

## Review

# Cognitive Features of Essential Tremor: A Review of the Clinical Aspects and Possible Mechanistic Underpinnings

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## Abstract

The classical concept of essential tremor (ET) as a monosymptomatic tremorogenic disorder has been questioned in the last decade as new evidence has been described. Clinical, neuroimaging, and pathological studies have described a probable structural basis (mainly in cerebellum) and evidence that ET is associated with subtle clinical cerebellar deficits and several non-motor clinical manifestations, such as cognitive and mood disorders. We performed literature searches in Medline, ISI Web of Knowledge, and PsycInfo databases. The aim of this review is to describe cognitive deficits associated with ET. First, we present a brief history of ET cognitive disorders presented. Second, we describe several clinical cross-sectional series demonstrating that ET is associated with mild cognitive deficits of attention, executive functions, several types of memory (working memory, immediate, short term, delayed, and possibly others) and, mood disorders (depression). Recent neuroimaging studies favor a cerebellar basis for these cognitive deficits. Population-based surveys confirm that mild cognitive dysfunction is not limited to severe ET cases, the entire ET group, including mild and undiagnosed cases, can be affected. Cohort studies indicated that ET cognitive deficits could be progressive and that ET patients had an increased risk of dementia. The mood and cognitive deficits in ET are in agreement with cognitive affective cerebellar syndrome described in patients with cerebellar disorders. New evidence, mainly from functional (neuroimaging) and prospective clinical studies would further bolster recent descriptions of ET clinical manifestations.

**Keywords:** Essential tremor, cognition, cognitive disorders, dementia, neurologic manifestations, cerebellar disorders

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## Introduction

The classical series did not detect cognitive deficits in essential tremor (ET) patients,<sup>1–6</sup> although the Mayo Clinic series described a high percentage of “psychoneurosis” (16% suffered from this out-of-date diagnosis), there was no comparison with a control group.<sup>4</sup> A study in 1990 performed controlled comparison of premorbid personality in Parkinson’s disease (PD) and ET patients and demonstrated similar premorbid personality with analogous neuropsychiatric symptoms (depressive, introverted, rigid, and “lonely” traits) in both disorders and found that the general intelligence of ET patients was similar to controls.<sup>7</sup> An analogous study was recently performed.<sup>8</sup>

That is to say, 20th-century clinical series and neurological reports<sup>9–11</sup> describe ET as a slowly progressing, monosymptomatic,

benign movement disorder that is frequently familial and is infrequently associated with incapacitating tremor, and very rarely with other neurological symptoms, such as gait ataxia.<sup>1,3,6,11,12</sup> Historically, it has not been associated with cognitive symptoms. This classical view was established in the well-known definition of ET by the Movement Disorders Society in the last years of the 20th century.<sup>13</sup>

The current history of cognitive disorders in ET began with the precise and extensive psychometric evaluation performed prior to thalamic deep brain stimulation (DBS) as a treatment for medication-refractory ET. The first documented ET neuropsychology was published by Tröster et al.<sup>14</sup> in 1999 without control cases. Later, several clinical series of psychometric evaluation in ET patients were described 1) in patients to be treated with thalamic DBS;<sup>15–22</sup> 2) in

clinic-based ET patients,<sup>23,24</sup> and, more recently, in 3) population-based ET cases,<sup>25-29</sup> many of them with control cases for comparison.

The present review analyses the cognitive aspects of ET patients. A review of the ET patient cognitive aspects in the new scenario of ET as a possible benign neurodegenerative disorder has been recently described.<sup>30</sup>

**Methods**

The review was performed using Medline, ISI Web of Knowledge, and PsycInfo databases with a combination of MESH terms: *essential tremor* and *cognitive disorders, cognition, and dementia*. In Medline and the ISI Web of Knowledge, *neurologic manifestations* and *psychiatric and neuropsychiatric symptoms* were also entered in the search. Only papers written in English, French, and Spanish were analyzed. Some papers were obtained from the main neurological text and article references were also included in the analysis.

**Main results**

In Medline there were nearly 2,250 articles (July 2011) on ET, but only a few were dedicated to descriptions of cognitive symptoms in ET patients ET patients.

**Essential tremor is not a monosymptomatic tremor disorder**

In the last few years of the 20th century, the Movement Disorders Society<sup>13</sup> considered ET as a tremorogenic monosymptomatic disorder. It is important to summarize more recent (21st century) clinical and pathological aspects of ET that include cognitive deficit in this new nosological concept of ET.

The most apparent clinical manifestation of ET is limb kinetic tremors (axial tremor is infrequent), although other infrequent neurological motor manifestations indicative of cerebellar deficits have been described (Table 1). The most frequent non-tremor manifestations are subtle (or subclinical) cerebellar motor neurologic deficits,<sup>31-40</sup> mild (or very mild) cognitive impairments,<sup>16-30</sup> and depression.<sup>8,17,22,25,29,41-45</sup> Nevertheless, there are not enough long-term population-based studies that evaluate the frequency of the symptoms shown in Table 1 in ET patients. Another important issue regarding ET nosology is the increasing evidence of cerebellar pathology, which is concordant with clinical deficits and is based on pathological and neuroimaging data.

Classically, ET had no pathology: it was a functional disorder. In 1991 Rajput et al.<sup>46</sup> reported that only eight cases had been studied pathologically, and they analyzed six additional patients. Although they did not find any specific neuropathological lesions in ET brain, there was no control group.<sup>46</sup> In the last decade, Louis and colleagues<sup>41,47,48</sup> performed controlled studies and demonstrated that the majority of ET cases had identifiable structural brain changes localized in the cerebellum itself (Purkinje cell loss and other neurodegenerative abnormalities, such as an elevated number of axonal torpedoes) or in the brainstem neurons that synapse with Purkinje cells. A smaller group of ET brains had only Lewy bodies limited to the brainstem (locus ceruleus and dorsal vagus nucleus).<sup>47</sup>

**Table 1.** Associated Disorders in Essential Tremor Patients

<b>Subtle Neurological Deficits</b>
Bradykinesia (mild)
Cerebellar dysfunction
abnormal eyeblink reflex conditioning
deficits in paced finger typing
dysfunction in hand–eye coordination and ocular movements
mirror movements
mild dysarthria
tandem gait ataxia
Olfactory and hearing deficits
<b>Non-motor deficits</b>
Mild cognitive deficits (Table 4)
Neuropsychiatric symptoms
anxiety
depression
specific personality traits
Sleep disorders
Decreased body mass index
<b>Nervous system pathology</b>
Pathology of the cerebellum and its brainstem connections
<b>Association with neurological or neurodegenerative disorders</b>
Parkinson’s disease
Dystonia
Myoclonus
Possibly associated with migraine, restless legs syndrome, Lewy body dementia and Alzheimer’s disease

These data were criticized by several authors. Rajput and Rajput<sup>49</sup> recently reported no cerebellum abnormalities in their series, but it should be mentioned that it only included two normal controls, which could lead to a type II error.<sup>50</sup> Other authors considered brainstem Lewy bodies as an incidental finding in old people and cerebellar abnormalities as secondary to “therapeutic” alcohol abuse,<sup>51</sup> but ET brain

cerebellar findings and brain weight<sup>47</sup> are not consistent with chronic alcoholic brain pathology.<sup>52</sup> The neuroimaging and neurophysiologic findings indicate a cerebellar dysfunction origin for ET. Two studies performed in the 1990s<sup>53,54</sup> suggested that the tremors of ET patients were related to activation in the cerebellar hemispheres and its connected brainstem structures. In the next decade, non-routine neuroimaging studies demonstrated a relationship between ET and cerebellar and brain abnormalities<sup>55-62</sup> (with some exceptions).<sup>63,64</sup>

In summary, recent clinical, pathological, and neuroimaging findings are consistent with the hypothesis that ET is a disorder of the cerebellum and its brain connections rather than a monosymptomatic tremor disorder. However, current ET nosology has several problems. The absence of clear monogenetic defects in a familial disorder (LINGO1 is only a genetic risk factor<sup>65</sup>) favors the hypothesis that ET may be a more heterogeneous disorder than was previously thought.<sup>41</sup> Cases of benign tremulous parkinsonism,<sup>66</sup> adult-onset dystonic tremor (AODT), in which the dystonia could appear many years after the tremor,<sup>67,68</sup> and other rare tremors, including fragile X-associated tremor/ataxia syndrome (FXTAS), could mimic ET cases.<sup>51,69,70</sup> However, the majority of ET cases, mainly in a community setting, may still be traditional ET. The problem is that traditional ET could comprise several families of *essential tremors*.<sup>41</sup> This issue might explain the absence of clear genetic abnormalities in a frequently familial disorder.

### Cognitive deficits in ET

#### Historical data

As stated in the introduction, the classical 20th century series did not detect cognitive deficits in ET patients<sup>1-6</sup> (with the exception of 16% of “psychoneurosis” in an uncontrolled study<sup>4</sup>). Disturbances in the premorbid ET personality described in 1990<sup>7</sup> went unnoticed, perhaps because they were published in a monograph series that was not included in Medline.

The current history of cognitive disorders in ET began with extensive psychometric evaluation performed prior to thalamic DBS for medication-refractory ET; the implanted brain hardware could modulate neurologic function with low morbidity.<sup>71</sup> The first investigation of ET neuropsychology was published in 1999 and comparing 40 patients using a thorough psychometric evaluation pre-DBS and 3 months after the operation.<sup>14</sup> The absence of a control group limited the impact of mild psychometric abnormalities described in ET patients. One year later, an interesting report described improvement<sup>15</sup> in a patient who had been assessed on bilateral thalamic DBS during the “on” and “off” periods. Without stimulation, the patient suffered from declines > 1 standard deviation (SD) on measures of verbal fluency and recall compared with active stimulation.<sup>15</sup> This report demonstrated that the amelioration of tremor by DBS mildly improved certain cognitive deficits, indicating that these deficits were in some way related to the ET. Both studies provided evidence that ET patients can have cognitive deficits, but the specific type of cognitive abnormalities remained unknown.

Three studies on cognitive dysfunction in ET were published in 2001.<sup>16-18</sup> The publication by Gasparini et al.<sup>16</sup> was based on theoretical reasons (“a deregulation of the mechanisms underlying both the cognitive and motor functions can be hypothesized”) and investigated “frontal lobe dysfunction” in a series of ET patients treated with thalamic and found evidence of cognitive dysfunction. Lombardi et al.<sup>17</sup> suggested that the cerebellar deficits in ET could be accompanied by psychological disturbances. Since then, several clinical series in patients to be treated with thalamic DBS<sup>16-22</sup> and clinical series from specialized clinics (Table 2) have confirmed psychometric abnormalities in ET patients;<sup>23,24</sup> (Table 3). Were these deficits a consequence of the tremor itself<sup>72</sup> as has been maintained by several authors? In 2003, Fields et al.<sup>73</sup> reported psychometric findings of ET patients pre- and 12 months after thalamic DBS. Some psychometric deficits were slightly improved, but the majority persisted. The stability of the majority of psychometric deficits in ET (after the amelioration of patient tremors) militates against an adverse tremor effect.<sup>30</sup>

Obviously, clinical series of ET have a selection bias (severe and longstanding ET cases). Are the psychological abnormalities described in the previous ET series an attribute of severe or chronic ET patients? The limitations of the clinical series have been overcome by the findings from a population-based survey, the Neurological Disorders in Central Spain (NEDICES) cohort study in 5,278 elderly people.<sup>74</sup> The survey analyzed the epidemiology of the main neurological disorders in elderly people,<sup>75</sup> including ET.<sup>76,77</sup> In the second (incidence) wave of this cohort, the whole participant population was invited to complete a brief psychometric test.<sup>25,30,78</sup> The result of this study confirmed that mild ET cases (the majority of them did not seek medical attention<sup>76,77</sup>) suffered from the main psychometric abnormalities described in clinical series.<sup>16-24,30</sup> (Table 4). Also, an increase in mild cognitive impairment cases was detected<sup>29</sup> together with a dementia risk in elderly ET participants in the NEDICES study.<sup>26</sup> This observation was corroborated in another community-based cohort in New York.<sup>27</sup> Other clinical ET patient series evaluated several neuropsychological or neuropsychiatric aspects of ET patients, but the objectives were to discover their role in the social or personal evolution of ET patients, not to analyze cognitive disturbances.<sup>79-83</sup> More recently, a clinical series with neuroimaging selection (ET cases must show integrity of the nigrostriatal dopaminergic terminals, as evidenced by a normal dopamine transporter scan) clarified the relationship between verbal memory executive dysfunction and cerebellar pathology.<sup>61</sup>

In summary, several cognitive abnormalities have been described in clinical and population-based series of ET patients in the last decade.

#### Cognitive deficits in ET

A summary of the cognitive deficits in ET patients is listed in Table 5.

It is not easy to establish a summary of cognitive deficits in ET for several reasons: the heterogeneity of patient series (age, ET duration, and severity); the variety of neuropsychological batteries; the limited

**Table 2.** ET Patient Series with Cognitive Evaluation (selection)<sup>1</sup>

Authors/Year	ET	Controls	Series Origin
	n Cases	n Cases	
Gasparini et al. <sup>16</sup>	27	Yes, 15	Thalamic DBS
Lombardi et al. <sup>17</sup>	18	No <sup>2</sup> and 18 PD	Thalamic DBS
Duane & Vermilion <sup>19</sup>	55	No <sup>2,3</sup>	Thalamic DBS
Lacritz et al. <sup>20</sup>	13	No <sup>2</sup> and 13 PD	Thalamic DBS
Tröster et al. <sup>21</sup>	101	No <sup>2</sup>	Thalamic DBS
Benito-León et al. <sup>25</sup>	232	Yes, 696	Population based
Sahin et al. <sup>23</sup>	16	Yes, 16	Specialized clinic
Higginson et al. <sup>22</sup>	24	Yes, 21 and 24 PD	Thalamic DBS
Kim et al. <sup>24</sup>	34	Yes, 33	Specialized clinic

<sup>1</sup>Passamonti et al. series<sup>61</sup> not included (see text)  
<sup>2</sup>Compared with normative data  
<sup>3</sup>Retrospective study  
Abbreviations: DBS, deep brain stimulation; ET, essential tremor; PD, Parkinson's disease patients to compare

number of ET patients (only 13–55 cases assessed), with the exceptions of the Tröster series (without controls)<sup>14,21</sup> and the NEDICES series<sup>25</sup> (short neuropsychological battery). The cross-sectional designs of the analyzed ET series do not permit the clinical evolutions of the described psychometric characteristics to be obtained. For these reasons, it is difficult to establish firm conclusions, and this summary will change with knowledge gained from future prospective series. Another fact that hinders firm conclusions is the mildness psychometric deficits described in ET series and the fact that these mild deficits do not affect all ET patients.<sup>30</sup> The association of frequent mild depression in clinical and population-based series has been postulated as a possible cause of cognitive ET deficits.<sup>72</sup> In fact, depression, measured by clinical and psychometric scales, is, in general, mild. It is also a constant finding in ET series,<sup>8,17,22,25,29,41–45</sup> probably has its own characteristics,<sup>43</sup> and could be related to motor dysfunction and social stigma associated with tremor.<sup>45</sup> However, it is likely that, it is also biologically determined; it is independent of the motor intensity and evolution,<sup>30,81,83</sup> and it is described in cerebellar disorders without tremor or mild motor impairment.<sup>90,91</sup>

The most consistent cognitive findings described in the ET series are discussed below.

**Deficits of attention–concentration and working memory.** The majority of the series demonstrated several deficits of attention–concentration in ET patients. The subtest of the Wechsler Adult Intelligence Scale (WAIS) and Digit Span (forward and backwards) was clearly disturbed in several series.<sup>17,22,24</sup> The Brief Test of Attention (auditory)<sup>21</sup> and selective test of auditory and visual attention (Stroop test) were altered in several series.<sup>16,20,21</sup> The Symbol Search<sup>22</sup>

and Trail Making Test (TMT) (series A, attention and time to complete;<sup>16,78</sup> and series B, executive function<sup>16</sup>) were also disturbed, except in the Sahin et al. series.<sup>23</sup> Complex attention and other related psychological functions were evaluated by the Stroop test,<sup>16,20,21,23</sup> and Wisconsin Card Sorting Test (WCST).<sup>16,17,20,23</sup> The majority of series observed disturbances in both evaluations.<sup>30</sup>

Other types of attention, such as visual attention, were evaluated in the Duane and Vermilion<sup>19</sup> series: 56% of ET patients had abnormal scores on the Letter Cancellation Task and 71% had low scores on the Test of Variables of Attention or the Conners' Continuous Performance Test. Others studies also demonstrated alterations in visual attention (Stroop task interference condition),<sup>16,21</sup> and one report described impaired visual attention reaction times.<sup>39</sup>

Working memory, the ability to carry out a series of actions or mental operations in which one is required to hold something in memory in order to do the following operation, was assessed specifically in the Lombardi et al.<sup>17</sup> study by means of Digit Span, forward plus backward total span (WAIS); Visual Span, forward plus backward total span (Wechsler Memory Scale [WMS]); and Letter–Number Sequencing (WAIS). All these tests revealed deficits, although the visual span was not affected.<sup>17</sup>

In summary, auditory, verbal, and visual attention and working memory are affected in many ET patients, and these deficits are usually mild in the great majority of series, including the population-based series. There are few studies with computerized attention evaluation (reaction times and others).<sup>19</sup>

**Deficits in executive functions.** Executive function, that is to say, the overall control and sequencing of multiple cognitive operations, is

**Table 3.** Main Cognitive Deficits in ET patients<sup>1</sup>

	Authors								
	Lombardi <sup>17</sup>	Gasparini <sup>16</sup>	Duane <sup>19</sup>	Lacritz <sup>20</sup>	Troster <sup>21</sup>	Sahin <sup>23</sup>	Higginson <sup>22</sup>	Kim <sup>24</sup>	Benito-León <sup>25</sup>
<b>Psychological functions</b>									
Global cognitive function	=	ND	ND	ND	ND	ND	ND	++	++
Attention-concentration	++	++	=	ND	ND	=	++	++	++
Working memory	++	++	ND	++	++	=	++	++	ND
Motor performance	ND	ND	ND	ND	++	ND	ND	ND	ND
Spatial fluency	ND	ND	ND	++	ND	ND	ND	ND	ND
Concept formation	++	++	+	++	=	++	ND	ND	ND
Reasoning	=	ND	ND	ND	ND	ND	+	ND	ND
Memory									
Verbal memory	++	ND	+	=	++	+	ND	-/+ <sup>++2</sup>	ND
Logical memory	ND	ND	ND	ND	=	ND	++	ND	ND
Visual memory	ND	ND	+	+	ND	=	++/= <sup>2</sup>	=	ND
Verbal fluency	++	++	++	+	++	++	+	++	++/= <sup>2</sup>
Naming	+	ND	ND	=	++	=	++	++	+
Visuoperception	=	ND	ND	ND	++/= <sup>2</sup>	++	ND	ND	+
Visuoconstruction	=	=	=	=	ND	=	++	ND	ND
Mood (depression)	+	ND	+	+	ND	ND	++	ND	++ <sup>3</sup>

<sup>1</sup>Modified from Bermejo-Pareja<sup>30</sup> (Passamonti et al.<sup>61</sup> is not included, see text)<sup>2</sup>Similar tests are discordant<sup>3</sup>See Lois et al.<sup>42</sup>

Reviewer's test selection and test gradation: =, similar or superior to controls or standard measures; +, mild alteration (statistically significant); ++, clear alteration (p&lt;0.01); ND, not done

Psychological functions and tests (for test abbreviations, see text):

Global cognitive function: IQ and MMSE

Attention-concentration: Digit forward Span (WAIS); TMT; Picture Completion (WAIS); Brief test of attention; Symbol digit and others

Working Memory: Digit backward span (WAIS); Stroop test, and others

Motor performance: Groove Pegboard

Concept formation: WMS-R VR: WCST

Reasoning: Matrix and similarities (WAIS)

Verbal memory: CVLT, HVLIT. Logical memory (WMS-R). Visual memory: Faces and Visual Reproduction (WMS-R), ROF test

Verbal Fluency: FAS test; listing animals and fruits during 1 minute; and others

Denomination: BNT and others

Visuoperception: Benton Recognition Face, BLO; HVOT and others

Visuoconstruction: Block design (WAIS) and others

Mood: Geriatric depression scale, Beck depression Inventory, DSM-IV diagnosis and others

**Table 4.** Essential Tremor and Cognitive Deficits (population-based series)<sup>1</sup>

<b>(A) Cognitive deficits clearly demonstrated</b>			
<b>Psychological tests</b>	<b>ET Subjects</b>	<b>Controls</b>	<b>p-Value</b>
	<b>232<sup>2</sup></b>	<b>696<sup>3</sup></b>	
<b>Global cognitive function</b>			
MMSE-37 (range 0–37)	27.0 (6.7)	28.9 (5.9)	0.001
<b>Attention/frontal executive function</b>			
Trail Making Test A (errors)	8.7 (11.0)	3.8 (7.6)	0.001
Trail Making Test A (time to complete)			
>5 minutes	91 (39.2%)	148 (21.3%)	0.001
0 or <5 minutes	141 (60.8%)	548 (78.7%)	
<b>Verbal fluency</b>			
Verbal fluency (fruits)	8.9 (3.9)	10.0 (3.5)	0.001
<b>Memory</b>			
Naming test (score 0–6)	5.4 (1.5)	5.7 (6)	0.019
Immediate free recall (score 0–6)	3.9 (1.6)	4.2 (1.4)	0.012
Delayed free recall (score 0–6)	3.5 (1.9)	3.9 (1.8)	0.009
Immediate logical memory (score 0–6)	3.9 (1.7)	4.3 (1.6)	0.003
Delayed logical memory (score 0–6)	3.1 (2.2)	3.6 (2.1)	0.008
<b>(B) Cognitive functions; no statistically significant difference</b>			
<b>Verbal fluency</b>			
(animals)	12.6 (5.0)	12.9 (4.7)	0.42
<b>Premorbid intelligence</b>			
Word accentuation test (score 0–30)	10.2 (10.3)	11.4 (10.3)	0.10

<sup>1</sup>Modified from Benito-León et al.<sup>25</sup>  
<sup>2</sup>Number of ET cases detected  
<sup>3</sup>Number of cognitively normal control cases  
 Abbreviations: ET, essential tremor; MMSE, Mini-Mental State Examination

thought to be frontal lobe-dependent (mainly dorsolateral prefrontal [DLPF]) or their connections (frontal–thalamic–cerebellar loop). Executive functions can be assessed by motor (go–no-go paradigm, fist–edge–palm, Luria loop test, and others) and psychometric tests. Motor test results are not different in ET patients.<sup>23,24</sup> This makes sense because these tests are usually only positive in patients with severe frontal deficits. The psychometric “frontal” tests evaluate many psychological functions, such as complex attention, set shifting, planning, mental flexibility and control, verbal fluency, social behavior, and insight. Its paradigmatic examples are the WCST, the

Stroop test, and TMT Part B, all of which were altered in the majority of the series.<sup>30</sup> Verbal fluency tests such as the Letter-cued Word Fluency (FAS test, number of animals, or fruit during 1 minute),<sup>16,17,20–24,78</sup> which is DLPF-dependent and the Ruff Figural Test Fluency<sup>20</sup> were also affected. The Frontal Assessment Battery (FAB), specific for detecting frontal deficits, obtained statistically significant alterations in a recent series.<sup>61</sup> The Matrix Reasoning (WAIS) was mildly abnormal in one study,<sup>22</sup> but the Tower of London,<sup>17</sup> Tower of Hanoi,<sup>16</sup> and Clock Drawing<sup>23</sup> Tests, which require executive and visuospatial abilities, were within normal ranges.

**Table 5.** Cognitive Deficits in ET: Summary

<b>General conclusion</b>
Cognitive deficits are mild (subclinical) and multiple.
<b>Consistent deficits</b>
(A) Attention–concentration and working memory
Digit Span, forward and backwards (WAIS)
Trail Making Test Part A, Symbol Search
Selective auditory attention (Brief Test of Attention)
Visual reaction time
Working memory
(Visual Span, WMS; Letter–Number Sequencing, WAIS; Stroop test)
(B) Executive functions
Set-shifting (Wisconsin Card Sorting Test, Stroop test, Trail Making Test Part B)
Verbal fluency (Letter-Cued Word Fluency; animals and others)
FAB battery
Other tests (Ruff Figural Fluency test; Matrix Reasoning –WAIS)
(C) Explicit verbal memory (immediate or short-term and delayed)
Short-term verbal memory (CVLT and other tests)
Delayed verbal memory (CVLT and other tests)
Wechsler Memory Scale (WMS-R), logical memory not clearly affected
Visual memory (ROF test) without alterations
(D) Language
Verbal fluency (letter-cued word fluency, listing fruit or animals during 1 minute)
Vocabulary (Benton Naming test)
<b>Possible deficits</b>
Mental processing speed (several tests)
Visuospatial functions (facial recognition)
General cognitive capacity (elderly ET)
<b>No deficit (or very dubious)</b>
Reasoning, abstract thinking, calculation
<b>Not evaluated</b>
Implicit memory (exception: eyeblink conditioning)
Abbreviations: CVLT, California Verbal Learning Test; ET, essential tremor; FAB, Frontal Assessment Battery; ROF, Rey–Osterreith Complex Figure; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale

In summary, mild executive dysfunction, as detected by tests that mainly require complex attention and set shifting, is a constant finding in ET series.

**Explicit verbal memory (immediate or short-term and delayed).** Several types of memory (working, short-term, and delayed [verbal learning]), but not implicit memory (unconscious memory of acts), were evaluated in ET patients. The most frequently employed measure is the California Verbal Learning Test (CVLT), which is affected in almost all clinical series (to a different degree in the various subscales).<sup>30</sup> In an analogous test, a Spanish test that includes naming of pictures, immediate and delayed verbal memory,<sup>78</sup> revealed mild memory deficits in a large number of ET patients in a population-based series. Also, the Hopkins Verbal Learning Test (HVLN) used in one study demonstrated that memory was impaired in ET versus controls.<sup>24</sup>

The complete Wechsler Memory Scale (WMS-R) or its subscales were performed in several clinical series, with different results. Logical memory (WMS subscale) was abnormal in one series,<sup>22</sup> but not in the large series by Tröster et al.<sup>21</sup> (only 12–15% of ET patients were 1 SD below the normative group) or in the Lacritz et al.<sup>20</sup> investigation. The figural subscale was affected in another series.<sup>22</sup>

Visual memory investigated with the Rey–Osterreith Complex Figure (ROF) test did not show statistically significant differences versus controls in two studies.<sup>23,24</sup> In the Kim et al.<sup>24</sup> investigation, only the ROF recognition subscale showed a statistical deficit, but the Faces (WMS)<sup>22</sup> and Visual Reproduction subscales (WMS)<sup>20</sup> were affected.

With the exception of eyeblink conditioning, implicit memory has not been assessed in ET patients<sup>38</sup>.

To summarize, only verbal memory (recognition, immediate, and delayed) was consistently disturbed in ET patients, and visual memory is possibly affected.

**Language.** As stated above, several tests of verbal fluency were consistently lower in ET patients. Other tests, such as the Benton Naming Test (BNT), were also affected,<sup>17,21,22,24</sup> but the results were more variable.<sup>20,23</sup>

### Other psychological functions

Other psychological functions are not consistently affected or have not been sufficiently investigated to draw firm conclusions (Table 5).

**Mental processing speed.** Fine motor speed was disturbed in one series,<sup>21</sup> and the timed TMT Part A was affected in the population-based series,<sup>78</sup> as was Symbol Search<sup>22</sup> (mental processing speed), indicating a possible slowing of mental processing that is also described in PD patients.<sup>17,20,22,84,85</sup> More data are needed to establish definite conclusions.

*Visuospatial functions* have been evaluated in several studies. The Benton Facial Recognition Test was implemented in three series; two found abnormal results in ET patients,<sup>21,23</sup> whereas the third showed them to be within the normal range.<sup>17</sup> The Hooper Visual

Organization Test (HVOT) and Benton Line Orientation (BLO) were statistically abnormal in one study,<sup>23</sup> but the HVOT was in the normal range in two other clinical series.<sup>17,21</sup> This fact, coupled with variable data from block designs (WAIS) (normal in two<sup>17,20</sup> and abnormal in one<sup>23</sup>) and normal visual memory in two clinical series<sup>23,24</sup> give a picture of possible normality in visuospatial functions, with facial recognition as one exception.<sup>30</sup>

*General cognitive function* was evaluated by intelligence quotient,<sup>21</sup> Mini-Mental State Examination (MMSE),<sup>24,25</sup> and Spanish verbal intelligence test.<sup>25,78</sup> The results showed that IQ was in the normal range (mean 109; but with >13 mean years of education), but MMSE scores were significantly lower than those in controls in the Kim et al. study<sup>24</sup> and in a population-based survey.<sup>25</sup> These findings indicate possible below-average cognitive performance in ET patients (mainly in elderly ET patients). In NEDICES, the increased rate of mild cognitive impairment<sup>29</sup> risk of dementia, and association of dementia in this cohort<sup>26,87</sup> suggested that cognition is affected in some ET patients.<sup>25</sup> This was confirmed in a community-based study in New York.<sup>27</sup> This fact is in agreement with the greater cognitive decline observed in ET patients versus controls in the prospective follow-up of the NEDICES survey.<sup>28</sup> These findings indicate that some ET cases could suffer from a progressive cognitive decline.<sup>30</sup> This point needs further prospective investigations to determine whether general cognitive function is below average in ET patients or if the decrement in general cognitive function is a consequence of a slow, mild degenerative process.<sup>30</sup>

*Abstract thinking and reasoning* are rarely investigated in ET patients. Several WAIS subscales were implemented in clinical series (block designs,<sup>17,20,23</sup> picture completion,<sup>17,22</sup> matrix reasoning,<sup>17,22</sup> similarities,<sup>17,22</sup> and vocabulary<sup>17</sup>) with contradictory results (abnormal in the Higginson et al.<sup>22</sup> series and normal in Lombardi et al.<sup>17</sup>). Elementary calculation was evaluated in the Kim et al.<sup>24</sup> series without abnormalities. Obviously, more data are needed.

### Clinical significance of cognitive deficits

There is a unanimous consensus that cognitive deficits in ET patients are mild (in general between 1 and 2 SD below the normative group or controls) and subclinical.<sup>21,30</sup> The abnormalities also seem generalized, affecting approximately 30–60% of ET cases<sup>19,21</sup> (visual attention deficits affect more than 70% of ET cases<sup>19</sup>). In the Lacritz et al.<sup>20</sup> study, 12 of 13 ET cases had one psychometric abnormality or more. The SDs of the majority of psychometric evaluations were greater in ET cases (232) versus controls (696), indicating greater variability of psychometric performance in ET cases than in controls.<sup>25</sup>

The results of the psychometric evaluation are quite similar in ET and PD patients.<sup>17,20,22</sup> ET patients performed, in general, worse in tests of word fluency and attention and better in reasoning and calculation than PD patients.<sup>30</sup>

Findings from the NEDICES cohort and other studies demonstrated that the functional incapacity of ET patients is more related to cognitive performance and depression than to tremor (clinical series,<sup>42–45</sup> population-based surveys,<sup>88</sup> and in nursing home series<sup>89</sup>).



### Cognitive studies limitations

It was stated at the beginning of the “Cognitive deficits in ET” section that these clinical series have several limitations, including a low number of cases, variable psychometric batteries (with different versions and subscales performed), an absence of adequate control cases in several series, only cross-sectional studies, and others.<sup>30</sup> These limitations motivated the criticisms by Deuschl and Elble,<sup>72</sup> who doubted the reality of cognitive deficits in ET patients, explaining that the selection bias (severe and longstanding ET cases) in thalamic DBS series, the presence of depression and sedative medications, and other limitations (type I error) may influence these deficits. Moreover, some limitations in the NEDICES cohort (low number of ET incident cases) may have influenced the psychological results.<sup>72</sup>

However, several series adjusted the presence of cognitive deficits for depression and sedative medication,<sup>17,20,22</sup> and the incidence of cognitive deficits remained statistically significant.<sup>30</sup> Despite the limitations of the ET clinical and population-based series, they consistently showed mild cognitive dysfunction, and in the NEDICES survey, in which the great majority of ET cases were mild and did not take medications, cognitive deficits were similar to the clinical series.<sup>25,30</sup>

### Why these cognitive deficits in essential tremor?

Cognitive evaluation consistently demonstrated that ET patients exhibit several deficits in attention, various executive functions, verbal memory (immediate and delayed), language, depression, and probably a very mild global cognitive impairment. These have been explained by three different physiopathological dysfunctions: 1) a deficit in the DLPC (thalamic–cerebellar loop),<sup>16,30</sup> 2) a subclinical or unapparent clinical cerebellar syndrome,<sup>17,30</sup> and 3) the noxious effect on the nervous system of the “dynamic oscillatory disturbance of the motor system.”<sup>72</sup>

Given the current knowledge, the most credible explanation is that cognitive dysfunctions and mood disorders in ET patients could be the consequence of subclinical cerebellar syndrome associated with ET. The cognitive and mood disturbances are similar to those described in cerebellar cognitive affective syndrome (CCAS),<sup>90,91</sup> which has been described in patients suffering from acute and chronic cerebellar disorders and has been explained by anatomical and neuroimaging findings showing a relationship between the associative cortex (mainly prefrontal) and the cerebellar hemispheres.<sup>90,91</sup> Cognitive dysfunction in CCAS has been termed “cerebral dysmetria” because the cerebellum “is not only a motor control device, but it is also an essential component of the brain mechanisms for personality, mood, and intellect.”<sup>91</sup> This syndrome would explain the neuropsychological and emotional findings in ET patients.<sup>16,21,25,30,92</sup> In fact, “frontal lobe syndrome” in ET patients may be secondary to dysfunction of the loop between the DLPC and parietal cortex–thalamic–cerebellar cortex determined by cognitive posterior cerebellar dysfunction.<sup>93</sup> That is to say, the frontal lobe and the cerebellar hypothesis are in fact analogous.

Functional MRI makes it possible to explore cognitive dysfunctions due to neural network disturbances. With this technique, several studies showed enhanced responses of brain regions implicated in cognitive function (such as working memory) in patients with neurodegenerative disorders compared with healthy controls.<sup>94,95</sup> An Italian team investigated the neurophysiology of verbal working memory in ET patients<sup>61,96</sup> and demonstrated a variety of brain dysfunctions that included: “i) abnormally enhanced cerebellar response (crus I/lobule VI) during high-load working memory trials; ii) altered functional connectivity between crus I/lobule VI and the executive control circuit, as well as the default mode network.”<sup>61,96</sup> These findings corroborated, with complex experimental data, that the posterior cerebellar loop dysfunction (and its executive control circuit DLFL, parietal lobule, thalamus) is the origin of some cognitive deficits in ET patients and opens a new avenue in ET cognitive deficit investigation.

The explanation<sup>72</sup> that attributes cognitive and mood derangements of ET to the noxious effect on the nervous system of the “dynamic oscillatory disturbance of the motor system” seem speculative given the current data. Although it is possible that tremors may have some deleterious effects on some aspects of cognitive performance or on the mood or social embarrassment and quality of life of ET patients, there are no clear data demonstrating this rational hypothesis in the majority of cognitive deficits associated with ET.

### Need for further cognitive testing in ET" if appropriate

Many aspects of cognitive disorders in ET need further study, including non-verbal aspects of memory (implicit memory), visuo-spatial abilities (in general and face recognition), and particularly general cognitive capacities and their evolution in clinical and population-based investigations. Also, the physiological basis of cognitive deficits (functional neuroimaging and others) requires more investigation, as the Passamonti et al.<sup>61</sup> series demonstrated.

Prospective surveys would be useful in confirming the risk of progressive cognitive deterioration and dementia that has been described and would allow for medications that could stall or stop such deterioration to be tested.

### Conclusions

A new nosology for ET has emerged in the last decade. Currently, ET is a clinical syndrome rather than a monosymptomatic disorder,<sup>12</sup> in which there is mild cerebellar dysfunction (in general subclinical) and many non-motor manifestations (mainly cognitive<sup>16–25,30,41</sup>) and mood disorders (depression<sup>17,19,20,22,25,30,41</sup>) (Table 1). There is also evidence of pathology affected the cerebellum and its connections.<sup>41</sup> Collectively, recent studies suggest that ET is a structural disorder rather than a functional disorder with unknown pathology.

The cognitive ET deficits are diverse,<sup>16–25,30</sup> but they usually affect attention (verbal, auditory, and visual), working memory (phonological and spatial deficits), executive functions (divided attention, shifting motor plan, generating lists of words, and others), certain language functions, and several types of verbal memory apart from working memory (recognition, immediate, and delayed memory). These deficits

are consistent with CCAS described in cerebellar lesions<sup>90,91</sup> and are likely due to cortical–subcortical–cerebellar loop dysfunction.<sup>30,61</sup> Other cognitive deficits such as visuospatial dysfunctions, require more data.

Another interesting point is the increasing cognitive dysfunction in ET patients (mainly in elderly ET patients) shown in population-based surveys,<sup>25,28</sup> which may be partly responsible for the observed increased risk of mild cognitive cases and dementia.

Studies exploring cognitive disorders with new neurophysiological tests (such as functional neuroimaging), clinical studies, and prospective population-based surveys are needed to corroborate the ET cognitive findings of the last decade.

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