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Tremor and Other Hyperkinetic Movements

Review

Neuroimaging of Essential Tremor: What is the Evidence for Cerebellar Involvement?

Luca Passamonti[1*], Antonio Cerasa[1] & Aldo Quattrone[1,2*]

[1] Unità di Ricerca Neuroimmagini, Istituto di Scienze Neurologiche, Consiglio Nazionale delle Ricerche, Catanzaro, Italy, [2] Dipartimento di Scienze Mediche, Unità Operativa di Neurologia, Università "Magna Graecia", Catanzaro, Italy

Abstract

Background: Clinical observations and electrophysiological studies have provided initial evidence for the involvement of the cerebellum in essential tremor (ET), the most frequent hyperkinetic disorder. Recently, this hypothesis has been reinvigorated by post-mortem studies that demonstrated a number of pathological changes in the cerebellum of ET patients compared with age-matched healthy controls. Advanced neuroimaging techniques have also made it possible to detect *in vivo* which cerebellar abnormalities are present in ET patients and to reveal the core mechanisms implicated in the development of motor and cognitive symptoms in ET.

Objective: We discuss the neuroimaging research investigating the brain structure and function of ET patients relative to healthy controls. In particular, we review 1) structural neuroimaging experiments assessing the density/volume of cortical/subcortical regions and the integrity of the white-matter fibers connecting them; 2) functional studies exploring brain responses during motor/cognitive tasks and the function of specific neurotransmitters/metabolites within cortical–cerebellar circuits.

Methods: A search in PubMed was conducted to identify the relevant literature.

Discussion: Current neuroimaging research provides converging evidence for the role of the cerebellum in the pathophysiology of ET, although some inconsistencies exist, particularly in structural studies. These discrepancies may depend on the high clinical heterogeneity of ET and on differences among the experimental methods used across studies. Further investigations are needed to disentangle the relationships between specific ET phenotypes and the underlying patterns of neural abnormalities.

Keywords: Essential tremor, voxel-based-morphometry, diffusion tensor imaging, fractional anisotropy, mean diffusivity, magnetic resonance imaging spectroscopy, positron emission tomography, radioligand, functional magnetic resonance imaging

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*To whom correspondence should be addressed. E-mail: l.passamonti@isn.cnr.it; a.quattrone@isn.cnr.it

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Introduction

The hypothesis that essential tremor (ET), the most frequent hyperkinetic movement disorder,[1,2] was caused by cerebellar dysfunctions was originally introduced after a series of clinical observations[3] and electrophysiological studies.[4] In particular, the action tremor, one of the main clinical features of ET, is generally considered to be indistinguishable from the intention tremor that occurs in cerebellar diseases.[3,5] In addition, electrophysiological results have shown that ET patients display an absent or delayed acquisition of the conditioned eye-blink,[4] an index of motor learning that depends on intact cerebellum.[6]

Recently, post-mortem studies have clearly revealed a broad spectrum of neuropathological changes (e.g., Purkinje cell loss, axonal torpedoes) within the cerebellum of ET patients.[7–11] Over the last years, these findings have been paralleled by a series of structural[12–21] and functional neuroimaging studies[22–30] that have confirmed, *in vivo*, the fundamental role of the cerebellum in the pathophysiology of ET. The aim of this review is to discuss the present neuroimaging literature

in ET. Hence, this work can be also considered an extension or update of a previous review on functional imaging in ET.[31]

In general, both structural and functional studies have reported alterations in the cerebellum of ET patients relative to controls, although some studies have obtained negative results (i.e., no cerebellar abnormalities in ET).[12,13] In addition, there is still a debate whether the cerebellar abnormalities described in ET would simply reflect electrophysiological disturbances within cortical–cerebellar networks (due, for example, to an ion channel disease and/or to the presence of false neurotransmitters) or whether, in contrast, the cerebellar disturbances would be driven by a neurodegenerative process.[5] Although we believe that these views are not mutually exclusive, a detailed discussion of the evidence in favor or against each theory is beyond the scope of the current article given that this issue has already been treated in other excellent papers.[5,7]

The present review is structured in three sections.

First, we will assess the contribution of structural neuroimaging studies in exploring brain anatomical abnormalities in ET, particularly within the cerebellum. In general, the most commonly employed structural neuroimaging techniques measure the volume and density of cortical and subcortical regions and the diffusivity of the water molecules within the neural tissues with strong anatomical orientation (i.e., axonal fibers). Voxel-based morphometry (VBM) is an example of a statistical analysis that assesses the morphology and/or density of the gray matter (GM) and white matter (WM) in cortical and subcortical regions in the whole brain.[32] Alternatively, manual and/or automatic volumetry can be used to quantify the volume/density of distinct *a priori* regions of interest (ROI).[16] Finally, diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) are techniques that provide a series of quantitative parameters reflecting microscopic aspects of the WM, including, for example, neuronal damage from demyelization, microtubule breakdown, and/or axonal loss.[33]

Second, functional neuroimaging studies in ET will be considered and discussed. Functional neuroimaging is a broad group of methods that typically measure 1) the change in brain oxygen consumption and the variation in the cerebral blood flow during the execution of specific motor and cognitive paradigms (e.g., positron emission tomography [PET]; functional magnetic resonance imaging [fMRI]); 2) the ratio between specific cellular metabolites (e.g., proton magnetic resonance spectroscopic imaging [^{1}H MRSI]); 3) the function of distinct neurotransmitters (e.g., gamma-aminobutyric-acid [GABA], dopamine [DOPA], 5-hydroxytryptamine [5-HT]), via the use of specific radioligands. The radioligand is a substance that is infused in the bloodstream and reaches its corresponding receptor localized in a number of brain regions. There, the radioactive decay associated with the quantity of the linked ligand can be detected via a PET scan. This method therefore relies on a series of sensitive markers (radioligands) that can be used to assess specific biological changes associated with different neurological disorders such as ET. On the other hand, fMRI experiments are commonly designed to localize the activations of specific brain regions engaged when patients and control subjects execute a particular motor (e.g., finger tapping) or cognitive task (e.g., working memory). These activations are thought to reflect the neural computations tightly associated with a particular motor or neuropsychological process. Alternatively, ^{1}H MRSI represents a different functional technique used to calculate the ratio between specific cellular metabolites such as the *N*-acetylaspartate and total creatine (NAA/tCr), a sensitive index of neuronal dysfunction and/or degeneration.

The third section of this review will represent a conclusive summary of the critical factors that may be responsible for the conflicting findings reported in the literature and will provide some suggestions to overcome the identified limitations.

Structural neuroimaging

In total, 10 structural neuroimaging studies have been considered (see Figure 1 for a brief overview of the studies included and Table 1 for details on the methods used and results obtained). Overall, GM and WM abnormalities of the cerebellum in ET represent the most prevalent result among structural studies,[14–18,20,21] although negative findings (i.e., no cerebellar abnormalities) and/or alterations in other brain areas (e.g., frontal and temporal cortices) have also been reported.[14,17,19–21]

The first VBM investigation in ET did not find anatomical alterations in the whole brain (including the cerebellum) of ET patients compared with age- and gender-matched healthy controls.[12] In addition, the lack of any significant effect was evident even at a liberal (uncorrected) statistical threshold. At first glance, this result would suggest that electrophysiological abnormalities are at the origin of ET rather than brain anatomical damage, as suggested by some authors.[5,7] However, when ET patients were divided on the basis of the type of tremor (ET patients with both intentional and postural tremor [ET-ip] versus ET patients with postural tremor alone [ET-p]), an unexpected increase in the GM volume in the bilateral temporal–parietal junction was found in ET-ip patients relative to healthy controls *but not* versus ET-p patients.[12]

In contrast to these initial findings, our group was the first in identifying the presence of cerebellar abnormalities in a sample of 50 patients with ET, via two approaches (VBM and automated/manual volumetry).[15,16] The abnormality of the cerebellum was particularly evident in those ET patients displaying hand and head tremor and not in patients with hand tremor alone. More specifically, we found volumetric abnormalities in the vermis and lobule IV of ET patients with hand and head tremor and a trend effect for global cerebellar volume loss (including cerebellar hemispheres) in ET patients with isolated hand tremor.[15,16] These findings may reflect the somatotopic organization of the cerebellum in which the head and neck are represented in the midline portion of the anterior lobe (mainly the vermis and lobule IV–V), while the hand and leg are located in the vermis/para-vermis and cerebellar hemispheres.[34] This hypothesis has been recently supported by Louis and collaborators[35] who described, *in vitro*, the presence of axonal torpedoes and other neuropathological changes in the cerebellar vermis of ET patients with prevalent head tremor.

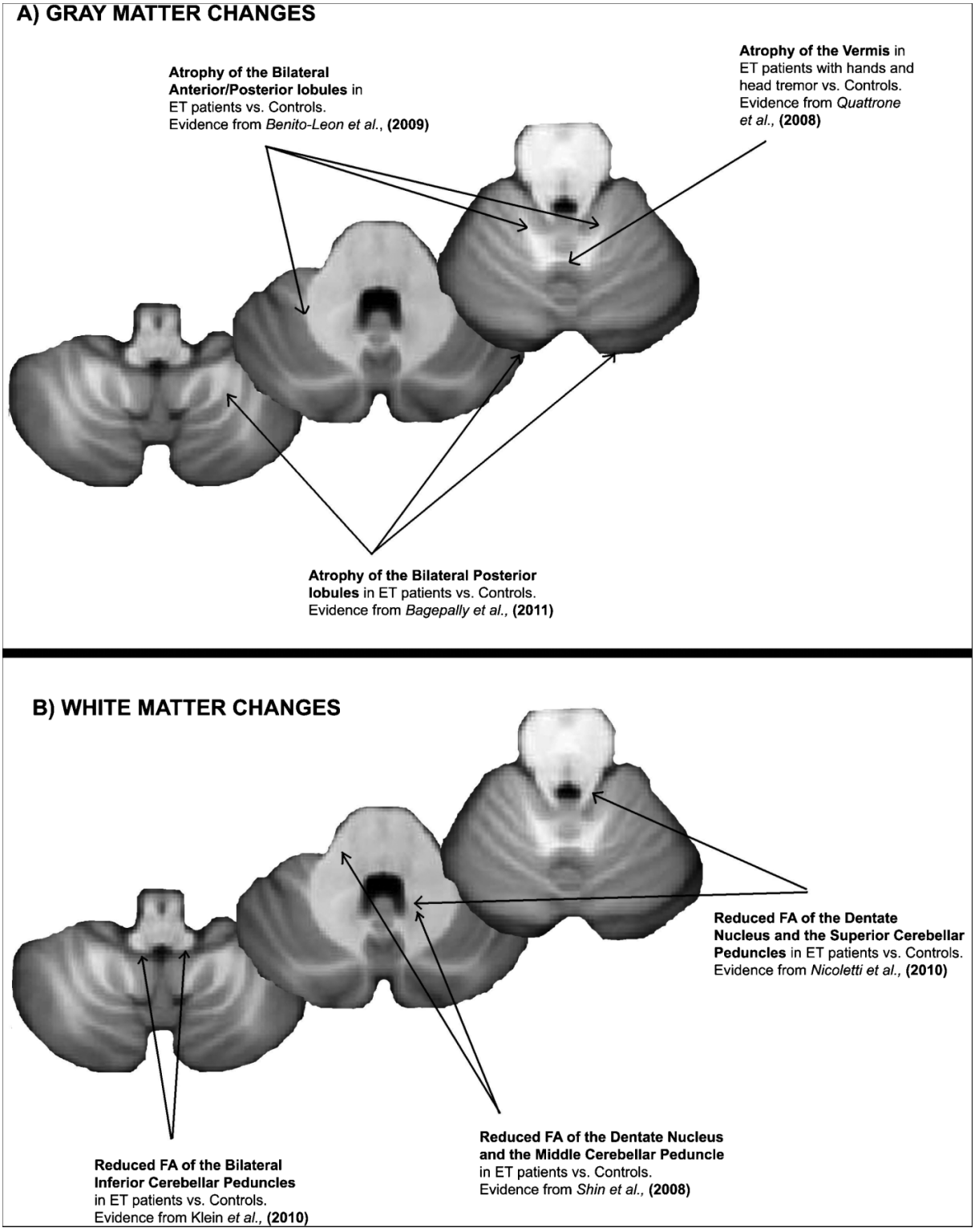

Figure 1. Spatial Location of the Structural Cerebellar Abnormalities in Essential Tremor (ET) Patients Relative to Healthy Controls.
(A) Evidence for gray matter abnormalities in ET patients relative to controls as detected by voxel-based morphometry (VBM) studies. (B) Evidence for white matter changes as obtained with diffusion imaging techniques. Abbreviations: FA, fractional anisotropy.

Table 1. Structural Neuroimaging Studies Reporting Anatomical Neurodegenerative Processes in ET

Reference	Sample	Neuroimaging Method	Main Finding
Daniels et al.[12]	27 patients (14 with ET-PT; 13 with ET-IT) 27 HC	VBM	ET<HC: No significant GM loss ET-IT > HC: GM increase in the temporal and occipital cortex
Martinelli et al.[13]	10 ET 10 HC	DWI (ADC)	ET<HC: No significant differences in ADC values
Shin et al.[14]	10 ET 8 HC	DTI (FA)	ET<HC: Reduced FA in pons, cerebellum, midbrain, orbitofrontal cortex, lateral frontal cortex, parietal cortex and temporal cortex
Quattrone et al.[15]	50 patients (30 ET arm; 20 ET head) 32 HC	VBM Manual volumetry	ET<HC: No significant GM loss ET head<HC: GM loss in the cerebellar vermis
Cerasa et al.[16]	46 ET (27 ET arm; 19 ET head) 28 HC	Automated subcortical Segmentation	ET<HC: No significant GM loss ET head<HC: GM volumetric atrophy of the entire cerebellum
Benito-Léon et al.[17]	19 ET 20 HC	VBM	ET<HC: GM/WM losses in the bilateral cerebellum, right frontal lobe, left medulla, parietal lobes, right insula and right limbic lobe
Nicoletti et al.[18]	25 FET 15 PD 15 HC	DTI (FA/MD)	FET<PD<HC: Reduced FA of dentate nucleus and superior cerebellar peduncle FET<PD<HC: Increased MD of superior cerebellar peduncle.
Jia et al.[19]	15 ET 15 HC	DTI (FA/ADC)	ET<HC: Increased ADC of red nucleus
Bagepally et al.[20]	20 ET 17 HC	VBM	ET<HC: GM loss in bilateral cerebellum, vermis, bilateral frontal and occipital lobes
Klein et al.[21]	14 ET 20 HC	DTI (FA/ADC) - TBSS VBM	DTI-TBSS: ET<HC: Increased MD of inferior cerebellar peduncle bilaterally, left parietal WM; reduced FA in the right inferior cerebellar peduncle. VBM: ET<HC: No significant GM or WM losses

Abbreviations: VBM, voxel based morphometry; GM, gray matter; WM, white matter; DTI, diffusion tensor imaging; MD, mean diffusivity; FA, fractional anisotropy; TBSS, tract-based spatial statistics; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; ET, essential tremor; ET-IT, essential tremor patients with intentional tremor; ET-PT, essential tremor patients with postural tremor; ET arm, essential tremor with arm tremor; ET head: essential tremor with head tremor; FET, familial essential tremor; PD, Parkinson's disease; HC, healthy controls.
DTI provides estimation of GM/WM tissue composition by using two distinct MRI measures (MD, FA). VBM provides a probabilistic intensity value of GM/WM volume/density voxel by voxel in the entire brain. Increased water in brain areas (where neuronal/axonal loss occurs) corresponds to increased ADC values. TBSS is a technique for analyzing group effects in diffusion-based imaging voxel by voxel in the entire brain.

Two later VBM studies have found that ET may be characterized not only by cerebellar damage, but also by neurodegenerative processes that extend to other cortical and subcortical regions.[17,20] Specifically, WM and GM losses have been observed within the midbrain and in the occipital, temporal and frontal lobes of ET patients relative to healthy controls.[17,20]

Partially conflicting results have also been obtained in structural studies examining the fractional anisotropy (FA), a sensitive index of the WM integrity. In particular, the first DTI study in ET[13] did not report WM abnormalities in *a priori* ROI (e.g., cerebellar regions) in patients relative to healthy controls while Shin et al.[14] have recently found a FA reduction in the cerebellum, brainstem, and cerebral

hemispheres in 10 ET patients relative to eight healthy individuals. Two further studies using similar methods (i.e., DTI, DWI) have been conducted in samples of ET patients with sporadic[21] or familial[18] forms of the disease and have reported the presence of WM abnormalities in the cerebellar peduncles (i.e., superior, middle, and inferior cerebellar peduncle) as well as in the dentate nucleus, the main output cerebellar nucleus. Finally, a recent DTI study[19] has demonstrated GM deficits within the red nucleus of ET patients relative to healthy controls.

Taken together, these structural neuroimaging studies provide support for the key role of the cerebellum in the pathophysiology of ET, although some inconsistencies between the results deserve further discussion. In particular, part of the conflicting findings might have arisen from differences in demographic and clinical characteristics across samples (e.g., age, gender, disease duration) and/or in the methodological approaches employed. For example, the mean age of ET patients reported in structural studies is extremely variable, ranging from 38[20] to 70 years.[17] Furthermore, not all studies enrolled samples of ET patients balanced for sex;[13] hence, future studies will need to take into account this demographic variable. A wide variability in disease duration may also represent another important factor for explaining variability in results. Some studies included ET patients with an average clinical history of 9 years[14,19] while others investigated samples with a significantly higher disease duration (i.e., up to 20 years of clinical history).[16,18]

It is also necessary to note that some of the discrepancies in the data and some of the negative findings could be ascribed to significant methodological differences among studies. For instance, some works used whole-brain methods such as VBM[12,14–15,17,20,21] while others were focused on ROI analyses.[13,18,19] In addition, VBM can produce different results on the basis of the techniques employed to pre-process the raw data (e.g., degree of smoothing and/or choice of template to normalize the anatomical scans).[32,36]

Last but not least, none of the structural studies took into consideration how non-motor symptoms (e.g., mild cognitive impairments or even dementia) may have influenced the neuroimaging results, although an increasing number of neuropsychological, epidemiological, and fMRI studies have highlighted the importance of evaluating the cognitive deficits in ET.[29,30,37–40] In theory, part of the variability in the anatomical results could be explained by the presence of complicating non-motor clinical features (i.e., cognitive impairments). In particular, the atrophy within the frontal and temporal cortices that has been described in some works[14,17,20,21] may depend on the presence of underestimated neuropsychological deficits.

In conclusion, some inconsistencies have been reported in the structural neuroimaging literature in ET, although the anatomical alteration of the cerebellum represents a consistent finding and an important pathophysiological mechanism of the disease. Nonetheless, current data do not allow one to conclude whether ET is characterized by abnormalities in specific regions of the cerebellum or whether, alternatively, the anatomical damage is widespread throughout the whole cerebellum. Pathological changes have been described in different parts of the cerebellum, including motor (from lobule I to V) and cognitive lobules (from lobule VI to IX, including crus I–II), although there have been no studies addressing the precise relationship between distinct clinical phenotypes and specific cerebellar areas. For instance, it remains to be determined whether the degree of abnormalities within the motor (i.e., anterior) lobules of the cerebellum is associated with tremor severity and whether the cognitive deficits in ET may eventually depend on structural damage of specific cerebellar areas (i.e., posterior "cognitive" lobules).

Functional imaging in ET (PET and fMRI studies)

Figure 2 and Table 2 provide a summary of the functional neuroimaging experiments discussed in this section and a brief overview on their results and methods.

In 1990, the cerebral blood flow of a small sample of ET patients and controls (n=4) was recorded for the first time using PET.[22] This pioneering study measured brain activations while participants held a specific pose (arms outstretched) that is known to trigger the typical postural tremor of ET patients. Comparing the brain activity associated with this position to that during a non-postural "resting" condition, Colebatch and collaborators[22] found that ET patients presented, relative to controls, enhanced blood flow in sensory motor and premotor cortices contralateral to the side of tremor, and in the cerebellar hemispheres bilaterally. Hence, the authors concluded that the cerebellar overactivity in ET was directly associated with the generation of tremor and that this would have depended on electrophysiological abnormalities within cerebellar pathways.[22] Of note, this experiment represented the first *in vivo* demonstration of the functional involvement of the cerebellum and other sensory motor regions in the pathophysiology of ET.

Next, Jenkins et al.[23] and Wills et al.[24] confirmed the increased activation of the bilateral cerebellum in a new sample of ET patients and healthy controls under the same experimental conditions (i.e., holding a posture versus a resting condition).

Later, Bucher and collaborators[25] extended these initial data by comparing the brain activations of ET patients to those of healthy controls and individuals suffering from a different type of tremor (i.e., the writing tremor). This fascinating research revealed that cerebellar overactivity was associated with the occurrence of tremor *per se*, independently of the triggering event (i.e., holding a posture in the case of ET or using a pen in the case of the writing tremor).[25]

Furthermore, Boecker and co-workers[26] explored how alcohol (i.e., ethanol), a common substance known to reduce tremor in ET, influenced brain activation in ET patients and controls. Similar to previous findings, this study[26] confirmed that ET patients *per se* (i.e., not under action of ethanol) displayed, relative to healthy controls, an increased bilateral cerebellar activation (including the vermis). In contrast, the administration of alcohol led to a bilateral decrease in cerebellar responses in both ET patients and controls and to increased activation of the inferior olivary nucleus in ET patients alone (not controls). Given the intense anatomical connections between the

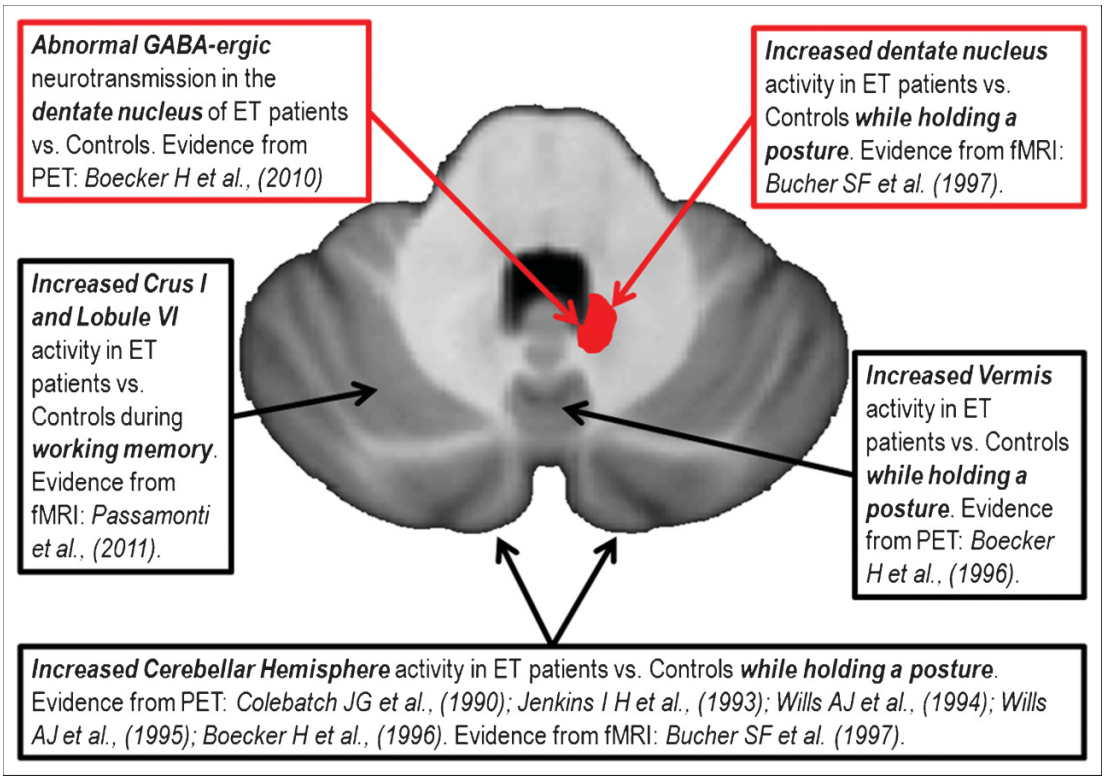

Figure 2. Summary of A Number of Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging Studies Demonstrating A Key Involvement of the Cerebellum in the Pathophysiology of Essential Tremor (ET) While Participants Executed A Specific Motor Task (i.e., Holding A Posture) or A Cognitive Paradigm (i.e., Keeping in the Working Memory A Series of Letters). A PET study (Boecker et al.[27]) that employed a specific gamma-aminobutyric-acid radioligand is also reported to further display the key role of functional abnormalities in the cerebellar circuits in ET patients.

olivary nuclei and cerebellum, these data suggested that the pharmacological mechanism of ethanol-induced suppression of tremor in ET may depend on the interactions between specific regions within the olivocerebellar circuit.[26]

Taken together, these PET experiments have consistently reported functional abnormalities in the cerebellum of ET patients, although the conclusions that can be drawn from these initial findings were limited by the scarce statistical power of the studies (the sample size typically comprised only four to seven individuals). On the other hand, a later fMRI experiment using a similar experimental setting to that employed in previous PET experiments (holding a posture vs. maintaining a resting position)[23,25,26,28] was conducted in a relatively larger sample (12 ET patients and 15 controls) and unequivocally confirmed that ET patients displayed, relative to controls, increased responses in the bilateral cerebellum and in the primary sensory motor cortex, globus pallidus, and thalamus contralateral to the side of the tremor.

More recently, a PET study using a $GABA_A$ receptor radioligand,[27] ^{11}C-flumazenil, has provided further insights into the core neurobiological underpinnings of ET. In particular, increased ^{11}C-flumazenil binding was detected in the cerebellum, ventrolateral thalamus, and lateral premotor cortex in eight ET patients compared with 11 healthy controls.[27] The enhancement of ^{11}C-flumazenil binding in the cerebellum of ET patients has been interpreted as reflecting receptor upregulation that may be consequent to the atrophy of Purkinje cells or, alternatively, to dysfunctions of the receptor itself.[27] Independently of the precise mechanism, this novel experiment has reinvigorated the hypothesis that abnormalities in GABA, the most important inhibitory neurotransmitter in the brain, play a key role in mediating functional impairments in cortical–cerebellar motor pathways of ET patients.[41,42]

Nonetheless, the reader will have noted that the research discussed thus far has only characterized the neural circuits implicated in the genesis of motor symptoms (e.g., postural tremor) but has not addressed how cognitive disturbances may emerge in ET. The importance of studying neuropsychological functions in ET has been emphasized by behavioral and epidemiological studies[37–40,43,44] that have challenged the historical notion that ET is a "pure" motor condition. This new research has indeed demonstrated a broad spectrum of cognitive deficits in ET, including attention, language, and working memory impairments,[37–40] and a significantly higher risk to develop dementia in ET patients relative to individuals of the same age.[41,42] These data have therefore shown that cognitive symptoms may be intrinsically linked to specific disease mechanisms in ET, although the underlying pathophysiology remains largely unclear.

Some authors have proposed that neuropsychological deficits in ET would depend on abnormalities similar to those described in

Table 2. Functional Neuroimaging Studies in ET

Reference	Sample	Neuroimaging Method	Main Finding
Colebatch et al.[22]	4 ET patients with postural tremor, 4 controls	PET	ET> HC: increased activation in sensorimotor cortex contralateral to the side of tremor and in both lateral premotor regions, and in cerebellar hemispheres when holding a posture (arms outstretched) vs. a rest condition.
Jenkins I H et al.[23]	6 ET with postural tremor, 6 controls	PET	Involuntary postural tremor in ET was associated with bilateral cerebellar activation, and contralateral striatal, thalamic, and sensorimotor cortex activation.
Wills AJ et al.[24]	6 ET with postural tremor, 6 controls	PET	ET patients > HC: during arm extension ET patients displayed abnormal increases in bilateral cerebellar and abnormal red nuclear activation.
Wills AJ et al.[25]	7 ET patients, 6 patients with writing tremor, and 6 controls	PET	ET patients > HC: abnormally increased bilateral cerebellar, red nuclear, and thalamic activation. Writing tremor was associated with abnormal bilateral cerebellar activation.
Boecker H et al.[26]	6 ET with postural tremor, 6 controls during administration of alcohol	PET	ET patients > HC: increased bilateral cerebellar activation including the cerebellar vermis. Ethanol ingestion: bilateral decreases of cerebellar blood flow in both ET patients and controls. In contrast, alcohol ingestion increased the activity in the inferior olivary nuclei in ET but not controls.
Boecker H et al.[27]	8 ET with postural tremor, 8 controls	PET with GABA radioligand	ET vs. controls: reduced $GABA_A$ receptor binding in the cerebellum, the ventrolateral thalamus, and the lateral premotor cortex.
Bucher SF et al.[28]	12 ET with postural tremor, 15 controls	fMRI	ET patients > HC: increased activation of the primary sensory motor areas, the globus pallidus, and the thalamus, contralaterally to the side of tremor. Bilateral increased activation of the nucleus dentate, the cerebellar hemispheres, and the red nucleus.
Cerasa et al.[29]	12 ET, 12 controls	fMRI	ET > HC: increased activation in the parietal cortex and dorsolateral prefrontal cortex during the execution of a Stroop task > a sensory motor baseline.
Passamonti et al.[30]	15 ET, 15 controls (different sample from that included in Cerasa et al. 2010)	fMRI	ET > HC: increased activation in the cerebellum during the execution of working memory trials with high attentional load. Functional connectivity: abnormalities were detected in the executive control circuit and in the default mode network of ET vs. controls. Patients with high cognitive scores also showed increased neural abnormalities.

Abbreviations: PET, positron emission tomography; fMRI, functional magnetic resonance imaging; ET, essential tremor; HC, healthy controls; GABA, gamma-aminobutyric-acid.

Alzheimer's and/or Parkinson's disease (PD);[7–11,45] however, there are several reasons to suspect that the cerebellum plays a significant role in cognitive symptoms in ET. Robust evidence from lesion studies (e.g., patients with strokes, tumors, or multiple sclerosis) and fMRI studies in healthy volunteers has shown that the posterior cerebellar lobules are critically implicated in high-level cognitive functions such as working memory, attention, and language.[46–52] We have therefore designed a set of experiments to test whether the cognitive impairments in ET were related to abnormalities of "cognitive" cortical–cerebellar loops, although initial findings did not support this hypothesis.[29] However, we acknowledge that our preliminary negative results may have depended on the use of a paradigm not directly assessing working memory, a cognitive function that strongly relies on cerebellar functions.[29] In fact, in a more recent experiment,[30] we have clearly demonstrated abnormally enhanced cerebellar responses in crus I and lobule VI in a selected group of ET patients, relative to age-, sex-, and education-matched healthy controls during the execution of a verbal working memory task that evoked robust cerebellar activations. Because the behavioral performances of ET patients were similar to those of controls, the cerebellar overactivations were thought to reflect compensatory mechanisms. This interpretation was further supported by the evidence that the ET patients with the highest cognitive scores (people scoring high in a test of executive functions) were those who showed the strongest responses in lobule VI of the cerebellum (vice versa for patients with the lowest scores).[30]

Not surprisingly, crus I and lobule VI are parts of the posterior cerebellar lobules that are known to be involved in a wide range of cognitive functions including working memory.[48,49,53–55] Specifically, crus I and lobule VI mediate the "articulatory loop",[48,49,55–57] a cognitive process needed to "mentally refresh" the content of working memory throughout a subvocal rehearsal that prevents memory decay.[57] Enhanced cerebellar response in ET patients would therefore reflect an increased cognitive effort to rehearse the stimuli that have to be kept in memory.

Of note, data from the same experiment have also been analyzed via functional connectivity methods exploring brain abnormalities in ET at a system (circuit) level rather than at the more simple level of single regions. Interestingly, we found altered functional connectivity, in ET patients versus controls, between crus I/lobule VI and regions belonging to the executive control circuit (ECC) (i.e., dorsolateral prefrontal cortex, inferior parietal lobule, and thalamus) and the default mode network (DMN) (i.e., precuneus, ventromedial prefrontal cortex, and hippocampus).[30] The regions constituting the DMN commonly show responses that are anti-correlated with those of the areas belonging to the ECC.[58] The interpretation of this phenomenon is that the DMN underlies a group of mental processes (e.g., free recall, future planning, mind wandering) that are unrelated to the ongoing task and that tend to interfere with behavioral performance during the execution of cognitive-demanding paradigms.[59] Of note, connectivity analyses also revealed that the degree of the individual cognitive deficit in ET patients modulated the functional "communications" between the cerebellum and regions of the ECC and DMN. In particular, lower neuropsychological scores were associated with abnormalities in the interplay between the cerebellar crus I/lobule VI and both the ECC and DMN.[30]

In conclusion, our results offered new insights into the pathophysiological mechanisms of cognitive dysfunctions in ET, suggesting a primary role of the cerebellum in mediating abnormal interactions between the ECC and DMN. However, we think that our initial identification of functional abnormalities within the DMN in ET deserves further investigation because other functional neuroimaging techniques (e.g., resting state analyses) are better suited to characterize the DMN. In addition, given that resting state imaging does not necessitate the execution of attention-demanding tasks and can thus be easily applied to ET patients with severe cognitive impairments, future studies using these approaches will be useful for advancing the knowledge of brain mechanisms underlying dementia in ET.

Functional imaging in ET (MRSI studies)

Additional evidence for the cerebellar involvement in the pathophysiology of ET comes from another line of research employing MRSI, a functional technique measuring the ratio between specific cell metabolites (e.g., *N*-acetylaspartate/total creatine ratio (NAA/tCr)). Significant reductions in the NAA/tCr ratio are thought to represent a sensitive measure of neuronal dysfunction and/or degeneration.

However, a major limitation of MRSI is that it only allows one to explore a restricted number of regions at the same time and thus requires a strong *a priori* hypothesis regarding the brain structures to be explored. The fact that the ventral intermediate nucleus of the thalamus (VIM) has been long considered the key region in the pathogenesis of ET may be the reason why one of the initial studies,[60] using MRSI in ET, concentrated on VIM rather than on the cerebellum. This research found that the NAA/Cr ratio in the right VIM was significantly higher than the same ratio in the left VIM in ET, although no differences in the NAA/Cr ratio in the right and left VIM were found when comparing ET patients versus controls.

More recently, Louis and collaborators[61] have found that the NAA/tCr ratio is reduced in the GM and WM of the cerebellum, thalamus, and basal ganglia in 12 ET patients compared with 12 healthy subjects. Of note, the blood concentrations of harmane, a neurotoxin implicated in the etiology of ET, were associated with reduction of the NAA/tCr ratio in the cerebellum *but not* in other brain regions. In contrast, a different toxin (i.e., lead) was not found to be linked with abnormalities in the NAA/tCr ratio in the cerebellum or other neural areas. These remarkably specific results highlight the central role of the cerebellum and harmane in mechanisms related to the development of ET. Furthermore, previous findings from the same and other groups[62,63] showed that the symmetry in the NAA/tCR ratio between the cerebellar hemispheres significantly differed between ET patients and controls. Specifically, ET patients displayed a more symmetric NAA/tCR ratio between the cerebellar hemispheres relative to controls, and this would represent the neural correlate of a common clinical feature of ET, the bilateral and symmetrical postural tremor.[62]

Conclusion

Our review of the structural and functional neuroimaging literature supports the hypothesis that the cerebellum is a key region involved in the pathogenesis of motor and non-motor symptoms associated with ET.

However, a number of earlier studies[14,19,24–26] have provided some evidence that abnormalities may also be present in other cortical and subcortical brain regions such as the frontal and temporal cortices and the red and olivary nuclei. More research is therefore necessary to disentangle the role of cortical regions in ET, and their links with cognitive dysfunctions. In addition, it is possible that the contribution of the red and olivary nuclei in the pathophysiology of ET has been underestimated because of technical difficulties in measuring the structure and function of these small areas. The future advent of sophisticated 7 Tesla scanners will likely facilitate new studies on the role of these subcortical structures in ET.

It is also important to highlight that the actual evidence of cerebellar involvement in the genesis of ET does not imply that the complex relationships between the cerebellar dysfunctions and ET have been fully characterized. A number of questions remain unanswered. First, some inconsistent findings in the structural neuroimaging literature have not been addressed yet. These discrepancies may depend on the failure to disaggregate the specific associations between distinct clinical phenotypes of ET and the corresponding brain markers, although variability among experimental designs may be another important source of confound. Second, it still remains to be determined whether the cerebellum is globally abnormal in ET or whether there are specific lobules that present more intense deficits than others. Third, ET is an extremely heterogeneous disease at the clinical and neuropathological level. For example, ET patients with Lewy body disease in the brainstem are thought to represent a distinct subgroup relative to patients with prominent cerebellar damage and no Lewy bodies. Furthermore, a recent study using dopamine transporter imaging[64] demonstrated that ET patients can present a degree of dopaminergic loss in the caudate nucleus, although the distribution of the dopaminergic depletion significantly varied between ET subjects and patients with PD. New studies are therefore necessary to clarify the boundaries between ET and PD syndromes, with clear implications for improving future diagnosis and treatment of both these disorders.

In conclusion, we recommend that future neuroimaging experiments should use standardized and quantitative approaches to describe different clinical phenotypes while examining how the key symptoms of ET are specifically associated with distinct patterns of abnormalities in the cerebellum and other brain regions. Providing a more detailed description of these relationships will greatly advance the refinement of the current taxonomy of ET and will reveal whether this disorder is constituted by a continuum of associated disturbances or whether it is more appropriate to define ET as an heterogeneous disorder constituted by separate clinical entities.

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