Cognitive and Neuropsychiatric Features of Orthostatic Tremor: A Case-Control Comparison

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Abstract. Introduction: Evidence suggests that the cerebellum could play a role in the pathophysiology of orthostatic tremor. The link between orthostatic tremor and the cerebellum is of interest, especially in light of the role the cerebellum plays in cognition, and it raises the possibility that orthostatic tremor patients could have cognitive deficits consistent with cerebellar dysfunction. Our aim was to examine whether orthostatic tremor patients had cognitive deficits and distinct personality profiles when compared with matched controls.

Methods: Sixteen consecutive orthostatic tremor patients (65.7±13.3 years) and 32 healthy matched controls underwent a neuropsychological battery and the Personality Assessment Inventory. In linear regression models, the dependent variable was each one of the neuropsychological test scores or the Personality Assessment Inventory subscales and the independent variable was orthostatic tremor vs. control.

Results: Adjusted for age in years, sex, years of education, comorbidity index, current smoker, and depressive symptoms, diagnosis (orthostatic tremor vs. healthy control) was associated with poor performance on tests of executive function, visuospatial ability, verbal memory, visual memory, and language tests, and on a number of the Personality Assessment Inventory subscales (somatic concerns, anxiety related disorders, depression, and antisocial features). Older-onset OT (>60 years) patients had poorer scores on cognitive and personality testing compared with their younger-onset OT counterparts.

Conclusion: Orthostatic tremor patients have 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.

Cognitive impairment and personality disturbances could be disease-associated nonmotor manifestations of orthostatic tremor.

INTRODUCTION

Orthostatic tremor (OT), also known as ‘shaky legs syndrome’,[1] is an enigmatic and rare condition characterized by unsteadiness while standing still, and relieved upon sitting down or walking; it is thought to arise from a central generator in the cerebellum or brainstem.[2, 3] OT may be a family of diseases, unified by the presence of regular, rapid lower limb tremor when standing, but further characterized by etiological and clinical heterogeneity.[3] OT may be idiopathic or secondary (symptomatic). Gerschlager et al.[4] suggested the subdivision of OT into two broad groups - those with “primary OT” with or without postural arm tremor, and those with “OT plus,” in whom there are additional associated movement disorders, mainly parkinsonism.

There is some evidence that suggests an important role of the cerebellum in the pathophysiology of OT. First, a small number of symptomatic OT cases have cerebellar atrophy.[5, 6] Second, one positron emission tomography study of four OT patients revealed bilateral activation of the cerebellar hemispheres as well as activation of the cerebellar vermis, thalamus, and lentiform nucleus.[7] Third, posturographic data from OT patients are indistinguishable from those seen in patients with cerebellar diseases.[8]

The link between OT and the cerebellum is of interest, especially in light of the role the cerebellum plays in cognition,[9] and it raises the possibility that OT patients could have cognitive deficits consistent with cerebellar dysfunction. However, detailed neuropsychological assessment in these patients has not previously been reported. In addition, there is considerable evidence from epidemiological and clinical studies that shows a consistent impact of other tremor disorders, such as essential tremor or Parkinson’s disease, on cognition

as well as other higher functions (e.g., personality)[10-12] Given these observations, we hypothesized that cognition and personality could be affected in OT. To investigate the possibility that OT patients have cognitive deficits and personality problems, we evaluated neuropsychological test performance, and psychopathology and personality symptoms in a consecutive cohort of OT patients, comparing their performance to a healthy control group.

METHODS

Participants

OT patients were consecutively recruited from December 2011 to May 2013 from the outpatient neurology clinics of the University Hospital “12 de Octubre” in Madrid (Spain), a public hospital, which covers an area of more than 400,000 inhabitants. Four neurologists with expertise in movement disorders (J.B.-L., J.P.R., M.M., and A.S.-F.), examined these patients, who were referred to the outpatient neurology clinics with a subjective feeling of unsteadiness when standing, which was absent while walking, seated or supine. The neurological examination comprised a general neurological examination and the motor portion of the Unified Parkinson’s Disease Rating Scale (m-UPDRS).[13] Mild parkinsonian signs were defined as present when any one of the following conditions was met: (1) two or more m-UPDRS[13] ratings = 1; or (2) one m-UPDRS[13] rating = 2; or (3) the m-UPDRS rest tremor rating = 1. Diagnoses of OT were assigned by the four neurologists using the Consensus Statement on Tremor by the Movement Disorder Society [14], that is, a suggestive clinical picture of OT (subjective feeling of unsteadiness while standing without problems when sitting and lying, and sparse clinical findings that are mostly limited to a

visible and occasionally only palpable fine amplitude rippling of the leg muscles when standing) that is confirmed by electromyogram (EMG) recordings (i.e., synchronized leg tremor present only on standing). A senior neuropsychologist (V.P.), specializing in cognitive problems associated with movement disorders, performed a mental status examination on each patient and control, applying DSM–IV criteria and excluding those persons who had dementia. Also excluded were those who could not complete the neuropsychological evaluations.

Of 21 eligible OT patients, five were excluded from the final cohort. One 92-year-old woman with OT was excluded because she could not complete the neuropsychological testing due to her advanced age; another 81 year-old woman with OT suddenly died just before neuropsychological testing; and two women (80 and 92 years) and one 66-year old man with OT refused to undergo the neuropsychological testing. No healthy control was excluded due to incomplete neuropsychological evaluation or refusal. No participants were excluded because of major acute comorbidities or dementia.

OT patients were 1:2 frequency-matched with healthy controls. Frequency-matching was based on age and years of education.

Healthy controls were relatives or friends of the health professionals working at the University Hospital “12 de Octubre” of Madrid (Spain) or relatives of patients who came to the neurological clinics for reasons other than OT (e.g., headache, dizziness). None reported having a first-degree or second-degree relative with OT or essential tremor. Each control was examined by two neurologists (J.P.R. and A.S.-F.), to further rule out any neurological conditions, and by a neuropsychologist, as noted above.

Procedure

During recruitment, patients and controls were told that the purpose of the study was to complete a testing battery to assess neuropsychological and personality status. After the study had been described to participants, informed consent to participate was obtained. Clinical characteristics were obtained from review of records from their outpatient neurological care. All of the neuropsychological and personality tests were performed on the same day by the same examiner (V.P.). All participants underwent a neuropsychological assessment of cognitive functioning, including attention and cognitive processing speed, executive function, visuospatial ability, verbal memory, visual memory, language, and mood (Table 1). The tests chosen for the battery attempted to make minimal demands on motor processes in order to avoid effects of any hand tremor.

To evaluate attention, participants underwent the Direct Digit Span and the Coding-Digit Symbol subtests from the Wechsler Adult Intelligence Scale - Third Edition (WAIS) (higher scores indicate better cognitive performance).[15] First, the examinee is required to repeat 3-9 digits forward (direct).[15] Second, the numbers 1-7 have to be paired with symbols on a key presented to the examinee.[15]

Executive function was evaluated with a series of tests. First, the Stroop Color–Word Trial is a test that requires participants to inhibit a natural response (reading a word) and replace it with another response (saying a color).[16] Participants completed 45-second word naming, color naming, and color–word naming trials of a computer-based Stroop task.[16] The score for this study was the number of correct responses in the color–word trial.[16] Second, 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.[17] The score for this study was the number of errors and perseverations (higher scores indicate worse performance).[17] Third, the Similarities subtest from the WAIS-III was administered;[15] in this test, which examines concrete, functional, and abstract concept formation, 19 items require the examinee to describe how two items are alike.[15] Higher scores indicate better cognitive performance.[15] Fourth, the Indirect Digit Span subtest from the WAIS-III was administered.[15] In this subtest that measures working memory, the examinee is required to repeat 2-9 digists backwards (indirect). Higher scores indicate better cognitive performance.[15] Fifth, the Controlled Oral Word Association Test (COWAT), a test that measures phonetic fluency, was administered.[18] Participants are provided three letters of the alphabet (F, A, and S), one letter at a time, and instructed to provide as many words as possible that begin with this letter in a 60-second interval.[18] Higher scores indicate better cognitive performance.[18] Sixth, the Tower of London was administered, a well-known test used for the assessment of executive function, specifically to detect deficits in planning.[19] The test consists of two boards with pegs and several beads with different colors.[19] The examiner uses the beads and the boards to present the examinee with problem-solving tasks.[19] For this study, we recorded the time required to execute the test.[19] Finally, the Frontal Assessment Battery, a brief tool, designed to assess frontal lobe functions, including conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy, was administered.[20]

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.[21] The second, the Hooper Visual Organization Test,[22] 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.[22] In both tests, higher scores indicate better cognitive functioning.[21, 22]

To evaluate verbal memory, we used the Wechsler Memory Scale-Third Edition (WMS-III) Word List,[23] which included four learning trials of 12 unrelated words. World List 1 is derived from the sum of the four trials.[23] A second list is then presented once for immediate recall, following which the examinee is asked to again recall the first list.[23] Free recall and recognition (yes-no format) of the initial words are later assessed after a delay interval.[23] Higher scores indicate better cognitive functioning.[23]

To evaluate visual memory, we used the Brief Visuospatial Memory Test-Revised.[24] In three learning trials, the examinee views the stimulus page and is asked to draw as many of the figures as possible.[24] A delayed recall trial is administered after a 25-minute delay.[24] Last, there is a recognition trial, in which the examinee is asked to identify which of 12 figures were included among the original ones.[24] Higher scores indicate better cognitive functioning.[24]

Language was evaluated using two tests. First, the Boston Naming Test,[25] 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, subjects were asked to name as many different animals as they could in 60 seconds (semantic fluency) (lower scores indicate

greater cognitive impairment).[26] Depressive symptoms were assessed with the 17-item version of the Hamilton Depression Rating Scale.[27] Higher scores reflect more depressive symptoms.[27]

Psychopathology and personality symptoms were assessed using the Personality Assessment Inventory (PAI), a widely used multidimensional 344-item self-report measure.[28] The PAI consists of 22 nonoverlapping scales: 4 validity scales, 11 clinical scales, 5 treatment consideration scales, and 2 interpersonal scales. For the present study, only clinical scales (somatic concerns, anxiety, anxiety related disorders, depression, mania, paranoia, schizophrenia, borderline features, antisocial features, alcohol-related problems, and drug-related problems) were used, and higher scores reflect greater psychopathology.

We also assessed the impact of neuropsychiatric disturbances on OT patients' health-related quality of life (HRQoL) by means of the Spanish version of EuroQol-5 dimension (EQ-5D), a standardised instrument developed by the EuroQol group, a consortium of investigators in Europe.[29] The EQ-5D was chosen as the generic HRQoL measure given its widespread use and its apparent applicability to other tremor disorders such as Parkinson's disease[30] and ET.[31] EQ-5D consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).[29] The EQ-5D descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[29] Each dimension has three levels (no problems, some problems, major problems) and together results in a numeric value that defines a health state. EQ-5D scores range between −0.594 and 1 (full health).[29] The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual

analogue scale with endpoints labelled ‘the best health you can imagine’ (100) and ‘the worst health you can imagine’ (0).[29]

According to a recently published comorbidity score developed in ambulatory care settings,[32] a comorbidity index was calculated. The presence of several items resulted in the assignment of more points than others, and the score ranged from 0 – 28 (i.e., all conditions present). [32]

All procedures were approved by the ethical standards committees on human experimentation at the University Hospitals “12 de Octubre” (Madrid) and “La Princesa” (Madrid). Written (signed) informed consent was obtained from all enrollees.

Statistically 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). Mean scores (age, years of education, age at onset, tremor duration, and neuropsychological and personality variables) were compared using two independent sample t-tests for continuous and normally distributed data, and Mann–Whitney U tests for non-normally distributed data, where appropriate. The $\chi 2$ test was used to analyze differences in several variables (sex and current smoker).

To assess differences between OT patients and controls in neuropsychological and personality scores while adjusting for age, sex, years of education, comorbidity index, current smoker, and depressive symptoms, linear

regression analyses were performed in which the outcome variables were each one of the neuropsychological and PAI scores. Using a one-sample Kolmogorov-Smirnov test, we tested whether neuropsychological and personality scores were normally distributed and, for several scores, a logarithmic transformation was performed prior to linear regression analyses.

RESULTS

Clinical details of the OT patients are provided in Tables 1 and 2. All 16 OT patients were right-handed and the mean age = 65.7 years (range 37 to 81). The mean age of onset was 56.8 years. There was a slight female preponderance (N = 12, 75%). All patients presented with unsteadiness that occurred within seconds of standing and was relieved by walking or sitting. The symptoms of unsteadiness coincided with the appearance of the tremor of the trunk and legs. On diagnosis, 9 (56.2%) patients presented with primary OT and 7 (43.7%) had additional neurological features (mild parkinsonian signs). Twelve (75%) patients reported a progressive disease course. Structural brain magnetic resonance imaging, or computed tomography imaging, was unremarkable in all OT patients; none had cerebellar atrophy. Routine blood and chemistry tests including thyroid function tests, serum protein electrophoresis, and vitamin B12 levels were also in the normal range in all patients. Before formal neuropsychological testing, all 16 OT patients underwent electromyographic analysis of their leg tremors. This revealed a synchronous 10- to 18-Hertz leg tremor that was present only on standing. No

patients were being treated with medication for OT (i.e., clonazepam, pramipexole, or barbiturates).

The 16 right-handed OT patients (12 women and 4 men) were compared with 32 right-handed healthy controls (19 women and 13 men). The 16 OT patients did not differ to a significant degree from the 32 controls in terms of age, sex, years of education, comorbidities, current smoking, and depressive symptoms (Table 1). The results of neuropsychological testing are shown in Table 1. In most domains, OT patients' cognitive performance was significantly worse than that of the healthy controls. These differences involved selected tests of executive function, visuospatial ability, verbal memory, visual memory, and language (Table 1). Further, OT patients exhibited an altered personality profile, with statistically higher mean scores for somatic concerns, anxiety related disorders, and depression, as well as borderline and antisocial features (Table 1).

Although OT patients and controls did not differ to a significant degree in terms of demographic and clinical features, if the sample size had been larger, several of these features could have differed significantly. Hence, we performed adjusted analyses to take any potential confounding into account. In linear regression analyses that adjusted for age in years, sex, years of education, comorbidity index, current smoker, and depressive symptoms, we found that diagnosis (OT vs. control) was associated with poor performance on most neuropsychological test scores, particularly on tests of attention, executive function, visuospatial ability, verbal memory, visual memory, and language, as well as with distinct personality profile (higher levels of somatic concerns, anxiety related disorders, depression, as well as antisocial features) (Table 3).

In additional analyses, we excluded OT-plus patients (N = 7) (i.e., those associated with mild parkinsonian signs on examination). The results were similar (Table 3). Finally, OT patients were stratified into younger onset (onset age ≤60 years, N = 8, current age = 57.1 ± 13.4 years) vs. older onset (onset age > 60 years, N = 8, current age = 74.4 ± 5.2 years) and, in linear regression analyses that adjusted for age in years, sex, years of education, comorbidity index, current smoker, and depressive symptoms, we found that OT diagnosis, and more so older onset OT, was associated with poor performance on many neuropsychological test scores (Table 3).

DISCUSSION

This study shows that OT patients seem to have cognitive deficits in widespread domains, including deficits in executive function, visuospatial ability, verbal memory, visual memory, and language. Further, OT patients scored higher (i.e., greater psychopathology) on several PAI subscales (somatic concerns, anxiety related disorders, depression, and antisocial features). These personality characteristics are suggestive of alterations of executive functioning (antisocial features) and affective dysfunction (anxiety related disorders and depression).

Of interest is that older-onset (>60 years) OT patients had poorer performance on neuropsychological test scores that those with younger-onset OT. Cognitive dysfunction in OT might therefore be influenced by the age at onset. In essential tremor as well, the association between older age of onset and cognitive impairment has been reported (i.e., in one study, essential tremor

patients with older age of onset are more likely to be cognitively impaired than are essential tremor patients with younger age of onset).[33]

The biological basis for these neuropsychiatric deficits in OT patients is not clear, but the circuitry involved could include the frontosubcortical pathways, which play a role in cognitive and affective processes.[34] Conversely, the constellation of cognitive and affective changes in OT patients shown here largely resembles Schmahmann's syndrome.[35] These authors argued that cognitive and affective changes may be related to a cerebellar disorder itself, particularly when the posterior lobe is involved, which led them to propose presence of this syndrome, characterized by the following features. First, disturbances of executive function (this includes deficient planning, set-shifting, abstract reasoning, working memory, and decreased verbal fluency); second, impaired spatial cognition; third, personality changes; and fourth, linguistic difficulties.[35] All these deficits have been attributed to the disruption of the neural circuits linking prefrontal, temporal, posterior parietal and limbic cortices with the cerebellum.[35]

The pathophysiology of OT is currently unknown. The observation that unilateral transcranial magnetic stimulation of the cortical leg area resets OT in both legs, whereas OT is not modified by any peripheral stimuli, supports the hypothesis of a unique supraspinal OT generator.[36] Classically, the tremor generator has been postulated to be located in the brainstem, since OT motor symptoms involve bilateral cranial structures, arms, trunk, and legs.[37] The circuitry involving in OT pathogenesis, however, may be complex, with feedback and feed forward modulation (i.e., involving several brain regions).[37] There is some research suggesting that the dopaminergic system may be involved in

OT.[3, 4] More specifically, an association with parkinsonism and treatment effects of L-dopa and dopamine agonists have been reported.[3, 4, 38] A study[38] using (123)I-FP-CIT ([(123)I]-2 beta-carbomethoxy-3beta-(-4-iodophenyl)-N-(3-fluoropropyl)-nortropane) as a dopamine transporter tracer showed a marked reduction in striatal tracer binding in 11 OT patients without parkinsonism. Finally, a positron emission tomography study demonstrated abnormal bilateral cerebellar and contralateral lentiform and thalamic activation in four OT patients.[7] Taken together, these findings suggest that, although the OT generator might be located in the brainstem, other brain regions such as the motor cortex, basal ganglia, and cerebellum may also be involved.

We hypothesize that cognitive and motor frontocerebellar circuits function abnormally in OT. It is worth noting how the observed OT-related neuropsychological deficits resemble those reported in the literature to occur after isolated cerebellar lesions. First, our patients experienced cognitive difficulties impacting executive functions (including working memory) and frontal lobe tasks and similarly, several reports of cerebellar patients have also noted impaired executive function.[39] For example, working memory, a cognitive process that can be considered an example of a test of executive function, has been consistently shown to strongly engage cerebellar circuits,[40] suggesting that the role of the cerebellum in working memory includes aspects of encoding, maintenance, and retrieval.[41] Second, the observed fluency deficits among OT patients also parallel those reported after cerebellar lesions.[35] Finally, given that the posterior parietal cortex receives afferent connections from cerebellum via the pons and thalamus,[42] the poor performance in visuospatial functions among OT patients may reflect the involvement of the cerebello-ponto-thalamo-

parietal pathways. On-going research in resting-state functional MRI and diffusion tensor imaging in OT will provide valuable new insights into the clinical nature of OT and its underlying pathophysiology.

The study was not without limitations. First, the sample size was relatively small. The OT literature, however, only includes studies with small sample sizes. One should keep in mind that OT is a very rare disease and hence it is rather difficult to recruit patients. Although there are no available epidemiological data, in the follow-up evaluation of the Neurological Disorders of Central Spain (NEDICES) study,[43] we detected only one patient with OT in a cohort of approximately 4,000 elderly subjects (data not published). Despite the small sample size, our sample was adequate to detect a number of robust differences between the two study groups. Second, the patients in the current study may represent a selected group of OT patients (i.e., patients seen in selected outpatient clinics), and hence it is questionable to what extent our results can be generalized to the entire OT population. However, in Spain, healthcare is fully state-subsidized, and community-dwelling OT patients are mostly seen by hospital-based and hospital-associated neurologists. Third, the recruited sample was quite heterogeneous, including primary OT cases and OT-plus cases. However, our aim was to examine whether OT patients in general had cognitive deficits when compared with matched controls. Further, after exclusion of OT-plus cases, the results remained similar. This study also had several strengths. First, this is the first study that has assessed the cognitive and personality profile of OT patients. Second, assessments were conducted prospectively in a standardized manner. Finally, the tests included are reported to be amongst the

most sensitive neuropsychological measures to detect cognitive impairment in other tremor disorders.[10, 11]

In conclusion, OT patients seem to have 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. We suggest that cognitive impairment and personality disturbances may be nonmotor manifestations of OT.

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Table 1: Comparison of demographic, clinical and neuropsychiatric domains of orthostatic tremor patients vs. healthy controls.

	Orthostatic tremor patients (N = 16)	**Healthy controls (N = 32)**	***p* value**
Age in years	65.7 (66.9) ± 13.3	67.8 (70.0) ± 11.1	0.564 [a]
Sex (female)	12 (75.0%)	19 (59.4%)	0.286
Education in years	7.8 (8.0) ± 4.7	8.6 (8.0) ± 3.3	0.505 [a]
Comorbidity index*	1.4 (0.0) ±1.8	1.0 (0.0) ± 2.2	0.104[b]
Current smoker	2 (12.5%)	1 (3.1%)	0.206
Depressive symptoms			
17-item Hamilton Depression Rating Scale total score[27]	8.1 (6.5) ± 6.9	5.8 (5.0) ± 5.2	0.205[a]
Age at onset, years	56.8 (60.5) ± 12.2	-	
Tremor duration, years	8.9 (6.8) ± 6.6	-	
EuroQol-5D index score	0.7 (0.7) ± 0.2	-	
EuroQol visual analogue scale	66.6 (77.5) ± 25.0		
Cognitive domains			
Attention			
Direct Digit Span subtest from the WAIS-III[15]	5.2 (5.0) ± 1.4	5.6 (6.0) ± 1.3	0.245[a]
Coding-Digit Symbol subtest from the WAIS-III[15]	35.3 (21.0) ± 30.4	45.6 (45.0) ± 17.1	0.252[a]
Executive function			
Stroop Color–Word Trial[16]	23.3 (19.5) ± 13.2	30.0 (31.5) ± 10.6	0.079[a]
Wisconsin Card Sorting Test[17]			
Perseverations	32.0 (24.0) ± 27.9	38.0 (32.0) ± 26.3	0.481[a]
Non-perseverative errors	67.6 (69.0) ± 24.8	59.2 (59.5) ± 23.7	0.269[a]
Similarities subtest from the WAIS-III[15]	**10.7 (9.0) ± 5.0**	**17.3 (17.0) ± 5.4**	**0.0001[a]**
Indirect Digit Span subtest from the WAIS-III [15]	**3.2 (3.0) ± 1.3**	**4.3 (4.0) ± 1.0**	**0.002[a]**
Controlled Oral Word Association Test[18]	**24.9 (22.0) ± 20.6**	**37.2 (39.0) ± 13.8**	**0.018[a]**
Tower of London (time of execution in seconds)[19]	**570.2 (602.5) ± 292.2**	**370.3 (320.5) ± 169.9**	**0.020[a]**
Frontal Battery Assessment[20]	**14.3 (15.0) ± 3.0**	**17.0 (17.0) ± 1.0**	**<0.001[b]**
Visuospatial ability			
Benton Judgment of Line Orientation Test[21]	8.6 (9.5) ± 3.0	10.0 (10.0) ± 2.5	0.100[a]
Hooper Visual Organization Test[22]	**26.3 (29.0) ± 14.7**	**36.5 (36.0) ± 9.4**	**0.023[a]**
Verbal memory			
WMS-III Word List[23]			
Learning trials total	25.1 (22.5) ± 7.4	28.0 (27.5) ± 5.8	0.150[a]
Immediate recall	**4.9 (4.5) ± 2.3**	**6.5 (6.0) ± 2.2**	**0.023[a]**
Delayed recall	**4.5 (4.0) ± 2.7**	**6.2 (6.0) ± 2.4**	**0.034[a]**
Recognition	**19.8 (20.5) ± 3.7**	**22.1 (22.0) ± 1.4**	**0.028[b]**
Visual memory			
Brief Visuospatial Memory Test-Revised[24]			
Learning trials	**14.8 (10.5) ± 11.5**	**27.7 (30.5) ± 8.0**	**0.002[a]**
Delayed recall trial	**5.1 (4.5) ± 4.7**	**10.0 (10.0) ± 2.1**	**0.001[b]**
Recognition trial	11.6 (12.0) ± 0.8	11.7 (12.0) ± 0.6	0.497[b]
Language			
Boston Naming Test[25]	**40.8 (37.0) ± 10.5**	**52.3 (53.5) ± 5.2**	**0.001[a]**
Total number of animals as possible in one minute[26]	**15.2 (13.0) ± 7.4**	**20.7 (19.5) ± 6.5**	**0.011[a]**
Personality and Psychopathology			
Personality Assessment Inventory[28]			
Somatic concerns	**15.6 (14.0) ± 7.0**	**8.1 (7.0) ± 5.5**	**<0.001[a]**
Anxiety	10.8 (13.0) ± 7.6	6.5 (6.0) ± 5.0	0.060[a]
Anxiety related disorders	**16.4 (13.0) ± 7.2**	**11.4 (11.0) ± 5.3**	**0.028[a]**

Depression	**12.5 (10.0) ± 8.0**	**5.9 (5.0) ± 4.5**	**0.009[a]**
Mania	8.0 (7.0) ± 5.9	6.8 (6.0) ± 4.4	0.458[a]
Paranoia	12.1 (11.0) ± 7.8	9.5 (10.0) ± 4.2	0.254[a]
Schizophrenia	7.5 (8.0) ± 5.0	5.2 (4.0) ± 3.2	0.133[a]
Borderline features	**9.5 (8.0) ± 5.3**	**6.5 (7.0) ± 4.1**	**0.048[a]**
Antisocial features	**3.4 (3.0) ± 2.1**	**2.0 (2.0) ± 1.7**	**0.023[a]**
Alcohol problems	0.5 (0.0) ± 1.5	0.1 (0.0) ± 0.6	0.223[b]
Drug problems	0.5 (0.0) ± 1.1	0.4 (0.0) ± 1.0	0.796[b]

Mean (median) ± SD and frequency (%) are reported. [a]Student's t tests or [b]Mann-Whitney U test were used for comparisons of continuous data, and X^2 test for sex, and current smoker.
*Comorbidity included 13 conditions: atrial fibrillation, nonmetastatic cancer, metastatic cancer, chronic obstructive pulmonary disease, depression, dementia, diabetes, epilepsy (treated), heart failure, myocardial infarction, psychiatric disorders, renal disease, and stroke.
WAIS-III = Wechsler Adult Intelligence Scale-Third Edition.
WMS-III = Wechsler Memory Scale-Third Edition.
Significant values are in bold font.

Table 2: Demographic and clinical characteristics of orthostatic tremor patients.

Age (years)	Sex	Age at onset (years)	Associated neurological features	Tremor frequency in lower limbs*
74	Female	67	None	16-18 Hertz
64	Female	55	None	10-12 Hertz
57	Male	54	None	16-18 Hertz
68	Female	62	Mild parkinsonian signs	16-18 Hertz
57	Female	51	None	16-18 Hertz
78	Female	64	Mild parkinsonian signs	16-18 Hertz
62	Female	60	Postural upper limb tremor on arm extension	12-16 Hertz
37	Female	34	None	16-18 Hertz
76	Female	50	Postural upper limb tremor on arm extension	12-16 Hertz
75	Female	62	Mild parkinsonian signs	12-16 Hertz
77	Female	68	Mild parkinsonian signs	12-16 Hertz
77	Male	70	Mild parkinsonian signs	12-16 Hertz
38	Male	17	Postural upper limb tremor on arm extension	16-18 Hertz
65	Male	61	Mild parkinsonian signs	10-12 Hertz
81	Female	74	Mild parkinsonian signs	12-16 Hertz
65	Female	60	None	16-18 Hertz

*Assessed with electromyography.

Table 3: Linear regression analyses using each neuropsychological test score as the outcome variable in separate adjusted models.

		Entire cohort (N=16)		**Primary OT (N=9)**		**Younger-onset OT (N=8)**		**Elderly-onset OT (N=8)**	
	Outcome variable *	**Beta**	***p value***	**Beta**	***p value***	**Beta**	***p value***	**Beta**	***p value***
Attention	Direct Digit Span test from the WAIS-III[15]	-0.059	0.691	0.057	0.738	0.038	0.829	-0.194	0.285
	Coding-Digit Symbol subtest from the WAIS-III[15]	-0.180	0.075	-0.097	0.403	-0.083	0.487	**-0.324**	**0.008**
Executive Function	Stroop Color–Word Trial[16]	-0.185	0.169	-0.096	0.531	-0.090	0.573	-0.293	0.082
	Wisconsin Card Sorting Test[17]								
	Perseverations	-0.147	0.358	-0.105	0.526	-0.048	0.777	-0.169	0.369
	Non-perseverative errors	0.136	0.333	0.124	0.442	0.150	0.370	0.109	0.496
	Similarities subtest from the WAIS-III[15]	**-0.490**	**<0.001**	**-0.459**	**0.002**	**-0.431**	**0.005**	**-0.468**	**0.002**
	Indirect Digit Span subtest from the WAIS-III[15]	**-0.350**	**0.010**	-0.296	0.063	-0.319	0.052	**-0.368**	**0.029**
	Controlled Oral Word Association Test[18]	-0.252	0.065	-0.179	0.250	-0.206	0.197	-0.329	0.053
	Tower of London (time of execution in seconds) [19]	**0.429**	**0.002**	**0.316**	**0.040**	0.298	0.065	**0.547**	**<0.001**
	Frontal Assessment Battery[20]	**-0.439**	**0.001**	**-0.407**	**0.009**	**-0.455**	**0.004**	**-0.526**	**0.001**
Visuospatial ability	Benton Judgment of Line Orientation Test[21]	-0.136	0.277	-0.118	0.373	-0.127	0.354	-0.131	0.392
	Hooper Visual Organization Test[22]	**-0.386**	**0.001**	**-0.276**	**0.025**	**-0.292**	**0.022**	**-0.473**	**0.001**
Verbal memory	WMS-III Word List[23]								
	Learning list	-0.221	0.069	-0.119	0.377	-0.074	0.596	**-0.393**	**0.009**
	Immediate recall	**-0.366**	**0.009**	**-0.348**	**0.027**	**-0.341**	**0.037**	**-0.313**	**0.049**
	Delayed recall	**-0.322**	**0.007**	**-0.308**	**0.020**	-0.264	0.055	-0.332	0.019

	Recognition	**-0.396**	**0.006**	**-0.452**	**0.005**	**-0.332**	**0.047**	**-0.498**	**0.003**
Visual memory	Brief Visuospatial Memory Test-Revised[24]								
	Learning trials total	**-0.351**	**0.007**	-0.301	0.116	-0.282	0.166	**-0.533**	**0.005**
	Delayed free recall trial	**-0.534**	**<0.001**	**-0.440**	**0.006**	**-0.431**	**0.010**	**-0.679**	**<0.001**
	Recognition trial	-0.082	0.586	-0.075	0.652	-0.018	0.918	-0.146	0.415
Language	Boston Naming Test[25]	**-0.574**	**<0.001**	**-0.535**	**<0.001**	**-0.598**	**<0.001**	**-0.601**	**<0.001**
	Total number of animals as possible in one minute[26]	**-0.347**	**0.006**	-0.281	0.059	-0.259	0.092	**-0.352**	**0.012**
Personality and Psychopathology	Personality Assessment Inventory[28]								
	Somatic concerns	**0.479**	**0.001**	**0.390**	**0.020**	**0.398**	**0.021**	**0.543**	**0.003**
	Anxiety	0.260	0.057	0.099	0.504	0.171	0.253	**0.345**	**0.033**
	Anxiety related disorders	**0.412**	**0.002**	**0.295**	**0.044**	0.297	0.050	**0.487**	**0.002**
	Depression	**0.440**	**0.001**	0.259	0.078	0.218	0.156	**0.560**	**<0.001**
	Mania	0.210	0.168	0.087	0.594	0.006	0.970	**0.409**	**0.024**
	Paranoia	0.266	0.098	0.058	0.741	0.078	0.669	**0.385**	**0.029**
	Schizophrenia	0.282	0.058	0.161	0.323	0.143	0.400	0.351	0.054
	Borderline features	0.255	0.079	0.107	0.462	0.003	0.985	**0.399**	**0.016**
	Antisocial features	**0.348**	**0.021**	0.172	0.225	0.126	0.382	**0.505**	**0.007**
	Alcohol problems	0.264	0.122	0.304	0.100	0.318	0.095	-0.033	0.875
	Drug problems	0.020	0.894	0.095	0.547	0.114	0.485	-0.119	0.503

* Adjusted for age, sex, years of education, comorbidity index, current smoker, and depressive symptoms. Significant values are in bold font.