported that ET is a heterogeneous entity that deserves increased attention from clinicians in terms of both pathophysiology and function.[5,59,64,65,67,124] A possible explanation for the results related to motor timing is provided by the results of a study using magnetic resonance volumetric and voxel-based morphometry, which revealed that head ET is associated with cerebellar vermis atrophy, whereas patients with arm ET did significantly differ from healthy controls. Arm ET and head ET might represent distinct subtypes of the same disease.[125]

Imaging and electrophysiological studies have shown inhibition of cerebellar activity and activation of primary and supplemental motor areas by DBS.[126–128] Research focused on comparing the effects of DBS and ablation (thalamotomy, TH) of the motor thalamus on the timing of simple, self-paced finger movements in patients with ET showed interesting results.[129] They found that the internal timing of movements in the hundreds of millisecond range was improved (reduced tremor, improved tapping regularity) on the contralateral hand after both TH and DBS with significantly more improvement among TH subjects. On the ipsilateral (non-targeted) hand, the timing of index finger taps was improved by stimulation. These results suggest that temporal processing is differentially affected by stimulating and lesioning thalamocortical fibers. The ventral intermediate nucleus thalamus is part of the cerebello-thalamo-cortical tract, a pathway important in the pathophysiology of ET and the timing of finger movement.[34,130,131] Study results have provided evidence that DBS affects a spatially distributed neural network involved in the timing of simple repetitive movements.[129]

Conclusions

The present findings agree with the hypothesis that cerebellar functions are affected in ET. The effect might be due to the generation of abnormal tremor rhythms in those parts of the cerebellum which are normally necessary to perform the functions that are defective in ET. It has been shown that patients with cerebellar lesion have disturbed rhythm formation, especially for event-based timing processes.[132] ET can no longer be considered as a pure motor disorder, and further studies of these non-motor aspects will be very helpful in understanding and comprehensively treating ET.[28] As the anatomical substrate in the generation of ET, the cerebellum causes problems with motor timing (as well as other cerebellar symptoms). Studies reporting that the cerebellar timing function is altered in patients with ET, such as an increased variability of rhythmic hand movements, impaired predictive motor timing, or rTMS studies documenting modification of hyperactivity of cerebellar structures in patients with ET, are emerging. Based on the current knowledge and observations, we argue that ET is essentially linked with cerebellar degeneration, or at least cerebellar dysfunction together with disturbance of motor timing. Further investigation is necessary to spread current knowledge and thus improve ET therapy, which is currently unsatisfactory.[133,134]

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