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

Félix Bermejo-Pareja & Verónica Puertas-Martín

1 Head of the Neurology Department, University Hospital “12 de Octubre”, Madrid, Spain, 2 Biomedical Research Network on Neurodegenerative Disorders (CIBERNED), Carlos III National Research Institute, Madrid, Spain, 3 Department of Biomedical Sciences (ANECA), Complutense University of Madrid, Spain, 4 Neurology Department, University Hospital “12 de Octubre”, Madrid, Spain

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

Citation: Bermejo-Pareja F, Puertas-Martín V. Cognitive features of essential tremor: a review of the clinical aspects and possible mechanistic underpinnings. Tremor Other Hyperkinet Mov 2012;2: http://tremorjournal.org/article/view/74

* To whom correspondence should be addressed. E-mail: fbermejop2004@yahoo.es

Editor: Elan D. Louis, Columbia University, United States of America

Received: October 18, 2011 Accepted: May 8, 2012 Published: September 14, 2012

Copyright: © 2012 Bermejo-Pareja et al. This is an open-access article distributed under the terms of the Creative Commons Attribution–Noncommercial–No Derivatives License, which permits the user to copy, distribute, and transmit the work provided that the original author(s) and source are credited; that no commercial use is made of the work; and that the work is not altered or transformed.

Funding: None.

Financial Disclosures: None.

Conflict of Interest: The authors report no conflict of interest.

Introduction

The classical series did not detect cognitive deficits in essential tremor (ET) patients, 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. 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. An analogous study was recently performed. That is to say, 20th-century clinical series and neurological reports 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. 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.

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. in 1999 without control cases. Later, several clinical series of psychometric evaluation in ET patients were described in patients to be treated with thalamic DBS. In recent years, several studies have described ET as a condition associated with mild cognitive deficits. The most common finding has been a decline in the areas of attention, executive functions, and memory. However, the extent to which these deficits are associated with overall cognitive impairment and the potential impact on the quality of life remain unknown. Further research is needed to better understand the cognitive profile of ET and its relationship with other neurological disorders.
essential tremor is not a monosymptomatic tremor disorder

In the last few years of the 20th century, the Movement Disorders Society13 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,31–40 mild (or very mild) cognitive impairments,16–30 and depression.8,17,22,25,29,41–45 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.46 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.46 In the last decade, Louis and colleagues41,47,48 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).47

| Table 1. Associated Disorders in Essential Tremor Patients |
|-----------------------------------------------------------|
| **Subtle Neurological Deficits**                          |
| Bradykinesia (mild)                                        |
| Cerebellar dysfunction                                    |
| abnormal eyeblink reflex conditioning                     |
| deficits in paced finger typing                           |
| dysfunction in hand–eye coordination and ocular movements |
| mirror movements                                           |
| mild dystarhria                                            |
| tandem gait ataxia                                        |
| Olfactory and hearing deficits                            |
| **Non-motor deficits**                                     |
| Mild cognitive deficits (Table 4)                         |
| Neuropsychiatric symptoms                                 |
| anxiety                                                   |
| depression                                                 |
| specific personality traits                                |
| Sleep disorders                                            |
| Decreased body mass index                                 |
| **Nervous system pathology**                               |
| Pathology of the cerebellum and its brainstem connections |
| **Association with neurological or neurodegenerative disorders** |
| 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 Rajput49 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.30 Other authors considered brainstem Lewy bodies as an incidental finding in old people and cerebellar abnormalities as secondary to “therapeutic” alcohol abuse,51 but ET brain...
cerebellar findings and brain weight are not consistent with chronic alcoholic brain pathology. The neuroimaging and neurophysiologic findings indicate a cerebellar dysfunction origin for ET. Two studies performed in the 1990s 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 (with some exceptions). 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) favors the hypothesis that ET may be a more heterogeneous disorder than was previously thought. Cases of benign tremulous parkinsonism, adult-onset dystonic tremor (AODT), in which the dystonia could appear many years after the tremor, and other rare tremors, including fragile X-associated tremor/ataxia syndrome (FXTAS), could mimic ET cases.

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. This issue might explain the absence of clear genetic abnormalities in a frequently dispersed 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 (with the exception of 16% of "psycho-neurosis" in an uncontrolled study). Disturbances in the premorbid ET personality described in 1990 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. 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. 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 in a patient who had been assessed on bilateral thalamic DBS during the "on" and "off" periods. Without stimulation, the patient suffered from declines on measures of verbal fluency and recall compared with active stimulation. 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 have cognitive deficits, but the specific type of cognitive abnormalities remained unknown.

Three studies on cognitive dysfunction in ET were published in 2001, and the publication by Gasparini et al. 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. 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 and clinical series from specialized clinics (Table 2) have confirmed psychometric abnormalities in ET patients (Table 3). Were these deficits a consequence of the tremor itself as has been maintained by several authors? In 2003, Fields et al. 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.

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. The survey analyzed the epidemiology of the main neurological disorders in elderly people, including ET. In the second (incidence) wave of this cohort, the whole participant population was invited to complete a brief psychometric test. The result of this study confirmed that mild ET cases suffered from the main psychometric abnormalities described in clinical series.

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.
number of ET patients (only 13–55 cases assessed), with the exceptions of the Tro¨ster series (without controls) 14,21 and the NEDICES series 25 (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.30 The association of frequent mild depression in clinical and population-based series has been postulated as a possible cause of cognitive ET deficits.72 In fact, depression, measured by clinical and psychometric scales, is, in general, mild. It is also a constant finding in ET series,8,17,22,25,29,41–45 probably has its own characteristics,43 and could be related to motor dysfunction and social stigma associated with tremor.45 However, it is likely that, it is also biologically determined; it is independent of the motor intensity and evolution,30,81,83 and it is described in cerebellar disorders without tremor or mild motor impairment.90,91

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.17,22,24 The Brief Test of Attention (auditory)21 and selective test of auditory and visual attention (Stroop test) were altered in several series.16,20,21 The Symbol Search22 and Trail Making Test (TMT) (series A, attention and time to complete;16,78 and series B, executive function16) were also disturbed, except in the Sahin et al. series.23 Complex attention and other related psychological functions were evaluated by the Stroop test,16,20,21,23 and Wisconsin Card Sorting Test (WCST).16,17,20,23 The majority of series observed disturbances in both evaluations.30

Other types of attention, such as visual attention, were evaluated in the Duane and Vermilion 19 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),16,21 and one report described impaired visual attention reaction times.39

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.17 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.17

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).19

Deficits in executive functions. Executive function, that is to say, the overall control and sequencing of multiple cognitive operations, is
| Authors          | Lombardi | Gasparini | Duane | Lacritz | Troster | Sahin | Higginson | Kim | Benito-León |
|------------------|----------|-----------|-------|---------|---------|-------|-----------|-----|-------------|
|                  | =        | ND        | ND    | ND      | ND      | ND    | ND        | ++  | ++          |
| Global cognitive function | ++        | ++        | =     | 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        | −/+2 | ND          |
| Logical memory | ND        | ND        | ND    | ND      | =       | ND    | ++        | ND  | ND          |
| Visual memory | ND        | ND        | +     | +       | ND      | =     | ++/−2     | =   | ND          |
| Verbal fluency | ++        | ++        | ++    | +       | ++      | ++    | +         | ++  | ++/−2       |
| Naming            | +         | ND        | ND    | =       | ++      | =     | ++        | +   |             |
| Visuoperception | =       | ND        | ND    | ++/−2   | ++      | ND    | ND        | +   |             |
| Visuoconstruction | =      | =         | =     | ++/−2   | ++      | ND    | ND        | ND  |             |
| Mood (depression) | +       | ND        | +     | +       | ND      | ND    | ++        | ++  | ++          |

1Modified from Bermejo-Pareja30 (Passamonti et al.61 is not included, see text)
2Similar tests are discordant
3See Lois et al.52
Reviewer’s test selection and test gradation: =, similar or superior to controls or standard measures; +, mild alteration (statistically significant); ++, clear alteration (p<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, HVLT, 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
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. 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. Verbal fluency tests such as the Letter-cued Word Fluency (FAS test, number of animals, or fruit during 1 minute), which is DLPF-dependent and the Ruff Figural Test Fluency were also affected. The Frontal Assessment Battery (FAB), specific for detecting frontal deficits, obtained statistically significant alterations in a recent series. The Matrix Reasoning (WAIS) was mildly abnormal in one study, but the Tower of London, Tower of Hanoi, and Clock Drawing Tests, which require executive and visuospatial abilities, were within normal ranges.

Table 4. Essential Tremor and Cognitive Deficits (population-based series)

| Psychological tests                          | ET Subjects | Controls | p-Value |
|----------------------------------------------|-------------|----------|---------|
| Global cognitive function                    |             |          |         |
| MMSE-37 (range 0–37)                         | 27.0 (6.7)  | 28.9 (5.9) | 0.001   |
| Attention/frontal executive function         |             |          |         |
| Trail Making Test A (errors)                 | 8.7 (11.0)  | 3.8 (7.6) | 0.001   |
| Trail Making Test A (time to complete)       | 91 (39.2%)  | 148 (21.3%) | 0.001   |
| >5 minutes                                   | 141 (60.8%) | 548 (78.7%) |         |
| 0 or <5 minutes                              |             |          |         |
| Verbal fluency                               |             |          |         |
| Verbal fluency (fruits)                      | 8.9 (3.9)   | 10.0 (3.5) | 0.001   |
| Memory                                       |             |          |         |
| 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) Cognitive functions; no statistically significant difference | | | |
| Verbal fluency                               |             |          |         |
| (animals)                                    | 12.6 (5.0)  | 12.9 (4.7) | 0.42    |
| Premorbid intelligence                       |             |          |         |
| Word accentuation test (score 0–30)          | 10.2 (10.3) | 11.4 (10.3) | 0.10    |

1Modified from Benito-León et al.25
2Number of ET cases detected
3Number of cognitively normal control cases
Abbreviations: ET, essential tremor; MMSE, Mini-Mental State Examination
### Table 5. Cognitive Deficits in ET: Summary

| General conclusion |
|--------------------|
| Cognitive deficits are mild (subclinical) and multiple. |

| Consistent deficits |
|--------------------|
| **(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) |

| Possible deficits |
|-------------------|
| Mental processing speed (several tests) |
| Visuospatial functions (facial recognition) |
| General cognitive capacity (elderly ET) |

| No deficit (or very dubious) |
|-----------------------------|
| Reasoning, abstract thinking, calculation |

| Not evaluated |
|---------------|
| 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 degrees in the various subscales). In an analogous test, a Spanish test that includes naming of pictures, immediate and delayed verbal memory, revealed mild memory deficits in a large number of ET patients in a population-based series. Also, the Hopkins Verbal Learning Test (HVLT) used in one study demonstrated that memory was impaired in ET versus controls.

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, but not in the large series by Trottier et al. (only 12–15% of ET patients were 1 SD below the normative group) or in the LaRoczy et al. investigation. The figural subscale was affected in another series.

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

With the exception of blink conditioning, implicit memory has not been assessed in ET patients. 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, but not in the large series by Trottier et al. (only 12–15% of ET patients were 1 SD below the normative group) or in the LaRoczy et al. investigation. The figural subscale was affected in another series.

Visual memory investigated with the Rey–Osterreith Complex Figure (ROF) test did not show statistically significant differences versus controls in two studies. In the Kim et al. investigation, only the ROF recognition subscale showed a statistical deficit, but the Faces (WMS) and Visual Reproduction subscales (WMS) were 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, but the results were more variable.

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, and the timed TMT Part A was affected in the population-based series, as was Symbol Search (mental processing speed), indicating a possible slowing of mental processing that is also described in PD patients. 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, whereas the third showed them to be within the normal range. The Hooper Visual Organization Test (HVOT) and Benton Line Orientation (BLO) were statistically abnormal in one study, but the HVOT was in the normal range in two other clinical series. This fact, coupled with variable data from block designs (WAIS) (normal in two and abnormal in one) and normal visual memory in two clinical series, give a picture of possible normality in visuospatial functions, with facial recognition as one exception.

General cognitive function was evaluated by intelligence quotient, Mini-Mental State Examination (MMSE), and Spanish verbal intelligence test. 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, and in a population-based survey. 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 risk of dementia, and association of dementia in this cohort suggested that cognition is affected in some ET patients. This was confirmed in a community-based study in New York. 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. These findings indicate that some ET cases could suffer from a progressive cognitive decline. 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.

Abstract thinking and reasoning are rarely investigated in ET patients. Several WAIS subscales were implemented in clinical series (block designs, picture completion, matrix reasoning, similarities, and vocabulary) with contradictory results (abnormal in the Higginson et al. series and normal in Lombardi et al.). Elementary calculation was evaluated in the Kim et al. 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. The abnormalities also seem generalized, affecting approximately 30–60% of ET cases (visual attention deficits affect more than 70% of ET cases). In the LaRoczy et al. 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. The results of the psychometric evaluation are quite similar in ET and PD patients. ET patients performed, in general, worse in tests of word fluency and attention and better in reasoning and calculation than PD patients.

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, population-based surveys, and in nursing home series).
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. These limitations motivated the criticisms by Deuschl and Elble, 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.

However, several series adjusted the presence of cognitive deficits for depression and sedative medication, and the incidence of cognitive deficits remained statistically significant. 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.

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 DLPF (thalamic–cerebellar loop), 2) a subclinical or unapparent clinical cerebellar syndrome, and 3) the noxious effect on the nervous system of the “dynamic oscillatory disturbance of the motor system.”

Given the current knowledge, the most credible explanation is that cognitive dysfunctions and mood disorders in ET patients could be the consequence of subcerebellar cerebellar syndrome associated with ET. The cognitive and mood disturbances are similar to those described in cerebellar cognitive affective syndrome (CCAS) 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. 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.” This syndrome would explain the neuropsychological and emotional findings in ET patients. In fact, “frontal lobe syndrome” in ET patients may be secondary to dysfunction of the loop between the DLPF and parietal cortex–thalamic-cerebellar cortex determined by cognitive posterior cerebellar dysfunction. 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. An Italian team investigated the neurophysiology of verbal working memory in ET patients 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.

The explanation 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), visuospatial 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. 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, in which there is mild cerebellar dysfunction (in general subclinical) and many non-motor manifestations (mainly cognitive and mood disorders) (Table 1). There is also evidence of pathology affected the cerebellum and its connections.

Collectively, recent studies suggest that ET is a structural disorder rather than a functional disorder with unknown pathology.

The cognitive ET deficits are diverse, 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\textsuperscript{90,91} and are likely due to cortical–subcortical–cerebellar loop dysfunction.\textsuperscript{30,61} 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,\textsuperscript{25,26} 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.

\section*{Acknowledgments}
We would like to thank Joe Healey, who reviewed the English version of the manuscript.

\section*{References*}
1. Larson T, Sjogren T. Essential tremor. A clinical and genetic population study. \textit{Acta Psychiatr Neurol Scand} 1960;36(Suppl 144):1–176.
2. Marshall J. Observations on essential tremor. \textit{J Neurol Neurosurg Psychiatry} 1962;65:122–125, \url{http://dx.doi.org/10.1136/jnnp.25.2.122}.
3. Crichtley E. Clinical manifestations of essential tremor. \textit{J Neurol Neurosurg Psychiatry} 1972;35:365–372, \url{http://dx.doi.org/10.1136/jnnp.35.3.365}.
4. Rajput AH, Offord KP, Beard CM, Kurland LT. Essential tremor in Rochester, Minnesota: A 45-year study. \textit{J Neurol Neurosurg Psychiatry} 1984;47:466–470, \url{http://dx.doi.org/10.1136/jnnp.47.5.466}.
5. Lou JS, Jankovic J. Essential tremor: Clinical correlates in 350 patients. \textit{Neurology} 1991;41:234–238, \url{http://dx.doi.org/10.1212/WNL.41.2_Part.1.234}.
6. Koller WC, Busenbark K, Miner K. The relationship of essential tremor to other movement disorders: report on 678 patients. Essential Tremor Study Group. \textit{Ann Neurol} 1994;35:717–723, \url{http://dx.doi.org/10.1002/ana.410350613}.
7. Poewe W, Karamat E, Kammers GW, Gerstenbrand F. The premorbid personality of patients with Parkinson's disease: a comparative study with healthy controls and patients with essential tremor. \textit{Adv Neurol} 1990;53:339–342.
8. Chatterjee A, Jurewicz EC, Applegate LM, Louis ED. Personality in essential tremor. \textit{J Neurol Neurosurg Psychiatry} 2004;75:958–961, \url{http://dx.doi.org/10.1136/jnnp.2004.037176}.
9. Adams RD, Victor M, eds. \textit{Principles of Neurology}, 5th edn. New York: McGraw-Hill, 1993;86–87.
10. Rowland RP, ed. \textit{Merritt's Textbook of Neurology}. Ninth Edition. Williams & Wilkins. Baltimore, 1993;712–713.
11. Dubois B, Pillon B. In: \textit{Parkinson's disease and movement disorders}. Jankovic J, Tolosa E, eds. New York: Lippincott Williams & Wilkins, 1998;837–838.
12. Singer C, Sanchez-Ramos J, Weiner WJ. Gait abnormality in essential tremor. \textit{Mov Disord} 1994;9:193–196, \url{http://dx.doi.org/10.1002/mds.870090212}.
13. Deuschl G, Bain P, Brin M. Consensus Statement of the Movement Disorder Society on Tremor. \textit{Mov Disord} 1998;13(Suppl. 3):2–23.
14. Tröster AI, Fields JA, Palhwa R, et al. Neuropsychological and quality of life outcome after thalamic stimulation for essential tremor. \textit{Neurology} 1999;53:1774–1780, \url{http://dx.doi.org/10.1212/WNL.53.8.1774}.
15. Lucas JA, Rippeth JD, Uitt RJ, Shuster EA, Wharen RE. Neuropsychological functioning in a patient with essential tremor with and without bilateral VIM stimulation. \textit{Brain Cogn} 2000;42:253–267, \url{http://dx.doi.org/10.1006/brcg.1999.1103}.
16. Gasparini M, Bonifati V, Fabrizio E, et al. Frontal lobe dysfunction in essential tremor: a preliminary study. \textit{J Neurol} 2001;248:399–402.
17. Lombardi WJ, Woolston DJ, Roberts JW, Gross RE. Cognitive deficits in patients with essential tremor. \textit{Neurology} 2001;57:785–790, \url{http://dx.doi.org/10.1212/WNL.57.5.785}.
18. Vermilion K, Stone A, Duan D. Cognition and affect in idiopathic essential tremor. \textit{Mov Disord} 2001;16(Suppl 1):S30.
19. Duan D, Vermilion KJ. Cognitive deficits in patients with essential tremor. \textit{Neurology} 2002;58:1706, \url{http://dx.doi.org/10.1212/WNL.58.11.1706}.
20. Lacritz LH, Dewey R Jr, Giller C, Cullum CM. Cognitive functioning in individuals with “benign” essential tremor. \textit{J Int Neuropsychol Soc} 2002;8:125–129.
21. Tröster AI, Woods SP, Fields JA. Neuropsychological deficits in essential tremor: an expression of cerebello-thalamo-cortical pathophysiology? \textit{Eur J Neurol} 2002;9:143–151.
22. Higginson CI, Wheeldon VL, Levine D, King DS, Pappas CT, Sigvardt KA. Cognitive deficits in essential tremor consistent with frontotubercolar dysfunction. \textit{J Clin Exp Neuropsychol} 2008;30:760–765, \url{http://dx.doi.org/10.1080/13803390701754738}.
23. Sahin HA, Terzi M, Uçak S, Yapici O, Basoglu T, Onar M. Frontal functions in young patients with essential tremor: a case comparison study. \textit{J Neuropsychiatry Clin Neurosci} 2006;18:64–72, \url{http://dx.doi.org/10.1176/appi.neuropsych.18.1.64}.
24. Kim JS, Song IU, Shim YS, et al. Cognitive impairment in essential tremor without dementia. \textit{J Clin Neurol} 2009;5:381–4.
25. Benito-León J, Louis ED, Bermejo-Pareja F. Neurological Disorders in Central Spain (NEDICES) Study Group. Population-based case-control study of cognitive function in essential tremor. \textit{Neurology} 2006;66:69–74, \url{http://dx.doi.org/10.1212/01.wnl.0000192393.05850.cc}.
26. Bermejo-Pareja F, Louis ED, Benito-León J. Neurological Disorders in Central Spain (NEDICES) Study Group. Risk of incident dementia in essential tremor: a population-based study. \textit{Mov Disord} 2007;22:1573–1580, \url{http://dx.doi.org/10.1002/mds.21553}.
27. Thawani SP, Schupf N, Louis ED. Essential tremor is associated with dementia: prospective population-based study in New York. \textit{Neurology} 2009;73:621–625, \url{http://dx.doi.org/10.1212/WNL.0b013e3181bb3891}.
28. Louis ED, Benito-León J, Vega-Quiroga S, Bermejo-Pareja F. Neurological Disorders in Central Spain (NEDICES) Study Group. Faster rate of cognitive decline in essential tremor cases than controls: a prospective study. \textit{Eur J Neurol} 2010;17:1291–1297.
29. Benito-León J, Louis ED, Mitchell AJ, Bermejo-Pareja F. Elderly-onset essential tremor and mild cognitive impairment: a population-based study (NEDICES). \textit{J Alzheim Dis} 2011;23:727–735.
30. Bermejo-Pareja F. Essential tremor—a neurodegenerative disorder associated with cognitive defects? Nat Rev Neurol 2011;7:273–382, http://dx.doi.org/10.1038/nrneurol.2011.44.
31. Montgomery EB, Baker KB, Lyons K, Koller WC. Motor initiation and execution in essential tremor and Parkinson’s disease. Mov Disord 2000;15:511–515, http://dx.doi.org/10.1002/1531-8257(200005)15:3<511::AID-MDS1014>3.0.CO;2-R.
32. Deuschl G, Wenzelburger R, Loffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction: clinical and kinematic analysis of intention tremor. Brain 2000;123:1568–1580, http://dx.doi.org/10.1093/brain/123.8.1568.
33. Koster B, Deuschl G, Lauk M, Timmer J, Guschlbauer B, Lucking CH. Essential tremor and cerebellar dysfunction: abnormal ballistic movements. J Neurol Neurosurg Psychiatry 2000;73:400–405, http://dx.doi.org/10.1136/jnnp.73.4.400.
34. Stolze H, Petersen G, Raethjen J, Wenzelburger R, Deuschl G. The gait disorder of advanced essential tremor. Brain 2001;124:2278–2286, http://dx.doi.org/10.1093/brain/124.11.2278.
35. Helmchen C, Hagemow A, Miesner J. Eye movement abnormalities in essential tremor may indicate cerebellar dysfunction. Brain 2003;126:1319–1332, http://dx.doi.org/10.1093/brain/awg132.
36. Duval C, Sadikot AF, Panisset M. Bradykinesia in patients with essential tremor. Brain Res 2006;1115:213–216, http://dx.doi.org/10.1016/j.brainres.2006.07.066.
37. Farkas Z, Szirmai I, Kamondi A. Impaired rhythm generation in essential tremor. Mov Disord 2006;21:1196–1199, http://dx.doi.org/10.1002/mds.20934.
38. Kronenburger M, Gerwig M, Brol B, Block F, Timmann D. Eyeblink conditioning is impaired in subjects with essential tremor. Brain 2007;130:1538–1551, http://dx.doi.org/10.1093/brain/awm081.
39. Jiménez-Jiménez FJ, Rubio I, Alonso-Navarro H, et al. Impairment of rapid repetitive finger movements and visual reaction time in patients with essential tremor. Eur J Neurol 2010;17:152–159.
40. Louis ED, Marder K, Jurewicz EC, Watner D, Levy G, Mejía-Santana H. Body mass index in essential tremor. Arch Neurol 2002;59:1273–1277, http://dx.doi.org/10.1001/archneur.59.8.1273.
41. Louis ED. Essential tremor. Handb Clin Neurol 2011;100:433–448, http://dx.doi.org/10.1016/B978-0-444-52014-2.00033-1.
42. Louis ED, Benito-León J, Bermejo-Pareja F. Neurological Disorders in Central Spain (NEDICES) Study Group. Self-reported depression and anti-de压ant medication use in essential tremor: cross-sectional and prospective analyses in a population-based study. Eur J Neurol 2007;14:1138–1140.
43. Li ZW, Xie MJ, Tian DS, et al. Characteristics of depressive symptoms in essential tremor. J Clin Neurosci 2011;18:52–56, http://dx.doi.org/10.1016/j.jocn.2010.05.021.
44. Chandra D, Pala PK, Reddy JY, Themararasu K, Yadav R, Shivashankar N. Non-motor features in essential tremor. Acta Neurol Scand 2012;125:332–337, http://dx.doi.org/10.1111/j.1600-0404.2011.01573.x.
45. Lorenz D, Poremba C, Papengut F, Schreiber S, Deuschl G. The psychosocial burden of essential tremor in an outpatient- and a community-based cohort. Eur J Neurol 2011;18:972–979.
46. Rajput AH, Rozdilsky B, Ang I, Rajput A. Clinicopathologic observations in essential tremor: report of six cases. Neurology 1991;41:1422–1424, http://dx.doi.org/10.1212/WNL.41.9.1422.
47. Louis ED, Faust PL, Vo'sattel JP, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain 2007;130:3297–3307, http://dx.doi.org/10.1093/brain/awm286.
48. Louis ED. Essential tremor: evolving clinicopathological concepts in an era of intensive post-mortem enquiry. Lancet Neurol 2010;9:613–622, http://dx.doi.org/10.1016/S1474-4422(10)70090-9.
49. Rajput AH, Rajput A. Significance of cerebellar Purkinje cell loss to pathogenesis of essential tremor. Parkinsonism Relat Disord 2011;17:410–412, http://dx.doi.org/10.1016/j.parkreldis.2011.05.008.
50. Louis ED, Faust PL, Vo'sattel JP. Purkinje cell loss is a characteristic of essential tremor. Parkinsonism Relat Disord 2011;17:406–409, http://dx.doi.org/10.1016/j.parkreldis.2011.05.004.
51. Quinn NP, Schneider SA, Schwingenshuh P, Bhatia KP. Tremor—some controversial aspects. Mov Disord 2011;26:18–23, http://dx.doi.org/10.1002/mds.23289.
52. Baker KG, Harding AJ, Halliday GM, Kril JJ, Harper CG. Neuronal loss in functional zones of the cerebellum of chronic alcoholics with and without Wernicke’s encephalopathy. Neuroscience 1999;91:429–438, http://dx.doi.org/10.1016/S0306-4522(98)00664-9.
53. Jenkins IH, Frackowiak RS. Functional studies of the human cerebellum with positron emission tomography. Rev Neurol (Paris) 1993;149:647–653.
54. Bucher SF, Seccos KC, Dodel RC, Reiser M, Oertel WH. Involuntary tremor of ET patients was associated with a significantly larger extent of activation in the cerebellar hemispheres. Ann Neurol 1997;41:32–40, http://dx.doi.org/10.1002/ana.410410108.
55. Louis ED, Shangdu DC, Chan S, Mao X, Jurewicz EC, Watner D. Metabolic abnormality in the cerebellum in patients with essential tremor: a proton magnetic resonance spectroscopic imaging study. Neurosci Lett 2002;333:17–20, http://dx.doi.org/10.1016/S0304-3902(02)00966-7.
56. Shin DH, Han BS, Kim HS, Lee PH. Diffusion tensor imaging in patients with essential tremor. Am J Neuroradiol 2009;29:151–153.
57. Benito-León J, Alvarez-Linera J, Hernández-Tamames JA, Alonso-Navarro H, Jiménez-Jiménez FJ, Louis ED. Brain structural changes in essential tremor: voxel-based morphometry at 3-Tesla. J Neurol Sci 2009;287:138–142, http://dx.doi.org/10.1016/j.jns.2009.08.037.
58. Cerasa A, Messori D, Nicoletti G, et al. Cerebellar atrophy in essential tremor using an automated segmentation method. Am J Neuroradiol 2009;30:1240–1243.
59. Nicoletti G, Manners D, Novellino F, et al. Diffusion tensor MRI changes in cerebellar structures of patients with familial essential tremor. Neurology 2010;74:988–994, http://dx.doi.org/10.1212/WNL.0b013e3181d5a460.
60. Klein JC, Lorenz B, Kang JS, et al. Diffusion tensor imaging of white matter involvement in essential tremor. Hum Brain Map 2011;32:896–904, http://dx.doi.org/10.1002/hbm.21077.
61. Passamonti I, Novellino F, Cerasa A, et al. Altered cortical-cerebellar circuits during verbal working memory in essential tremor. Brain 2011;134:2274–2286, http://dx.doi.org/10.1093/brain/awr164.
Bermejo-Pareja F, Puertas-Martín V. Cognitive Features of Essential Tremor.

62. Bagepally BS, Bhatt MD, Chandran V, et al. Decrease in cerebral and cerebellar gray matter in essential tremor: A voxel-based morphometric analysis under 3T MRI. J Neuroimaging 2012;22:275–278, http://dx.doi.org/10.1111/j.1552-6569.2011.00598.x.

63. Daniels C, Peller M, Wolf S, et al. Voxel-based morphometry shows no decreases in cerebellar gray matter volume in essential tremor. Neurology 2006;67:1452–1456, http://dx.doi.org/10.1212/01.wnl.0000240130.94408.99.

64. Martinelli P, Rizzo G, Manners D, et al. Diffusion-weighted imaging study of patients with essential tremor. Mov Disord 2007;22:1182–1185, http://dx.doi.org/10.1002/mds.21297.

65. Deng H, Gu S, Jankovic J. LINGO1 variants in essential tremor and Parkinson’s disease. Acta Neurol Scand 2012;125:1–7, http://dx.doi.org/10.1111/j.1600-0404.2011.01516.x.

66. Josephs KA, Matsumoto JY, Ahlskog JE. Benign tremulous parkinsonism. Arch Neurol 2006;63:354–357, http://dx.doi.org/10.1001/archneur.63.3.354.

67. Rivest J, Marsden CD. Trunk and head tremor as isolated manifestations of dystonia. Mov Disord 1990;5:60–63, http://dx.doi.org/10.1002/mds.870050115.

68. Schneider SA, Edwards MJ, Mir P, et al. Patients with adult-onset dystonic tremor resembling parkinsonian tremor have scans without evidence of dopaminergic deficit (SWEDDs). Mov Disord 2007;22:2210–2215, http://dx.doi.org/10.1002/mds.21658.

69. Leechey MA, Munhoz RP, Lang AE, et al. The fragile X premutation in sporadic cases of essential tremor. J Neurol Neurosurg Psychiatry 2008;21:28–33, http://dx.doi.org/10.1136/jnnp.2009.202838.

70. Louis ED, Benito-León J, Vega-Quiroga S, Bermejo-Pareja F & Neurological Disorders in Central Spain (NEDICES) Study Group. Cognitive and motor functional activity in non-demented community-dwelling essential tremor cases. J Neurol Neurosurg Psychiatry 2010;81:997–1001, http://dx.doi.org/10.1136/jnnp.2009.202838.

71. Cooper JA, Sagar HJ, Tidswell P, Jordan N. Slowed central processing in simple and go/no-go reaction time tasks in Parkinson’s disease. Brain 1994;117:517–512, http://dx.doi.org/10.1093/brain/117.3.517.

72. Berry EL, Nicolson RI, Foster JK, Behrmann M, Sagar HJ. Slowing of reaction time in Parkinson’s disease: the involvement of the frontal lobes. Neuropsychologia 1999;37:787–795, http://dx.doi.org/10.1016/S0028-3932(98)00137-7.

73. Del Ser T, Gonzalez-Montalvo JI, Martinez-Espinosa S, Delgado-Villalobos C, Bermejo F. Estimation of premorbid intelligence in Spanish people with the Word Accentuation Test and its application to the diagnosis of dementia. Brain Cogn 1997;33:343–356, http://dx.doi.org/10.1006/brcg.1997.0877.

74. Morales JM, Benito-León J, et al. Methods and demographic findings of the baseline survey of the NEDICES cohort: a door-to-door survey of neurological disorders in three communities from Central Spain. Public Health 2004;118:426–433, http://dx.doi.org/10.1016/j.puhe.2003.10.007.

75. Bermejo F, Gabriel R, Vega S, Morales JM, Rocca WA, Anderson DW; Neurological Disorders in Central Spain (NEDICES) Study Group. Problems and issues with door-to-door, two-phase surveys: an illustration from central Spain. Neuroepidemiology 2001;20:225–231, http://dx.doi.org/10.1159/000054794.

76. Benito-León J, Bermejo-Pareja F, Morales JM, Vega S, Molina JA. Prevalence of essential tremor in three elderly populations of central Spain. Mov Disord 2003;18:389–394, http://dx.doi.org/10.1002/mds.10576.

77. Benito-León J, Bermejo-Pareja F, Louis ED; Neurological Disorders in Central Spain (NEDICES) Study Group. Incidence of essential tremor in three elderly populations of central Spain. Neurology 2005;64:1721–1725, http://dx.doi.org/10.1212/01.WNL.0000161832.70374.01.

78. Bermejo-Pareja F, Benito-León J, Vega S, Medrano MJ, Roman GC; on behalf of the Neurological Disorders in Central Spain (NEDICES) Study Group. Incidence and subtypes of dementia in three elderly populations of central Spain. J Neurol Sci 2008;264:63–72, http://dx.doi.org/10.1016/j.jns.2007.07.021.

79. Nguyen HV, Nguyen V, Cordato D, Shen Q, Chan DK. Quality of life in a random sample of community dwelling older patients with essential tremor. Acta Neurol Scand 2007;116:289–292, http://dx.doi.org/10.1111/j.1600-0404.2007.00863.x.

80. Woods SC, Scott JC, Fields JA, Poquette A, Tröster AI. Executive dysfunction and neuropsychiatric symptoms predict lower health status in essential tremor. Cogn Behav Neurol 2008;21:28–33, http://dx.doi.org/10.1097/WNN.0b013e3181684414.

81. Frisina PG, Tse W, Hallig TD, Libow LS. The pattern of cognitive-functional decline in elderly essential tremor patients: an exploratory-comparative study with Parkinson’s and Alzheimer’s disease patients. J Am Med Dir Assoc 2009;10:238–242, http://dx.doi.org/10.1016/j.jamda.2008.10.013.

82. Louis ED. Functional correlates of lower cognitive test scores in essential tremor. Mov Disord 2010;25:481–485, http://dx.doi.org/10.1002/mds.22920.

83. Louis ED, Benito-León J, Vega-Quiroga S, Bermejo-Pareja F & Neurological Disorders in Central Spain (NEDICES) Study Group. Cognitive and motor functional activity in non-demented community-dwelling essential tremor cases. J Neurol Neurosurg Psychiatry 2010;81:997–1001, http://dx.doi.org/10.1136/jnnp.2009.202838.

84. Galvin JE. When a tremor is not just a tremor: cognitive and functional decline in essential tremor, a more complex disorder than we thought. J Am Med Dir Assoc 2009;10:218–220, http://dx.doi.org/10.1016/j.jamda.2009.02.005.

85. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998;121:561–79, http://dx.doi.org/10.1093/brain/121.4.561.
91. Schmahmann JD. Disorders of the cerebellum: Ataxia, dysmetria of thought, and the Cerebellar Cognitive Affective Syndrome. *J Neuropsychiatry Clin Neurosci* 2004;16:367–378, http://dx.doi.org/10.1176/appi.neuropsych.16.3.367.

92. Findley LJ. Expanding clinical dimensions of essential tremor. *Neurol Neurosurg Psychiatry* 2004;75:948–949, http://dx.doi.org/10.1136/jnnp.2004.041293.

93. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. *Neuroimage* 2009;44:489–501, http://dx.doi.org/10.1016/j.neuroimage.2008.08.039.

94. Desmond JE, Gabrieli JD, Wagner AD, Ginier BL, Glover GH. Lobular patterns of cerebellar activation in verbal working memory and finger tapping tasks as revealed by functional MRI. *J Neurosci* 1997;17:675–685.

95. Bookheimer SY, Ströijvs MA, Cohen MS, et al. Patterns of brain activation in people at risk for Alzheimer’s disease. *N Engl J Med* 2000;343:450–6.

96. Cerasa A, Passamonti L, Novellino F, et al. Fronto-parietal over-activation in patients with essential tremor during Stroop task. *Neuroreport* 2010;21:148–51, http://dx.doi.org/10.1097/WNR.0b013e32833b422c.