Cognition in non-demented Parkinson's disease vs. essential tremor: a population-based study

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Abstract

Objectives—Patients with Parkinson's disease (PD) and essential tremor (ET) have a higher risk of cognitive impairment than age-matched controls. Only a few small studies (11–18 subjects per group) have directly compared the cognitive profile of these conditions. Our aim was to compare the cognitive profile of patients with these two conditions to each other and to healthy individuals in a population-based study of non-demented participants.

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Materials & Methods—This investigation was part of the NEDICES study, a survey of the elderly in which 2,438 dementia-free participants underwent a short neuropsychological battery. We used non-parametric techniques to evaluate whether there are differences and/or a gradient of impairment across the groups (PD, ET and controls). Also, we performed a head-to-head comparison of ET and PD, adjusting for age and education.

Results—Patients with PD (N=46) and ET (N=180) had poorer cognition than controls (N=2,212). An impaired gradient of performance was evident. PD scored lower than ET, and then each of these lower than controls, in memory ($P < 0.05$) and verbal fluency ($P < 0.001$) tasks. When we compared PD and ET, the former had lower scores in verbal fluency ($P < 0.05$), whereas the later had a poorer cognitive processing speed ($P < 0.05$).

Conclusions—This large population-based study demonstrates that both conditions influence cognitive performance, that a continuum exists from normal controls to ET to PD (most severe), and that although deficits are in many of the same cognitive domains, the affected cognitive domains do not overlap completely.

1 INTRODUCTION

Patients with Parkinson's disease (PD) and essential tremor (ET) have a higher risk of cognitive impairment than healthy individuals who are matched by age and education [1,2]. Their pattern of dysfunction has traditionally been labeled as that of a fronto-subcortical type [3]. Deficits in areas such as attention [4,5], verbal fluency [2,5] and memory [6] may be noted even at early stages of both conditions [2,7]. In PD, this impairment has been linked with degeneration of cortical association areas [8]. In ET, the neuropathological correlates of cognitive impairment have not been completely elucidated [9].

While considerable efforts are being made to fully characterize and better understand the non-motor features of ET and PD, the two most common tremor disorders [10–12], only three studies have directly compared the cognitive profile of these two disorders, and each of these had small sample sizes (11–18 patients in each group) [6,13,14]. Furthermore, two of the studies [6,13] enrolled surgical patients, a highly selected group whose cognitive deficits are likely to differ from (i.e., be less marked than) those of the average patient. All three studies assessed patients who self-selected for treatment (i.e., patients attending clinics) rather than those sampled directly from the population. Clinic patients often differ phenotypically from those in the population. Finally, patients with both ET and PD may have Alzheimer's disease (AD) and other forms of dementia, and none of the studies explicitly removed these from the sample in order to obtain a less-confounded and cleaner picture of cognition. Hence, there is a need for more comprehensive study.

In this population-based study of non-demented participants, we performed a head-to-head comparison of the cognitive profile of 180 individuals with ET and 46 with PD, comparing them to 2,212 healthy aged controls. Our four *a priori* hypotheses were that (1) both

conditions affect cognitive performance relative to that of controls, even in the absence of a clinical diagnosis of dementia, (2) a continuum exists in this performance from normal controls to ET to PD (most severe), (3) the deficits in ET and PD are in many of the same cognitive domains; however, (4) the affected cognitive domains do not overlap completely, and there are demonstrable differences between ET and PD.

2 MATERIAL AND METHODS

2.1 Study population

This investigation was part of the Neurologic Disorders in Central Spain (NEDICES), a population-based survey of the prevalence, incidence, and determinants of major elderly-associated conditions. Detailed accounts of the background, study population, and methods of the survey have been reported [15–17].

2.2 Standard protocol approvals, registrations, and patient consents

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

2.3 Study evaluation

Detailed accounts of the study assessments have been published [16,18,19]. Face-to-face evaluations were performed at baseline (1994 – 1995) and at one follow-up (1997–1998). The face-to-face interview included data collection on demographics, current medications (including medications with central nervous system [CNS] effects), medical conditions (e.g., diabetes mellitus, hypertension, and heart disease), lifestyle habits, and the presence of depressive symptoms (the question, "do you suffer from depression?"). As described [18], a neurological examination was performed, comprising a general neurological examination, a tremor examination, and the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) [20] and the Hoehn-Yahr scale [21].

2.4 Diagnostic criteria for Parkinson's disease and essential tremor

Diagnostic criteria for ET [18], PD [19] and dementia [1] have been described elsewhere. For the diagnosis of Parkinson's disease, the study questionnaire had 3 questions to screen for parkinsonism (i.e. previous diagnosis of PD, presence of tremor, and presence of bradykinesia). Persons who screened positive (i.e. they responded positively to   1 of these 3 questions) for PD underwent a general neurological examination and the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) [20]. Parkinsonism was diagnosed when at least 2 cardinal signs (resting tremor, rigidity, bradykinesia, and impaired gait/postural reflexes) were present. PD was diagnosed in patients without secondary causes of parkinsonism or atypical features [19]. A Hoehn and Yahr stage was assigned to each case [21].

The evaluation of tremor and diagnosis of ET involved a screening question in the questionnaire ("have you ever had tremor of the head, hands, or legs that has lasted longer than several days?") with 68.6% sensitivity[22]. The same examination as in PD was performed. It also included an assessment of postural and kinetic tremors (sustained bilateral

arm extension, bilateral finger–nose–finger maneuver, drawing Archimedes spirals) and UPDRS [20]. Participants were diagnosed with ET if they had an action tremor of the head, limbs, or voice without any other recognizable cause. Second, the tremor had to be of gradual onset (i.e., slow and progressive) and 1) present for at least 1 year or 2) accompanied by a family history of the same disorder (at least one reportedly affected first-degree relative). In addition, on an Archimedes spiral, tremor severity had to be moderate or greater (rating >2 according to the Washington Heights-Inwood Genetic Study of ET Rating Scale) [23]. Participants with tremor related to alcohol withdrawal, hyperthyroidism, anxiety, PD, anti-dopaminergic drug intake, lithium therapy, or other known causes of tremor were not considered to have ET. If ET was diagnosed, the age of onset of tremor was elicited [22].

2.5 Neuropsychological tests

During the follow-up evaluation (1997–1998), all participants underwent a short neuropsychological evaluation [24,25]. The tests used were:

1. Global cognitive performance: This was assessed with an expanded, 37-item version of the Mini Mental-State Examination (37-MMSE) that ranged from 0 to 37 [26,27].

2. Psychomotor or cognitive-processing speed: This was assessed with the Trail Making test part A [28]. Here, we report the number of errors while performing the task.

3. Verbal fluency: For semantic fluency, participants were asked to name as many different animals and fruits as they could within 60 s [29].

4. Memory: This was evaluated with the following tests: a) Six-objects test [24,30](Naming Test): This was the ability to recall six objects 5 min later [range 0 (greater cognitive impairment) to 6]). b) Story recall: The "story recall" task was derived from the Wechsler Memory Scale-Rev. and measured memory (delayed logical memory) for aurally presented contextual material. The total number of words recalled was summed (range 0 [greater cognitive impairment] to 6) [31].

5. Premorbid intelligence: This was evaluated with the "word accentuation" test. This test assesses the accentuation of 30 infrequently used Spanish words written without the accent marks (range 0 [greater impairment]-30) [32].

2.6 Final selection of participants

Of the 5,278 participants who were enrolled at baseline, 672 were lost to follow-up (112 declined and 560 were unreachable), and 790 died before they were contacted the second time. Of the remaining 3,816, we excluded 921 with missing neuropsychological information and 457 subjects with stroke or dementia. The final sample (N = 2,438) included patients with PD (N = 46) and ET (N = 180), as well as the remaining healthy controls (N = 2,212) (Figure 1). This sample was similar to the initial 3,816 individuals in terms of sex (1,403 [57.4%] vs. 2,231 [58.5%] women, chi-square = 0.47, p = 0.489), but on average, was 0.9 years younger (75.6 ± 5.7 vs. 76.5 ± 6.4 years, p < 0.001) and included a lower

percentage of illiterate subjects (238 [10.0%] vs. 489 [12.9%], chi-square = 11.50, p < 0.001).

2.7 Statistical analyses

Statistical analyses where performed using R [33]. Significance was accepted at the 5% level (two-sided). Neuropsychological tests scores were not normally distributed (Kolmogorov-Smirnov tests for all items, p < 0.001). Therefore, although mean and median values were reported, differences across groups and cognitive domains were assessed with a Kruskal-Wallis test correcting for post-hoc multiple comparisons. The chi-square test was used to analyze categorical variables. We used the Jonckheere-Terpstra test, a non-parametric method, to detect a trend (gradient) of performance in the neuropsychological results. In addition, we computed adjusted T-scores for each test [34]. To do this, healthy participants were divided in twelve groups by age in tertiles (*68 years*, from 69 to 74 years, and *75 years),* and educational category (illiterate, can write and read, primary studies, secondary studies or higher). Then, with the mean and standard deviation of their respective healthy control group the T-score was calculated for each PD and ET patient. With these adjusted T-scores, we compared the performance of the ET and PD groups in the different cognitive domains avoiding for the confounding effects of age and education. The cutoff for normality was defined as one (T-score < 40) or two standard (T-score < 30) deviations from the reference values [34].

In order to further adjust for confounding, a series of non-parametric stratified analyses was performed. The purpose of these tests was to understand the magnitude and directionality of the effect of these confounders on the cognitive tests results rather than their significance (i.e., if PD or ET scored lower than the controls' across the different strata). The strata were defined by age in tertiles (*68 years*; from 69 to 74 years and *75 years*), gender (male vs. female), education (illiterate, can write and read, primary studies, secondary studies or higher), presence of depressive symptoms (no vs. yes), and medications with CNS effects (no vs. yes). In addition, we double-checked the results of the stratified results in the younger and more educated subjects. We performed a final subanalysis to define the influence of the age of onset (65 years) on the cognitive performance of the ET patients. The purpose was to evaluate whether there was a different cognitive phenotype of those with an older onset [35].

3 RESULTS

3.1 Demographic features

The final sample included 46 PD patients, 180 ET patients and 2,212 healthy controls (Table 1). The groups differed in terms of age, sex, educational level, intake of medications with CNS effects, and depressive symptoms. The patients had mean disease duration of 5.3 [4.0] ± 5.1 years (PD) and 10.4 [6.0] ± 12.2 years (ET). In the PD group, 29 [63.0%] had unilateral disease (stage I) or bilateral disease without axial symptoms (stage II), based on the Hoehn-Yahr scale.

3.2 Cognitive performance - ET and PD vs. controls (Hypothesis 1)

ET and PD patients performed significantly more poorly than controls in several tests and in global cognition (Table 2; Supplementary Figure). When the PD and ET patients were compared with the controls, the mean raw difference for the global cognition test (i.e., the MMSE-37) was −2.3 points and −1.6 points, respectively. The six object and the story delayed recall tests scores were −0.7 and −0.8-points significantly worse in the PD patients than the controls. In the verbal fluency tasks, there was a greater than one-point difference for both the animal and fruit naming tests between the PD group and the controls. Finally, the ET patients erred one point more than the controls in the cognitive processing speed task, the Trail Making Test part A, although the significance was lost in the post-hoc comparison. In analyses that stratified by age in tertiles, gender, prior education, presence of depressive symptoms and CNS drug intake), the group differences observed in the primary analyses persisted (data not shown).

3.3 Cognitive performance - trend analyses (Hypothesis 2)

Based on the Jonckheere-Terpstra test (Table 2), a significant trend was detected: the PD patients scored less well than the ET patients, and these scored less well than the controls. This trend was evident for global cognition ($P < 0.001$), both memory tasks ($P < 0.05$) and the fruit-naming test ($P < 0.001$). The only test in which ET patients performed more poorly than PD patients and controls was cognitive speed processing, in which ET patients showed a non-significant trend of increased number of errors ($P = 0.071$). Again, these relationships continued in stratified analyses that considered the same variables as in hypothesis 1 (data not shown).

3.4 Cognitive profile - ET vs. PD (Hypotheses 3 and 4)

The head-to-head comparison of the ET and PD patients is detailed in Table 3. The calculated T-scores were consistently lower in the PD patients, except for the cognitive processing speed task, but they only reached significance in the lower number of animals that the PD individuals named ($P = 0.05$). With respect to the percentage of patients with abnormal results, defined by a T-score below forty, in all tests there were subjects who could be considered impaired. In the animal-naming test, 12 PD patients (26.1%) scored abnormally in comparison with 25 ET patients (13.9%) ($P = 0.07$). When all of the cognitive tests were considered, there were 26 PD (56.5%) and 82 ET (45.6%) patients with at least one abnormal domain. By domain, there were 19 PD (41.3%) and 59 ET (32.8%) patients with a poorer performance in memory tasks, 16 PD (34.8%) and 41 ET (30.0%) with abnormal language functioning and 2 PD (5.7%) vs. 18 ET (12.5%) patients showing more errors in the cognitive speed-processing task. None of these differences reached significance.

When we excluded the illiterate and older (third tertile i.e. 75 years) patients (N= 78 ET and 13 PD), the difference in language performance of the two groups was significant ($P = 0.02$) with 7 PD (53.8%) vs. 15 ET (16.7%) scoring in the abnormal range. The other domains' differences remained similar and did not reach significance.

3.5 Age of tremor onset and its influence on the cognitive performance of ET

When we stratified ET patients by age of tremor onset, 58 (32.2%) had their onset prior to age 65 years and 122 (67.8%) had an onset 65 years. The two groups differed in terms of their median current age (71.5 vs. 75.5 years respectively; p < 0.05). Their neuropsychological performance was similar in all tests, with only the one exception of the animal naming task (p < 0.05). When we computed the adjusted T-scores by age and educational attainment, this difference was no longer significant (p = 0.10).

4 DISCUSSION

In this study, we characterized the cognitive performance of a population-based sample of 46 PD patients, 180 ET patients and 2,212 healthy controls. Our goal was to test four *a priori* hypotheses about the cognitive profile of PD and ET patients relative to that of controls and relative to one another.

Our first *a priori* hypothesis was that both ET and PD would have poorer cognitive performance relative to that of controls, even in the absence of a clinical diagnosis of dementia. Our results confirm this hypothesis by demonstrating the existence of significant differences in an important percentage of patients with each of these movement disorders when they were compared with healthy individuals. These results support those previously reported by Lombardi et al. in a small sample of 18 ET and 18 PD patients, although that study did not enroll healthy controls; rather, data from enrolled ET and PD patients were compared to published normative data [6].

Our second *a priori* hypothesis was that a gradient of neuropsychological performance would exist between PD, ET and healthy controls, with the former being the most affected. This continuum was demonstrated by the raw and stratified trend analyses we performed in language and memory domains. Gasparini et al., in a clinic-based study, previously suggested the likely presence of such a continuum of impairment. They studied 15 PD patients, 15 ET patients with familial history of ET, 15 ET patients with a familial history of PD, and 15 controls. Their research highlighted an altered performance in attentional tasks for both ET and PD groups, but with the PD group showing broader deficits [13]. A more recent study of surgical patients by Benge et al [14], which validated an executive scale in a sample of deep brain stimulation candidates, included 15 PD patients and 11 ET patients. The PD patients performed more poorly that the ET patients in this scale [14]. Most prior studies enrolled and assessed PD or ET patients, but not both. None of these studies were population-based or specifically ruled out AD and other dementia subtypes.

The third and fourth hypotheses suggested an overlap of the affected cognitive domains in ET and PD, yet not a complete overlap. In the study of Lombardi et al., the ET group performed more poorly in verbal fluency tests, whereas the PD patients also had poorer performance in visuospatial, memory and attentional tasks [6]. Moreover, Gasparini et al reported an altered performance in some attentional tasks for both ET and PD, but with the PD patients performing less well in some verbal fluency and executive tasks [13]. In our cohort, in the trend analyses, the PD participants performed less well than the ET patients, and both groups performed less well than the controls, in tests measuring global cognition,

memory and verbal fluency. These results confirm the existence of an overlap of affected domains [36]. Nonetheless, when the intensity and the percentage of subjects with an impaired function in a specific domain was compared, the two groups showed differences. In this head-to-head comparison, ET patients consistently scored less well than the PD patients in cognitive-processing speed, although this result was marginally significant in the trend analyses. This fact could be related to greater cerebellar involvement of the ET cases [37,38] as, in our opinion, tremor itself could not justify an increased number of errors [38]. Nonetheless, this last point will have to be confirmed in future studies, as it is fairly hypothetical. On the other hand, our results differ from those of Lombardi et al [6] as the PD, and not the ET, had a significantly poorer performance in verbal fluency. This is in agreement with what Gasparini et al. [13] and larger epidemiological studies [39]. Overall, the differences noted for some of the tests were modest when compared with previous studies [39]. The largest difference was noted for the six objects test in the PD patients and ET patients.

These NEDICES study results highlight the current view that PD and ET patients have non-motor cognitive features even when there are no signs of dementia [7,12]. The PD sample mainly included mild cases (63% cases had a Hoehn-Yahr stage   2) and hence a cortical neuropathological involvement, according to Braak staging, seemed unlikely. Considering the five-year mean disease duration, the chance of misdiagnosing PD with Dementia with Lewy Bodies also seems improbable [40].

In the current sample of ET and PD patients, we observed certain domains to be affected. It is worthwhile noting that there may be some overlap with what may be found in other neurodegenerative conditions. For example, during the preclinical stage of Alzheimer's disease, selective impairment of memory function may be observed [41]. In preclinical stages of frontotemporal dementia, executive and language deficits have been reported [42].

Regarding the clinical consequences of our findings, various reports have evidenced that subtle cognitive deficits, even in the absence of dementia, can impact the quality of life, predict "loss of independence" and impair activities of daily living in these frequent movement disorders [43–46]. Nonetheless, the clinical and prognostic implications of these deficits will have to be studied further.

Recently, it has been proposed that late onset of tremor (i.e.   65 years) could represent a different clinical entity than earlier onset ET [35]. With this in mind, we performed a sub-analysis, stratifying ET patients by age of onset. The neuropsychological performance of the two groups was similar in all tests. Based on our data, there does not seem to be a distinct cognitive phenotype in participants with younger tremor onset (i.e. < 65 years) compared with later tremor onset (i.e.   65 years); however, additional studies are needed before firm conclusions may be reached.

Our study has several limitations. First, we had to exclude a large proportion of subjects because of loss to follow-up, missing neuropsychological data, and other attrition issues. The excluded subjects were slightly older and had a slightly higher percentage of illiterates than those who were included. The potential bias introduced would most likely have been

towards a poorer performance among those who were excluded. In addition, the NEDICES study only included participants aged 65 years or older. Therefore, these analyses will have to be replicated in younger subjects. Second, the number of tests we could include was limited because the evaluation was part of a larger epidemiological study. It would have been interesting to characterize additional domains (e.g. visuospatial function). Another important limitation of our study is the lack of additional time-point evaluations, from which the evolution of these cognitive phenotypes could have been addressed. Certainly, future efforts should include follow-up visits to confirm and expand our results. Additionally, our evaluation of depression was limited and we may have under-ascertained depression, resulting in residual confounding. Nevertheless, a validation study showed a high level of agreement between the data generated from the screening question we used and a more detailed in-person psychiatric assessment, suggesting that such residual confounding is likely to have been low [47]. Further, we could not completely rule out confounding effects of other covariates. Because of the non-normality of the neuropsychological data, our approach to minimize the effect of these confounders in the tests' scores was to perform stratified analyses, evaluate T-scores adjusted by age and education and also reproduce some of the analyses in younger subjects with a higher educational category.

We believe that our conclusions are important for the definition and characterization of the cognitive aspects of ET and PD. We have confirmed that PD and ET impair cognitive performance, even in the absence of dementia, and that a continuum of severity exists between the two conditions, with PD showing a greater impact than ET. Also, there is some overlap in the type of impairment that they produce, but with disease-specific features, such as the predominant effect in verbal fluency of PD and in cognitive processing speed of ET. The last aspect should be further investigated to elucidate the mechanisms and structural correlates producing these diverse early cognitive effects. Besides their pathophysiological implications, these data could have added value in the differential diagnosis, prognosis and management of these frequent movement disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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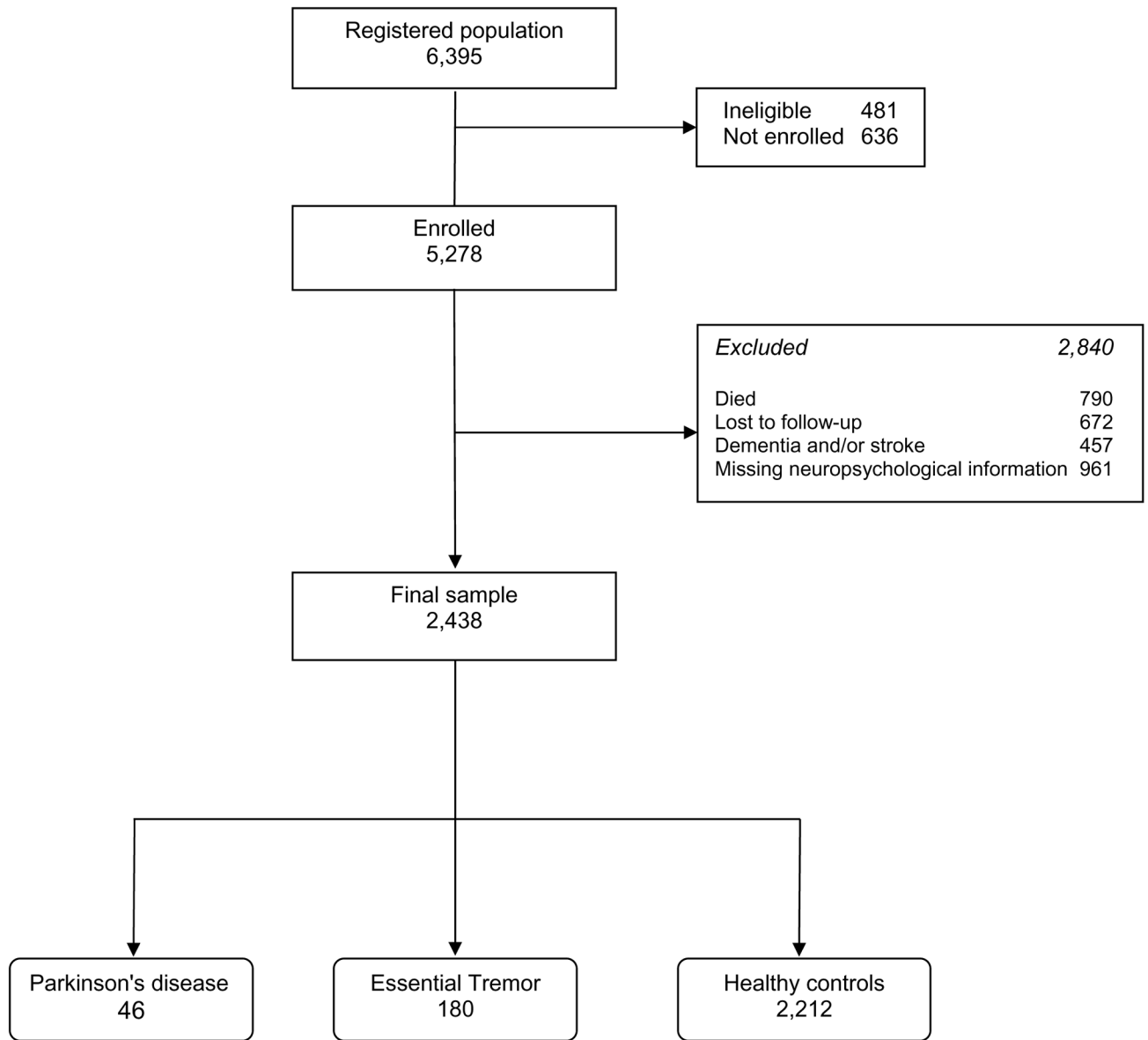
Figure 1.
Flow-chart of the Study

Table 1

Demographic and baseline features of the participants (N=2,438)

	Parkinson's disease [PD] (N=46)	Essential Tremor [ET] (N=180)	Healthy Controls [CNT] (N=2,212)	Significance test * *Post-hoc comparison*
Age (years)	78.1 [77.5] ± 5.5	76·2 [75.5] ± 5.7	75.4 [74.5] ± 5.7	**P < 0.001** PD > CNT
Sex (female)	17 (37.0)	107 (59.4)	1279 (57.8)	**P = 0.016** PD < CNT; PD < ET
Education				
Illiterate	9 (19.6)	31 (17.2)	198 (9.0)	**P = 0.006** (Illiterate percentage) PD > CNT; ET > CNT
Can write and read	18 (39.1)	73 (40.6)	942 (42.6)	
Primary studies	17 (37.0)	52 (28.9)	743 (33.6)	
Secondary or higher	2 (4.3)	24 (13.3)	328 (14.8)	
Medications with CNS effects (yes) [1]	18 (39.1)	67 (37.2)	431 (19.5)	**P < 0.001** PD > CNT; ET > CNT
Answered yes to the question "do you suffer from depression?"	16 (34.8)	75 (41.7)	476 (21.5)	**P < 0.001** ET > CNT

Quantitative data as mean [median] ± standard deviation for continuous variables or frequencies (percentages) for categorical variables; significant results are in bold;

*
Kruskal-Wallis and Chi-square tests adjusted for post-hoc pairwise comparisons

[1]
Medications potentially influencing cognitive performance (anxiolytics, stimulants, antipsychotics, antidepressants, antihistamines, antihypertensive agents, or antiepileptic drugs).

Table 2

Neuropsychological performance of the NEDICES participants grouped by diagnostic category (N=2,438)

	Parkinson's disease [PD] (N=46)	Essential Tremor [ET] (N=180)	Healthy Controls [CNT] (N=2,212)	Significance test* Post-hoc comparison	Trend analysis Jonckheere-Terpstra test
Global cognition *37-Mini Mental State Examination*	27.8 [28.5] ± 6.0	28.5 [29.0] ± 5.2	30.1 [31.0] ± 4.8	**P < 0.001** *PD < CNT; ET < CNT*	**P < 0.001**
Memory *Six Object test delayed recall*	3.4 [4.0] ± 1.7	3.9 [4.0] ± 1.7	4.1 [4.0] ± 1.5	**P = 0.005** *PD < CNT*	**P = 0.011**
Memory *Story delayed recall*	2.9 [3.0] ± 2.2	3.5 [4.0] ± 2.1	3.7 [4.0] ± 2.0	**P = 0.007** *PD < CNT*	**P = 0.007**
Verbal fluency *Number animals in 1'*	12.0 [11.0] ± 5.6	13.5 [13.0] ± 4.7	13.4 [13.0] ± 4.4	**P = 0.020** *PD < CNT; PD < ET*	P = 0.200
Verbal fluency *Number fruits in 1'*	9.3 [8.5] ± 3.2	9.9 [10.0] ± 3.1	10.5 [10.0] ± 3.0	**P = 0.001** *PD < CNT*	**P = 0.001**
Cognitive Speed Processing ** *Trail Making Test errors*	1.7 [0.0] ± 4.1	2.8 [0.0] ± 5.7	1.8 [0.0] ± 4.4	**P = 0.047** Post-hoc comparison N.S	P = 0.071
Premorbid Intelligence ** *Word Accentuation Test*	13.8 [15.0] ± 8.2	15.6 [16.0] ± 9.1	16.4 [16.0] ± 8.7	P = 0.226	P = 0.160

Data as mean [Median] ± standard deviation for continuous variables or frequencies (percentages) for categorical variables; significant results are in bold; N.S=non-significant

*
Kruskal-Wallis test adjusted for post-hoc pairwise comparisons

**
N=2,171 for Trail Making Test part A time (PD=34; ET= 148; Controls=1,989), N=2,161 for Trail Making Test part A errors (PD=35; ET= 144; Controls=1,982), and N=1,823 for the Word Accentuation Test (PD=33; ET= 133; Controls=1,657)

Table 3

Comparison of the different cognitive domains ("T-scores") in the Parkinson's disease (N = 46) and essential tremor (N = 180) participants

	Parkinson's disease (PD)	Essential Tremor (ET)	Significance test*	PD vs. ET cases with a T-score < 40 (%)	PD vs. ET cases with a T-score < 30 (%)
Global cognition *37-Mini Mental State Examination*	48.1 [50.8] ± 10.5	48.4 [50.4] ± 9.93	P = 0.922	15 (32.6) vs. 44 (24.6)	2 (4.3) vs. 8 (4.5)
Memory *Six Object test delayed recall*	46.3 [47.5] ± 10.9	48.7 [51.4] ± 11.3	P = 0.115	12 (26.1) vs. 36 (20.0)	5 (10.9) vs. 18 (10.0)
Memory *Story delayed recall*	47.3 [49.4] ± 10.8	49.3 [53.0] ± 10.8	P = 0.279	15 (32.6) vs. 43 (23.9)	2 (4.3) vs. 13 (7.2)
Verbal fluency *Number animals in 1'*	48.6 [46.5] ± 12.8	51.4 [51.4] ± 11.0	P = 0.050	12 (26.1) vs. 25 (13.9)	1 (2.2) vs. 0 (0.0)
Verbal fluency *Number fruits in 1'*	47.8 [43.9] ± 10.3	49.3 [48.2] ± 10.8	P = 0.209	8 (17.4) vs. 28 (15.6)	1 (2.2) vs. 3 (1.7)
Cognitive Speed Processing[1] *Trail Making Test errors*	50.9 [54.1] ± 9.4	47.8 [53.8] ± 14.3	P = 0.100	2 (5.7) vs. 17 (11.8)	1 (2.2) vs. 10 (6.9)

Quantitative data as mean [median] ± standard deviation

*Mann-Whitney test

[1]Trail Making Test part A: PD=35; ET= 145; A T-score of 40 or 30 represents, respectively, one or two standard deviations from the normal values of their age and schooling group.