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Tremor and Other Hyperkinetic Movements

Articles

A Comparison Study of Cognitive and Neuropsychiatric Features of Essential Tremor and Parkinson's Disease

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Abstract

Background: Essential tremor (ET) and Parkinson's disease (PD) are two of the most common movement disorders. Leaving aside their motor features, these two conditions share several non-motor features, including cognitive dysfunction and personality changes. However, there are few data comparing the cognitive and personality profiles of ET with PD. Here we compare the cognitive and personality profiles of the two diseases.

Methods: Thirty-two consecutive non-demented ET patients (13 females and 19 males) (67.7 ± 9.8 years), 32 non-demented PD patients (13 females and 19 males) (67.7 ± 9.5 years), and 32 healthy matched controls (14 females and 18 males) (67.9 ± 10.1 years) underwent a neuropsychological test battery, including a global cognitive assessment and tests of attention, executive function, memory, language, and visuospatial function, as well as the Personality Assessment Inventory. Multivariable linear regression analyses were performed, adjusted for age, sex, years of education, medications that potentially affect cognitive function, number of medications, and the 17-item Hamilton Depression Rating Scale Total Score.

Results: Neuropsychological scores were similar in PD and ET patients, but patients with disease performed more poorly than control subjects in cognitive tasks such as attention, executive function, memory, and naming.

Discussion: ET and PD exhibited similar deficits in specific aspects of neuropsychological functioning, particularly those thought to rely on the integrity of the prefrontal cortex, and this suggests involvement of frontocerebellar circuits. These findings further challenge the traditional view of ET as a benign and monosymptomatic disorder.

Keywords: Essential tremor, Parkinson's disease, neuropsychology, neurobehavioral manifestations, cognitive impairment, movement disorders, cerebellum, thalamus

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Introduction

Essential tremor (ET) is one of the most common neurological diseases.[1,2] Traditionally, it has been considered a benign and monosymptomatic disorder characterized primarily by kinetic tremor in the arms. However, an emerging view that is gaining wider support is that it may actually be a family of diseases unified by the presence of kinetic tremor, while also displaying etiological, pathologic, and clinical heterogeneity.[3–5] The biological mechanisms that underlie ET are not entirely clear, although there is evidence that indicates that it may be a neurodegenerative disease.[6]

In addition to motor manifestations, ET is also associated with a number of non-motor manifestations, including depressive symptoms,[7] changes in sleep patterns,[8] and hearing impairment.[9] Aside from the above non-motor features, a proportion of ET patients show mild cognitive deficits, mainly in attention and frontal executive function, verbal memory, and visuospatial processes, which might be explained by frontal cortical or frontal cortical–cerebellar pathway dysfunction.[10–14] Of interest is that these cognitive deficits in ET might not be static and appear to progress at a faster rate than those seen in normal older people.[13] Furthermore, patients with ET (especially late-onset ET) appear to have an increased prevalence of mild cognitive impairment and dementia[15,16] and have a higher risk of incident dementia.[17]

Cognitive dysfunction, even in the early stages, is one of the most common non-motor features of another common movement disorder, Parkinson's disease (PD).[18] In this neurodegenerative disease, cognitive dysfunction is thought to be attributed to dysfunction of the basal ganglia circuit (i.e., the striatal-thalamic-cortico loop) triggered by deficits in dopaminergic nigrostriatal neurons.[19] As reviewed in detail elsewhere,[20] several epidemiological studies have reported an elevated odds or elevated risk of PD in patients with ET. These epidemiological studies, which estimate measures of association, provide significant controlled, quantitative evidence that ET is associated with PD and, more specifically, that baseline ET seems to increase the risk of developing PD by a factor of four to five.[21–23]

Despite the links between these two conditions, there are a limited number of comparison studies of the cognitive profile of ET with PD.[24–30] Furthermore, these studies used small sample sizes and only two of them utilized a complete neuropsychological examination.[24,26] Further, only one study compared the personality features of both diseases.[31]

In the present study, our aim was to compare the cognitive and personality profiles of individuals with ET and PD, using a healthy control group for additional comparison.

Methods

All procedures were approved by the ethical standards committees on human experimentation at the University Hospital "12 de Octubre" (Madrid). Written (signed) informed consent was obtained from all enrollees.

Participants

ET and PD patients were consecutively recruited from October 2012 to July 2013 from the outpatient neurology clinics of the University Hospital "12 de Octubre" in Madrid, Spain. Two neurologists with expertise in movement disorders (J.P.R. and J.B.-L.) examined the patients and used the Fahn–Tolosa–Marin Tremor Rating Scale to assign a total tremor score tor the ET patients,[32] and the Unified Parkinson's Disease Rating Scale (motor section) for those with PD.[33] Diagnoses of ET and PD were assigned by these two neurologists using the Consensus Statement on Tremor by the Movement Disorder Society[34] and the UK PD Society Brain Bank Clinical Diagnostic Criteria,[35] respectively. Furthermore, all ET patients had a normal 123 I-labelled N-(3-fluoropropyl)-2ß-carbomethoxy-3ß-(4-iodophenyl)-nortropane single photon emission computed tomography scan. Patients with a history of stroke, epilepsy, or head injury were excluded. Furthermore, based on a detailed clinical mental status examination, we excluded patients with Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for dementia.[36] All ET and PD patients underwent a detailed videotaped neurological examination. Each videotape was reviewed by a senior neurologist specializing in movement disorders (E.D.L.) who re-assessed ET or PD diagnosis using the Consensus Statement on Tremor by the Movement Disorder Society,[34] and the UK PD Society Brain Bank Clinical Diagnostic Criteria,[35] respectively. The ET and PD patients were also followed at regular intervals (3, 6, or 12 months, based on clinical need) and their clinical assessment, described above, was repeated.

Healthy controls were recruited either from relatives or friends of the health professionals working at the University Hospital "12 de Octubre", Madrid (Spain), or among the relatives of patients who came to the neurological clinics for reasons other than ET or PD (e.g., headache, dizziness). None reported having a first-degree or second-degree relative with ET. Each control was examined by two neurologists (J.P.R .and J.B.-L.) to further rule out any neurological conditions.

Procedure

During recruitment, patients and controls were told that the purpose of the study was to complete a test battery to assess neuropsychological and personality status. After the study had been described to participants, informed consent to participate was obtained. Clinical characteristics were also obtained from review of records from their outpatient neurological care. All the neuropsychological and personality tests were performed on the same day by the same examiner (V.P.-M.).

All participants underwent a detailed neuropsychological assessment covering the domains of attention, executive function, verbal memory, visual memory, visuospatial ability, and language. These tests have previously been described.[37,38] They were selected in part to avoid the effects of any hand tremor because they made minimal demands on motor processes. Individual cognitive measures were grouped into several cognitive domains, as described below.[37,38]

Global cognitive performance was evaluated with the Spanish version of the Mini-Mental State Examination (MMSE) (higher scores indicate better cognitive performance).[39]

Attention and executive function were evaluated with a series of tests. First, participants underwent the Direct and Indirect Digit Span and the Coding-Digit Symbol subtests from the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) (higher scores indicate better cognitive performance).[40] In the first, the examinee is required to repeat three to nine digits forward (direct) and backward (indirect).[40] In the second, the numbers one to seven have to be paired with symbols on a key presented to the examinee.[40] Second, the Similarities subtest from the WAIS-III was also administered;[40] in this test, which examines concrete, functional, and abstract concept formation, 19 items require the examinee to describe how two given things are alike.[40] Higher scores indicate better cognitive performance.[40] The Trail-making Test is a measure of visuomotor coordination in which subjects must connect circles in one form (A) on the basis of a simple rule of consecutive numbers and in the second form (B) by alternating between numerical and alphabetical sequences.[41] For both forms, A and B, the time for completion is the primary index of performance. The score for this study was Trail B minus Trail A (lower scores indicate better cognitive performance). Third, the Stroop Color–Word Trial requires the participant to name the color of the ink in which a colored word is printed.[42] The task involves three test cards, one containing rows of colored rectangles, with the task being to name the colors as quickly as possible, one containing rows of color words (printed in black ink), with the task being to read the words as quickly as possible, and the third "interference" test consisting of rows of color words printed in ink colors incongruent with the word represented, with the task being to name the ink colors as quickly as possible.[42] The subject must ignore the word and name the color.[42] The score for this study was the interference effect (scores close to zero indicate better cognitive performance). Fourth, the Wisconsin Card Sorting Test, a test of "set-shifting," requires the examinee to discern the sort criterion of a set of cards based upon "correct" versus "incorrect" feedback given by the examiner.[43] The score for this study was the number of errors and perseverations (higher scores indicate worse performance).[43] Fifth, the Tower of London was administered, a well-known test used for the assessment of executive function specifically to detect deficits in planning.[44] The test consists of two boards with pegs and several beads with different colors.[44] The examiner uses the beads and the boards to present the examinee with problem-solving tasks.[44] For this study, we recorded the time required to execute the test.[44] Finally, the Frontal Assessment Battery (FAB), a brief tool designed to assess frontal lobe function, including conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy, was administered.[45]

To evaluate visuospatial ability, two tests were used. The first, the Benton Judgment of Line Orientation Test, is a standardized test of visuospatial skills, that measures a person's ability to match the angle and orientation of lines in space.[46] The second, the Hooper Visual Organization Test,[47] is an instrument that measures visual organizational skills, and consists of line drawing of simple objects that have been cut into pieces and rearranged, such as in a puzzle. The examinee's task is to name what the object would be if the pieces were put back together.[47] In both tests, higher scores indicate better cognitive function.[46,47]

To evaluate verbal memory, we used the Wechsler Memory Scale—Third Edition (WMS-III) Word List,[48] which included four learning trials of 12 unrelated words. World List 1 is derived from the sum of the four trials.[48] A second list is then presented once for immediate recall, following which the examinee is asked to again recall the first list.[48] Free recall and recognition (yes–no format) of the initial words are later assessed after a delay interval.[48] Higher scores indicate better cognitive function.[48]

To evaluate visual memory, we used the Brief Visuospatial Memory Test—Revised.[49] In three learning trials, the examinee views the stimulus page and is asked to draw as many of the figures as possible.[49] A delayed recall trial is administered after a 25-minute delay.[49] Last, there is a recognition trial, in which the examinee is asked to identify which of 12 figures were included among the original ones.[49] Higher scores indicate better cognitive function.[49]

Language was evaluated using the following tests. First, the Boston Naming Test,[50] which assesses the ability to name pictures of objects through spontaneous responses and the need for various types of cueing (lower scores indicate greater cognitive impairment). Second, participants were asked to name as many items as possible from a semantic category (animals) (semantic fluency) (lower scores indicate greater cognitive impairment).[51] Finally, the Controlled Oral Word Association Test, a test that measures phonetic fluency, was administered.[52] Participants are provided with three letters of the alphabet (F, A, and S), one letter at a time, and instructed to say as many words as possible that begin with this letter in a 60-second interval.[52] Higher scores indicate better cognitive performance.[52]

Depression was assessed with the 17-item version of the Hamilton Depression Rating Scale.[53] Higher scores reflect more depressive symptoms.[53] The 17-item Hamilton Depression Rating Scale also includes six items that assess anxiety features: psychic anxiety (Item 10), somatic anxiety (Item 11), gastrointestinal somatic symptoms (Item 12), general somatic symptoms (Item 13), hypochondriasis (Item 15), and insight (Item 17).[53]

Psychopathology and personality symptoms were assessed using the Personality Assessment Inventory (PAI), a widely used multidimensional 344-item self-report measure.[54] The PAI consists of 22 non-overlapping scales: four validity scales, 11 clinical scales, five treatment consideration scales, and two interpersonal scales. For the present study, only clinical scales (somatic concerns, anxiety, anxiety-related disorders, depression, mania, paranoia, schizophrenia, borderline features, antisocial features, alcohol problems, and drug problems) were used, and higher scores reflect greater psychopathology.

All patients were using medications for their disease. Specifically, propranolol and/or primidone for ET, and levodopa, rasagiline and/or dopamine agonists for PD. The neuropsychological examination was performed while taking their regular treatment.

Table 1. **Comparison of Demographic and Clinical Characteristics of Essential Tremor and Parkinson's Disease Patients vs. Healthy Controls**

	Essential Tremor Patients (N=32)	Parkinson's Disease Patients (N=32)	Healthy Controls (N=32)	p
Sex (women)	13 (40.6%)	13 (40.6%)	14 (43.7%)	0.959
Age in years	67.7 (69.0)±9.8 (range 40–80)	67.7 (68.5)±9.5 (range 44–80)	67.9 (70.0)±10.1 (range 41–83)	0.994
Years of education	7.2 (8.0)±3.5 (range 1–15)	7.6 (6.5)±4.4 (range 2–19)	8.9 (8.5)±3.7 (range 2–15)	0.189
Number of medications	4.7 (4.5)±3.5 (range 0–14)	5.6 (5.0)±3.0 (range 2–14)	2.4 (1.0)±2.6 (range 0–9)	<0.001
Taking a medication that potentially affects cognition function	10 (31.2%)	11 (34.4%)	6 (18.7%)	0.339
Disease severity[1]	32.2 (31.0)±14.1 (range 6–60)	14.9 (15.0)±6.8 (range 5–31)		
Disease duration in years	20.1 (17.5)±14.8 (range 4–66)	6.4 (5.5)±3.3 (range 1–14)		<0.001

Values are expressed as mean (median)±standard deviation, and range. Analysis of variance test or the Student t test were used for comparison of continuous data where appropriate, and the chi-square test for proportions.
[1]Fahn–Tolosa–Marìn Tremor Rating Scale for essential tremor and the Unified Parkinson's Disease Rating Scale (motor section) for Parkinson's disease.

Statistical analyses

Statistical analyses were performed in SPSS Version 21.0 (IBM Corp., NY, USA). All tests were two sided, and significance was accepted at the 5% level (alpha=0.05). Comparison of means of groups was made by an analyses of variance (ANOVA) test for normally distributed data and by a Kruskal–Wallis test for non-normally distributed data, where appropriate. The chi-square test was used to analyze differences in categorical variables.

To assess differences between ET and PD patients, ET and control subjects, and PD and control subjects in neuropsychological and personality scores while adjusting for age, sex, years of education, medications that potentially affect cognition function (i.e., anxiolytics, stimulants, antipsychotics, antidepressants, antihistamines, antihypertensives, or antiepileptics drugs), total number of medications, and 17-item Hamilton Depression Rating Scale Total Score, linear regression analyses were performed in which the outcome variables were each one of the neuropsychological and PAI scores.

All test scores were normally distributed (Kolmorov–Smirnov test, for all items, $p<0.05$), except for the MMSE, FAB, Direct and Indirect Digit Span Tests, delayed recognition of the WMS-III Word List, delayed recall and delayed recognition of the Brief Visuospatial Memory Test—Revised, and perseverations of the Wisconsin Card Sorting Test. For these latter tests that were not normally distributed, a logarithmic transformation was performed prior to linear regression analyses.

Results

Ninety-six participants were evaluated, with 32 in each of the three groups. Clinical details of the patients and healthy controls are provided in Table 1. The 32 ET patients (13 females and 19 males) were compared with 32 PD patients (13 females and 19 males) and 32 healthy controls (14 females and 18 males). The three groups did not differ to a significant degree in terms of age, sex, years of education or intake of drugs with effect on cognition (Table 1). However, there were differences in disease duration (in years), as ET patients had had their disease for more time (13.7 years more) than PD patients. Further, both ET and PD patients were taking more medications than the control group. Our PD sample comprised mild cases: 100% patients had a Hoehn–Yahr stage of I or II.

The raw mean scores on the different neuropsychological test are detailed in Table 2. Significant differences between ET and PD were not found in any test. In some tests, scores of ET patients were slightly better than scores of PD patients, especially in the Trail-making Test (Trail B minus Trail A), the Boston Naming Test, the Judgment of Line Orientation Test, and the Hooper Visual Organization Test. PD patients performed marginally better than the ET group in Similarities, Wisconsin Card Sorting Test (perseverations), and phonetic fluency. In other tests, the scores were similar in both groups.

Table 2. **Comparison of Cognitive and Neuropsychiatric Domains of Patients vs. Healthy Controls**

	Essential tremor patients (N=32)	Parkinson's disease patients (N = 32)	Healthy controls (N = 32)	p	Bonferroni test
Global cognitive performance					
Mini-Mental State Examination	**33.0 (33.0)±1.8**	**32.4 (32.0)±2.0**	**34.2 (35.0)±1.2**	**<0.001**[1]	ET<HC; PD<HC
Executive function and Attention					
Direct Digit Span subtest from the WAIS-III	5.2 (5.0)±1.2	5.2 (5.0)±1.2	5.7 (6.0)±1.2	0.293[1]	Not significant
Indirect Digit Span subtest from the WAIS-III	**3.6 (3.5)±1.1**	**3.6 (4.0)±1.2**	**4.4 (4.5)±1.0**	**0.004**[1]	ET<HC; PD<HC
Coding-Digit Symbol subtest from the WAIS-III	**29.2 (25.5)±14.9**	**30.2 (27.5)±17.2**	**46.8 (46.0)±16.2**	**<0.001**	ET<HC; PD<HC
Similarities subtest from the WAIS-III	**12.4 (12.0)±5.7**	**13.7 (11.5)±7.0**	**17.7 (18.0)±5.4**	**0.002**	ET<HC; PD<HC
Trail-making Test, B – A	**147.9 (137.0)±101.6**	**178.3 (144.5)±152.4**	**78.1 (60.5)±71.8**	**0.004**	EP<HC
Stroop Color–Word Trial (interference effects)	-3.3 (-3.4)±6.8	-4.3 (4.2)±8.3	-1.7 (-2.5)±7.5	0.401	Not significant
Wisconsin Card Sorting Test (errors)	60.6 (63.0)±26.2	60.8 (65.0)±22.3	59.1 (62.5)±24.6	0.954	Not significant
Wisconsin Card Sorting Test (perseverations)	47.4 (31.0)±39.4	40.4 (35.0)±28.4	37.2 (32.0)±26.5	0.902[1]	Not significant
Tower of London (time of execution in seconds)	454.5 (415.0)±223.6	477.7 (456.0)±268.4	357.0 (317.0)±151.0	0.072	Not significant
Frontal Assessment Battery	**15.4 (16.0)±2.0**	**15.3 (16.0)±2.1**	**17.2 (17.0)±0.7**	**<0.001**[1]	ET<HC; PD<HC
Visuospatial ability					
Benton Judgment of Line Orientation Test	9.6 (10.5)±3.1	8.3 (8.0)±3.6	10.1 (10.0)±2.7	0.072	Not significant
Hooper Visual Organization Test	**33.0 (33.5)±8.4**	**28.4 (28.5)±11.8**	**36.5 (36.0)±9.0**	**0.007**	PD<HC
Verbal memory					
WMS-III Word List					
Learning	25.3 (26.0)±5.9	24.5 (24.0)±7.3	28.0 (27.5)±5.5	0.071	Not significant
Immediate recall	**5.1 (5.0)±2.3**	**5.6 (5.0)±2.3**	**6.5 (6.0)±1.9**	**0.047**	ET<HC
Delayed recall	**4.6 (4.5)±2.1**	**4.9 (4.0)±2.2**	**6.1 (6.0)±2.3**	**0.020**	ET<HC
Delayed recognition	**20.6 (21.0)±2.0**	**21.2 (21.5)±2.2**	**22.1 (22.0)±1.4**	**0.008**[1]	ET<HC
Visual memory					
Brief Visuospatial Memory Test—Revised					
Learning trials	**19.5 (18.0)±8.7**	**20.2 (19.0)±7.9**	**27.9 (27.5)±5.3**	**<0.001**	ET<HC; PD<HC
Delayed recall trial	**7.3 (8.0)±3.4**	**7.4 (7.0)±3.4**	**10.3 (10.5)±1.6**	**<0.001**[1]	ET<HC; PD<HC
Recognition trial	**11.4 (12.0)±0.9**	**11.2 (12.0)±1.1**	**11.8 (12.0)±0.5**	**0.025**[1]	PD<HC
Language					
Boston Naming Test	**44.6 (45.5)±10.0**	**43.1 (46.0)±11.7**	**52.1 (53.5) 5.4**	**<0.001**	ET<HC; PD<HC
Total number of animals as possible in one minute	17.7 (15.0)±8.0	18.5 (17.0)±7.1	21.2 (21.0)±6.0	0.128	Not significant
Controlled Oral Word Association Test	**23.6 (19.5)±13.1**	**26.7 (23.0)±17.2**	**37.6 (40.5)±12.8**	**<0.001**	ET<HC; PD<HC
Depressive symptoms					
17-item Hamilton Depression Rating Scale total score	6.4 (7.0)±4.5	5.5 (6.0)±4.16	5.0 (4.0)±5.0	0.736	Not significant

Table 2. Continued

	Essential tremor patients (N=32)	Parkinson's disease patients (N = 32)	Healthy controls (N = 32)	p	Bonferroni test
Personality and Psychopathology					
Personality Assessment Inventory					
Somatic concerns	**13.0 (12.0)±7.3**	**12.0 (11.0)±6.3**	**7.6 (6.0)±5.1**	**0.003**	ET>HC; PD>HC
Anxiety	**11.0 (10.0)±6.9**	**8.2 (7.0)±4.9**	**6.0 (5.0)±5.3**	**0.005**	ET>HC
Anxiety related disorders	**14.1 (13.0)±6.3**	**10.5 (10.0)±5.4**	**10.4 (10.0)±5.7**	**0.025**	Not significant
Depression	**10.6 (8.0)±6.8**	**9.2 (8.0)±5.0**	**5.6 (5.0)±4.5**	**0.003**	ET>HC; PD>HC
Mania	8.3 (8.0)±5.5	6.2 (5.0)±4.7	6.5 (6.0)±4.2	0.207	Not significant
Paranoia	10.5 (9.0)±4.4	8.7 (8.0)±4.6	8.9 (9.0)±4.3	0.218	Not significant
Schizophrenia	**7.5 (7.0)±5.9**	**4.6 (4.0)±3.9**	**4.9 (4.0)±3.5**	**0.029**	Not significant
Borderline features	**8.6 (7.0)±5.4**	**5.3 (4.0)±4.0**	**6.3 (7.0)±3.9**	**0.018**	ET>PD
Antisocial features	3.2 (3.0)±2.7	2.7 (2.0)±3.0	1.9 (2.0)±1.6	0.150	Not significant
Alcohol problems	0.6 (0.0)±1.4	0.2 (0.0)±0.7	0.2 (0.0)±0.6	0.140	Not significant
Drug problems	0.2 (0.0)±0.6	0.1 (0.0)±0.5	0.4 (0.0)±1.0	0.199	Not significant

Abbreviations: ET, Essential Tremor; HC, Healthy Controls; PD, Parkinson's Disease; WAIS-III, Wechsler Adult Intelligence Scale—Third Edition; WMS-III, Wechsler Memory Scale—Third Edition.
Significant values are in bold font.
Mean (median)±standard deviation is reported.
Analysis of variance test or [1]Kruskal–Wallis U test.

The performance of the ET group was worse than the control group for most neuropsychological tests. These differences were significant (ANOVA) for several tests: the MMSE, Coding-Digit Symbol subtest from the WAIS-III, Indirect Digit Span subtest from the WAIS-III, verbal memory (immediate recall, delayed recall, and delayed recognition), visual memory (learning trials and delayed recall trial), verbal fluency, Boston Naming Test, FAB, and Similarities subtest from the WAIS-III. In addition, the performance of the PD group was worse than the control group for most neuropsychological tests. These differences were significant (ANOVA) for several tests: MMSE, Trail-making Test (Trail B minus Trail A), Coding-Digit Symbol subtest from the WAIS-III, Indirect Digit Span subtest from the WAIS-III, FAB, Hooper Visual Organization Test, visual memory (learning trials, delayed recall trial, and recognition trial), verbal fluency, Boston Naming test, and Similarities subtest from the WAIS-III.

In the linear regression analyses that were adjusted for age in years, sex, years of education, medications that potentially affect cognition, number of medications, and 17-item Hamilton Depression Rating Scale total score, the results were similar to that of the ANOVA (Table 3). The ET group did not differ from the PD group, and scored slightly worse than the healthy control group in the FAB, Trail-making Test (Trail B minus A), Coding-Digit Symbol subtest from the WAIS-III, verbal memory (immediate and delayed recall, and delayed recognition), visual memory (learning trials and delayed recall trial), verbal fluency, Boston Naming Test, and Similarities subtest from the WAIS-III. The PD group performed more poorly than healthy controls in the MMSE, FAB, Trail-making Test (Trail B minus Trail A), Coding-Digit Symbol subtest from the WAIS-III, Hooper Visual Organization Test, visual memory (learning trials, delayed recall trial, and recognition trial), Boston Naming Test, and Tower of London (time of execution).

In the PAI, we observed differences in the ANOVA tests between the ET and the control group in somatic concerns, anxiety, and depression, where the ET group had higher scores (i.e., greater psychopathology) (Table 2). The last two domains remained different in regression models (Table 3). There were also differences between PD patients and the control group in somatic concerns and depression, but these differences were not observed in the regression analyses, except for schizophrenia, borderline features, and drug problems. When we compared the two diseases, there were differences in borderline features, both in the ANOVA and the regression analyses. In addition, there were differences between both diseases in anxiety-related disorders and schizophrenia in the regression analyses.

We recognize that we entered many variables into the regression models; however, our rationale was that many of these are classic

Table 3. **Linear Regression Analyses Using Each Neuropsychological Test Score and the Personality Assessment Inventory as the Outcome Variable in Separate Adjusted Models[1]**

	Essential Tremor vs. Healthy Controls		Essential Tremor vs. Parkinson's Disease		Parkinson's disease vs. healthy controls	
	β	p	*β*	p	*β*	p
Global cognitive performance						
Mini-Mental State Examination	0.221	0.097	–0.119	0.281	**0.367**	**0.004**
Executive function and attention						
Direct Digit Span subtest from the WAIS-III	0.012	0.929	–0.120	0.251	0.063	0.638
Indirect Digit Span subtest from the WAIS-III	0.216	0.086	–0.058	0.618	0.179	0.164
Coding-Digit Symbol subtest from the WAIS-III	**0.370**	**<0.001**	0.018	0.831	**0.343**	**<0.001**
Similarities subtest from the WAIS-III	**0.285**	**0.013**	0.029	0.734	0.208	0.054
Trail-making Test, B – A	**–0.323**	**0.017**	0.171	0.195	**–0.417**	**0.002**
Stroop Color–Word Trial (interference effects)	0.118	0.422	–0.108	0.390	0.258	0.068
Wisconsin Card Sorting Test (errors)	0.108	0.389	0.050	0.690	0.049	0.697
Wisconsin Card Sorting Test (perseverations)	0.103	0.440	0.055	0.683	–0.018	0.891
Tower of London (time of execution in seconds)	–0.180	0.137	0.079	0.519	**–0.266**	**0.043**
Frontal Assessment Battery	**0.318**	**0.011**	–0.033	0.789	**0.391**	**0.003**
Visuospatial ability						
Benton Judgment of Line Orientation Test	0.092	0.453	–0.216	0.063	0.187	0.176
Hooper Visual Organization Test	0.183	0.157	–0.193	0.114	**0.366**	**0.002**
Verbal memory						
WMS-III Word List						
Learning	0.170	0.177	–0.079	0.472	0.176	0.154
Immediate recall	**0.265**	**0.044**	0.135	0.247	0.038	0.783
Delayed recall	**0.279**	**0.026**	0.065	0.576	0.174	0.187
Delayed recognition	**0.312**	**0.013**	0.150	0.293	0.221	0.128
Visual memory						
Brief Visuospatial Memory Test-Revised						
Learning trials	**0.388**	**0.002**	0.002	0.983	**0.468**	**<0.001**
Delayed recall trial	**0.380**	**0.003**	0.002	0.989	**0.430**	**<0.001**
Recognition trial	0.186	0.198	–0.208	0.123	**0.318**	**0.018**
Language						
Boston Naming Test	**0.297**	**0.013**	–0.132	0.222	**0.376**	**0.003**
Category-cued Word Fluency	0.079	0.534	0.029	0.780	0.116	0.336

Table 3. Continued

	Essential Tremor vs. Healthy Controls		Essential Tremor vs. Parkinson's Disease		Parkinson's disease vs. healthy controls	
	β	p	*β*	p	*β*	p
Controlled Oral Word Association Test	**0.270**	**0.019**	0.070	0.479	0.166	0.174
Personality and Psychopathology						
Personality Assessment Inventory						
Somatic concerns	–0.223	0.093	–0.154	0.200	–0.051	0.694
Anxiety	–0.230	**0.033**	–0.220	0.064	–0.022	0.874
Anxiety related disorders	–0.123	0.311	**–0.274**	**0.028**	0.209	0.154
Depression	–0.309	**0.003**	–0.134	0.186	–0.057	0.604
Mania	–0.069	0.636	–0.194	0.153	0.041	0.791
Paranoia	–0.114	0.413	–0.196	0.147	0.174	0.248
Schizophrenia	–0.068	0.591	**–0.256**	**0.026**	**0.296**	**0.039**
Borderline features	–0.073	0.559	**–0.341**	**0.008**	**0.284**	**0.049**
Antisocial features	–0.230	0.081	–0.086	0.516	–0.116	0.405
Alcohol problems	–0.120	0.421	–0.093	0.495	0.036	0.828
Drug problems	0.199	0.179	–0.082	0.578	**0.299**	**0.044**

Significant values are in bold font.
[1]Adjusted for age, sex, years of education, medications that potentially affect cognitive function, total number of medications, and 17-item Hamilton Depression Rating Scale total score.

variables that are generally used in research that evaluates cognition.[55,56] In a sensitivity analysis, we removed several of the variables (age, sex, and years of education) and the results were similar (data not shown).

Discussion

In this study we characterized the cognitive performance of three different groups: 32 ET patients, 32 PD patients, and 32 healthy controls. Our goal was to compare the cognitive profile of PD and ET using a healthy control group as a reference point. The importance of this effort relies on the fact that that the three groups had similar age, sex, and education. Moreover, previous studies on this topic have been conducted in small samples, allowing us to benchmark these results with our larger sample of individuals.

We observed that both the ET and the PD groups performed worse than the control group. These results are in agreement with other studies.[24–26,29] ET and PD had similar deficits in specific aspects of neuropsychological functioning, particularly those thought to rely on the integrity of the prefrontal cortex, which suggests involvement of frontocerebellar circuits,[57] characterized by worse performance in functions such as attention, executive function, memory, and naming. Other studies have also noted these similarities between ET and PD.[26,28] Lombardi et al.[24] studied 18 ET and 18 PD patients without dementia, and compared the results with normative data. The ET group showed a poorer performance only in verbal fluency tests and digit span, whereas the PD patients, in addition, had a significantly lower performance in visuospatial, memory, and attentional tasks.[24] The authors suggested a frontosubcortical impairment for these findings.[24] Gasparini et al.[25] reported data from a sample of 27 ET patients (15 familial cases and 12 cases with a family history of PD), 15 PD patients, and 15 healthy controls, all of them without dementia. The ET patients showed significant impairments both in attentional and conceptual thinking tasks, similar to those observed in the PD group.[25] The authors suggested the presence of frontal lobe dysfunction in ET.[25] Higginson et al.[26] studied 24 ET patients, 24 PD patients, and 21 healthy controls. The results indicated that the ET group performed significantly worse than controls across multiple cognitive domains, but performed remarkably similar to PD patients, consistent with frontosubcortical dysfunction. A more recent study by Benge et al.[30] validated an executive dysfunction scale in a sample of deep

brain stimulation candidates, including 15 PD patients and 11 ET patients. The PD group had a poorer performance than the ET in that scale and in the memory tests.[30]

In our study, PD patients performed more poorly than ET patients and the controls in tests measuring global cognition and frontal activities (i.e., FAB) and attentional, visuospatial, and denomination tasks. On the other hand, the ET group scored marginally worse than the PD group in memory, verbal fluency, and abstraction capacity. When we compared the ET patients with the control group, they performed less well in the same tasks as the PD group. However, in multivariate analyses adjusted for confounding effects of age, sex, years of education, number of medications, intake of drugs that may affect cognition, and 17-item Hamilton Depression Rating Scale Total Score, the results were similar between ET and PD patients. An unexpected result, in multivariate analyses, was that schizophrenia scores were higher in ET than PD. We do not have a biological explanation for this result. As this was one of many differences, and it was not reproducible in the ANOVA models after a Bonferroni correction (see Table 2), it could be a spurious association. This is furthermore supported by the observation that no prior studies have reported an association between ET and schizophrenia/psychosis and that there is no compelling biological/mechanistic basis to suspect a higher incidence of psychotic disorders in ET patients.

Our findings suggest a similar cognitive profile for PD and ET groups in the absence of dementia and, interestingly, an overlap in the affected domains. In our opinion, these results highlight the existing view that the PD and ET clinical picture exceeds motor features, even at an early stage, where cognitive effects can be observed.[14,18] Our PD sample included mostly mild cases (100% had a Hoehn–Yahr stage of I or II), reducing the possibility of cortical involvement, and the 5-year mean disease duration also minimized the chances of a misdiagnosis of dementia with Lewy bodies.

In PD, the cognitive features have been attributed to the dysfunction of the basal ganglia circuit (i.e., the striatal-thalamic-cortico loop).[19] Likewise, there is strong evidence that suggests a dysfunction of the cerebello-thalamo-cortical circuit in ET.[37,58] The thalamus is thought to be highly implicated in modulation of cognitive performance, representing a fundamental subcortical relay to the prefrontal cortex.[59] The connections with the frontal lobes could be impaired in both diseases and therefore explain the similar cognitive profile.[18,19]

The study was not without limitations. First, ET patients had a longer disease duration than PD patients. This suggests that cognitive impairment in PD might start before that in ET and that the cognitive decline could be slower in ET. Second, the sample size was relatively small. The literature, however, only includes studies with smaller sample sizes. Further, despite the small sample size, our sample was adequate to detect a number of robust differences between the patients and the healthy control group. Third, the patients in the current study may represent a selected group of ET or PD patients (i.e., patients seen in selected outpatient clinics), and hence our results may not necessarily be generalized to the entire ET or PD population. However, in Spain, healthcare is fully state-subsidized, and community-dwelling ET or PD patients are mostly seen by hospital-based and hospital-associated neurologists. This study also had several strengths. First, this is the first study that has assessed the cognitive and personality profile at the same time in ET and PD patients. Second, assessments were conducted prospectively in a standardized manner. Finally, the tests included are reported to be among the most sensitive neuropsychological measures to detect cognitive impairment in tremor disorders.

In conclusion, our results are important for the definition and characterization of the non-motor cognitive aspects of ET and PD. So far, this study represents one of the largest samples where both conditions were compared, hence being closer to the real cognitive performance of both populations. The possibility to adjust for known confounding covariates has also helped us to interpret these results. Interestingly, we confirmed that both entities exhibited poorer cognitive performance compared with healthy subjects, thus further challenging the old mono-symptomatic motor view of ET.

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