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More unaffected first-degree relatives of essential tremor cases have mild cognitive deficits than age-matched controls

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ABSTRACT

Background: In numerous case-control studies, essential tremor (ET) has been associated with cognitive impairment. ET is often familial. However, cognitive impairment has not been studied in family members of ET cases. Endophenotypes are measurable clinical characteristics that may be present in individuals with increased risk for disease; as such, they may be present before disease onset. We administered a global cognitive screen to first-degree relatives of ET cases (FD-ET) and age-matched controls (Co).

Methods: We administered the Montreal Cognitive Assessment (MoCA) to 156 FD-ET and 73 Co, none of whom were diagnosed with ET or reported tremor. MoCA < 26 was considered suggestive of cognitive impairment.

Results: FD-ET and Co were similar with respect to age (60.1 ± 8.3 vs. 60.9 ± 7.4 years) and numerous demographic factors. FD-ET and Co also had similar MoCA scores; however, 34 of 156 (21.8%) FD-ET had a MoCA score < 26 vs only 5 (6.9%) of 73 Co ($p = 0.004$). In a univariate logistic regression model, FD-ET were 3.79 times more likely to have a low (< 26) MoCA than were Co (odds ratio = 3.79, $p = 0.008$). In a multivariate logistic regression model, adjusting for age and other covariates, FD-ET were 4.83 times more likely to have a low MoCA than were Co (odds ratio = 4.83, $p = 0.003$).

Conclusion: More FD-ET had low MoCA scores when compared with Co. These data provide additional support for the scientific notions that (1) cognitive difficulties are a disease-associated feature of ET and (2) there may be a pre-tremor phase of illness in ET.

1. Introduction

Historically, essential tremor (ET) was viewed as a mono-symptomatic motor disease, defined by an 8–12 Hz action tremor, occurring without additional neurological signs [1]. The definition of ET has evolved substantially over the past two decades, and recent research has brought to attention two additional aspects of the disease. First, numerous case-control studies have reported the presence of non-motor features (especially cognitive dysfunction) in some ET patients [2–4]. Second, the concept of a "pre-motor phase" of ET has been put forth; during this phase, select cognitive and psychological symptoms may manifest before the onset of motor features [5,6].

ET is often familial and first-degree relatives of ET cases are approximately five times more likely to develop ET than are members of the population [7]. Relatives of ET cases are also more likely to exhibit mild, subclinical tremor than are relatives of control subjects, indicating that the burden of ET extends beyond the boundaries of clinically-defined disease, and partially expressed features of ET occur in ET families [8,9]. Mild ataxia has been observed in ET cases in numerous studies [10]; it may also be partially expressed in first-degree relatives of ET cases, who exhibit more imbalance than age-matched controls [11].

As such, both mild tremor and mild imbalance may represent disease endophenotypes. Endophenotypes are measurable clinical characteristics that may be present in individuals with increased risk for disease; as such, they may be present before disease onset [11,12].

The extent to which cognitive dysfunction may also be an ET endophenotype is unknown. Cognitive dysfunction has been associated

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with ET in numerous case-control studies. However, the timing of its presentation and whether it affects family members with no evidence of tremor, remain unknown.

Case-control studies provide investigators with the opportunity to test whether clinical features are disease-associated. Family studies, which use a different design, allow this as well, as these features may be present to a greater extent in first-degree relatives of cases than in matched controls. In this study, we used a family design to compare the prevalence of mild cognitive deficits in unaffected first-degree relatives of ET cases (FD-ET) to that of age-matched controls (Co). We hypothesized that a higher proportion of FD-ET would exhibit such impairment than Co. If this were the case, it would: (1) provide additional support for the scientific notions that cognitive difficulties are a disease-associated feature of ET, (2) raise the possibility that these difficulties are an endophenotype for ET and, (3) provide further support for the notion that there may be a pre-tremor phase of illness in ET.

2. Methods

2.1. Introduction

FD-ET and their spouses (Co) were screened for enrollment in an environmental epidemiological study of ET (May 2016 – present) [11]. As described previously, ET cases were ascertained from study advertisements to the members of the International Essential Tremor Foundation, the members of current ET research studies at Yale University, and the clinical practice of the Yale Movement Disorders Group [11].

2.2. Screening process for unaffected FD-ET and Co

The screening process for reportedly unaffected relatives included the following steps. First, ET cases informed the investigator of all reportedly unaffected living first-degree relatives age ≥50. With permission, these FD-ET were contacted by telephone. During this telephone call, they were consented (using a protocol approved by the Yale University Institutional Review Board) and interviewed. During the interview, a 12-item tremor screening questionnaire was administered, and they were asked about a prior diagnosis of ET, Parkinson's Disease (PD), and dystonia. They also completed and mailed 4 hand-drawn spirals (2 right, 2 left), which were rated by a senior movement disorder neurologist (E.D.L.) using the following scale: 0, 0.5, 1, 1.5, 2, and 3 (see definitions and examples in Louis et al. [13]).

Relatives were initially categorized as unaffected if they met each of the following criteria: (1) they did not report tremor during the 12-item telephone-administered tremor screening questionnaire [14], (2) they had never been assigned an ET diagnosis by a treating physician, and (3) their 2 right and 2 left-hand-drawn screening spirals were assigned tremor scores < 2.0.

As a comparison, the spouses of these unaffected FD-ET were also screened, if they were available. Each underwent the same screening process as described above and were enrolled as Co if they were initially categorized as unaffected and if they reported no family history of ET.

2.3. In-person clinical evaluation

FD-ET and Co were invited for an in-person clinical evaluation if initially categorized as unaffected. All enrollees were evaluated in person by a trained tester who administered structured clinical questionnaires to ascertain demographic, lifestyle and clinical information (e.g., age, education, race, language spoken at home, current cigarette smoker, number of prescription medications, use of medications with potential cognitive side effects [e.g., diazepam, gabapentin]). The Cumulative Illness Rating Scale (CIRS) (range = 0–42 [maximum co-morbidity]) [19], a measure of medical co-morbidity, was administered; this assessed the presence and severity of comorbid conditions in 14 body systems. Depressive symptoms were assessed using the Beck Depression Inventory, for which 21 items were rated from 0 to 3 (total score = 0–63 [maximal symptoms]) [15].

We administered the Montreal Cognitive Assessment (MoCA). When compared to the Mini-Mental State Examination (MMSE), MoCA has been shown to yield better sensitivity and specificity [16,17], to have less educational bias [17] and to discriminate better between mild cognitive impairment and more serious disorders [16,18].

Each enrollee also underwent a 30–40-min standardized videotaped neurological examination, which included a detailed assessment of postural tremor, five tests for kinetic tremor, the motor portion of the Unified Parkinson's Disease Rating Scale [19] excluding an assessment of rigidity, and a comprehensive assessment of dystonia. A senior movement disorders neurologist reviewed all videotaped examinations blinded to MoCA results. The severity of postural and kinetic arm tremors was rated on 12 examination items using a reliable rating scale [20]. Ratings were 0, 0.5, 1.0, 1.5, 2, 3 and 4 (for some items); these resulted in a total tremor score (range = 0–46 [maximum]) [11].

FD-ET and Co were then re-evaluated for a potential ET diagnosis based on review of questionnaires and videotaped neurological examination data. Diagnoses of ET were assigned based on published diagnostic criteria (moderate or greater amplitude kinetic tremor during three or more activities, or a head tremor in the absence of PD or another known cause [e.g., medication-induced tremor, tremor from hyperthyroidism]) [21] with established reliability [20] and validity [22].

2.4. Final sample and study power

From the initial sample of 311 FD-ET and Co, we excluded 46 who were diagnosed with ET based on published diagnostic criteria [21] and another 29 who were considered to have borderline ET – that is, they did not fully meet strict diagnostic criteria for ET (defined above) based on the in-person evaluation, but were nonetheless considered by the study clinician to have clinical features that aligned with ET to some extent [23]. We also excluded 7 individuals with dystonia. Hence, the final sample was 229 (156 FD-ET and 73 Co).

A sample size calculation, which used pilot data on the expected proportion of Co with MoCA < 26 (i.e., 5.0%) and which assumed alpha = 0.05 and two-sided testing, indicated that our study was adequately powered (i.e., power = 83.6%) to detect a situation in which 20% of FD-ET had a MoCA < 26.

2.5. MoCA performance

The MoCA is used to stratify individuals as cognitively normal or impaired based on a previously validated cutoff score of < 26 (i.e., a score ≥26 is suggestive of normal cognition whereas a score below 26 is consistent with mild cognitive impairment [MCI], although it is not in itself sufficient to diagnose MCI) [18,24,25].

Performance on the MoCA may be affected by certain demographic characteristics such as primary language, education, age, race, sex, and comorbidities. However, the demographic features of the individuals in our sample were similar to those of the individuals in the paper which introduced the MoCA (i.e., white, educated, culturally homogenous) [18]. Thus, we use the cutoff score < 26 in our primary analyses, but also conduct sensitivity analyses with alternative cutoff scores.

2.6. Statistical analyses

For continuous variables, we assessed normality using a Kolmogorov-Smirnov test; when the distribution was not normal ($p < 0.05$), nonparametric tests were used (e.g., Mann-Whitney test, Spearman's correlation coefficient). We first compared FD-ET to Co in terms of demographic and clinical features using Mann-Whitney tests, chi-square tests, and Fisher's exact tests (Table 1). For these analyses, we compared MoCA score, MoCA subscores, and our dichotomous

Table 1
Demographic and clinical features of FD-ET vs. Co (229 participants).

Demographic and clinical features	FD-ET (N = 156)	Co (N = 73)	Significance
Age (years)	60.1 ± 8.3 [58]	60.9 ± 7.4 [62]	0.19[a]
Female gender	101 (64.7)	22 (30.1)	**< 0.001**[b]
Education (years)	16.6 ± 2.7 [16]	16.5 ± 2.8 [16]	0.55[a]
White race	151 (96.8)	73 (100)	0.18[b]
English language	153 (98.1)	72 (98.6)	1.00[b]
Current cigarette smoker	2 (1.30)	0 (0.00)	1.00[b]
Total CIRS Score	4.5 ± 3.3 [4.0]	3.9 ± 3.2 [3.0]	0.20[a]
Number of prescription medications	2.3 ± 2.3 [2.0]	2.5 ± 2.9 [2.0]	0.96[a]
Takes medication with potential cognitive side effects	10 (6.4)	6 (8.2)	0.59[b]
Years since last hospitalization	15.3 ± 12.9 [12.0]	12.6 ± 15.0 [6.0]	**0.03**[a]
Vitamin B12 supplements or thyroid medication	20 (12.8)	5 (6.9)	0.26[b]
Beck Depression Inventory	4.5 ± 4.7 [3.5]	3.9 ± 4.2 [3.0]	0.38[a]
Total tremor score	6.8 ± 2.3 [6.5]	6.5 ± 2.6 [6.5]	0.35[a]
MoCA Score	27.13 ± 2.44 [28.0]	27.42 ± 1.52 [27.0]	0.97[a]
MoCA Score < 26	34 (21.8)	5 (6.9)	**0.004**[b]
MoCA Subtests			
Visuospatial/Executive	4.58 ± 0.87 [5.0]	4.48 ± 0.71 [5.0]	**0.05**[a]
Naming	2.92 ± 0.29 [3.0]	2.99 ± 0.12 [3.0]	0.07[a]
Attention	5.60 ± 0.69 [6.0]	5.58 ± 0.62 [6.0]	0.49[a]
Language	2.53 ± 0.70 [3.0]	2.59 ± 0.57 [3.0]	0.88[a]
Abstraction	1.83 ± 0.39 [2.0]	1.92 ± 0.28 [2.0]	0.11[a]
Delayed Recall	3.66 ± 1.31 [4.0]	3.79 ± 1.12 [4.0]	0.70[a]
Orientation	5.97 ± 0.21 [6.0]	5.97 ± 0.16 [6.0]	0.94[a]

All values represent means ± standard deviation [median] or number (percentage).
Values in bold are significant.
For some variables, < 5% of values are missing.
AbbreviationsCumulative Illness Rating Scale (CIRS), Controls (Co), FD-ET (First-degree relatives of ET cases), Montreal Cognitive Assessment (MoCA).
[a] Mann-Whitney test.
[b] Chi-square or Fisher's exact test.

MoCA variable (< 26 vs ≥ 26) across the two participant groups. We repeated this analysis, stratifying by gender. When we compared MoCA subscores in FD-ET and Co, there were seven comparisons; therefore, we applied a Bonferroni correction, which set the significant p value at 0.007.

Our core sample of participants was age 50 and older. We next performed a series of sensitivity analyses in which we limited our sample to progressively older participants (≥60 and ≥ 70) to gauge the possible enhancing effects of a progressively older sample on our main finding (Table 2), and repeated our main analyses, comparing MoCA in FD-ET and Co. Using our core sample of participants age 50 and older, we next performed a series of sensitivity analyses in which we used different MoCA cut offs (< 23, < 24, < 25, < 27) (Table 2) and repeated our main analyses, comparing MoCA in FD-ET and Co. We also assessed the clinical correlates of our dichotomous MoCA variable (Table 3).

In an initial univariate logistic regression model using our core sample of participants, we assessed whether subject type (FD-ET vs. Co) was associated with our dependent variable, low MoCA (< 26); these analyses generated odds ratios (OR) with 95% confidence intervals. In an initial multivariate logistic regression model in which we adjusted for age, gender, education, and CIRS score, we assessed whether subject type (FD-ET vs. Co) was associated with our dependent variable, low MoCA (< 26). The choice of these covariates was based on the results of bivariate analyses (Tables 1 and 3) as well as prior biological plausibility. In another multivariate logistic regression model, we adjusted for number of prescription medications, use of a medication that could interfere with cognitive ability, and years since last hospitalization (i.e., additional measures of medical co-morbidity).

We performed two additional analyses. First, we excluded 25 participants taking thyroid medication or Vitamin B12 supplements, as these may be indicative of health problems with confounding neurocognitive effects, and we repeated our main analyses, comparing MoCA in FD-ET and Co. We also performed an additional analysis in which we precisely balanced the two groups for sample size (i.e., 73 in each group), randomly selecting a sub-group of 73 FD-ET who were age- and gender-matched to our 73 controls, and compared the two groups with respect to MoCA score.

3. Results

There were 156 FD-ET and 73 Co. The probands (i.e., primary affected relative of each FD-ET) had a mean age of tremor onset of 42.3 ± 22.3 years. The 156 FD-ET and 73 Co were similar with respect to age, education, race, language spoken, smoking status, CIRS score and other clinical variables (Table 1). A larger proportion of FD-ET than Co were women, and a larger proportion of Co had visited a hospital more recently (Table 1). FD-ET and Co had similar MoCA scores on average; however, 34 of 156 (21.8%) FD-ET had a MoCA score < 26 vs. only 5 of 73 (6.9%) Co (Fisher's exact test p = 0.004, Fig. 1, Table 1). After Bonferroni correction, none of the MoCA subtest scores differed across groups (Table 1). When we removed all 10 FD-ET and 6 Co who were taking medication with potential cognitive side effects, 31 of 146 (21.2%) FD-ET had a MoCA score < 26 vs. only 5 of 67 (7.5%) Co (p = 0.017). When we stratified by gender, 16 of 55 (29.1%) male FD-ET vs. 4 of 51 (7.8%) male Co had a MoCA score < 26 (Fisher's exact test p = 0.006), and 18 of 101 (17.8%) female FD-ET vs. 1 of 22 (4.5%) female Co had a MoCA score < 26 (Fisher's exact test p = 0.19).

Our core sample of participants was age 50 and older. We next performed a series of sensitivity analyses in which we limited our sample to progressively older participants (≥60 and ≥ 70 years) (Table 2). Among the smaller sample of participants age 60 and older, 22 of 79 (27.9%) FD-ET had a MoCA < 26 vs. only 2 of 46 (4.4%) Co (p = 0.001) (Table 2B). Among the even smaller sample of participants age 70 and older, 12 of 26 (46.2%) FD-ET vs. only 1 of 12 (8.3%) Co had a MoCA score < 26 (p = 0.03) (Table 2C).

Using our core sample of participants age 50 and older, we next performed a series of sensitivity analyses in which we used different MoCA cut offs (< 23, < 24, < 25, < 27) (Tables 2A–2C). The difference between FD-ET and Co did not persist to a significant degree with

Table 2
Demographic and clinical features of FD-ET vs. Co using alternative age cohorts and MoCA cutoff scores.

Table 2A. Participants age ≥50

Demographic and clinical features	FD-ET (N = 156)	Co (N = 73)	Significance
Age (years)	60.1 ± 8.3 [58]	60.9 ± 7.4 [62]	0.19[a]
Female gender	101 (64.7)	22 (30.1)	< **0.001**[b]
Education (years)	16.6 ± 2.7 [16]	16.5 ± 2.8 [16]	0.55[a]
White race	151 (96.8)	73 (100)	0.18[b]
English language	153 (98.1)	72 (98.6)	1.00[b]
Current cigarette smoker	2 (1.30)	0 (0.00)	1.00[b]
Total CIRS Score	4.5 ± 3.3 [4.0]	3.9 ± 3.2 [3.0]	0.20[a]
Number of prescription medications	2.3 ± 2.3 [2.0]	2.5 ± 2.9 [2.0]	0.96[a]
Takes medication with potential cognitive side effects	10 (6.4)	6 (8.2)	0.59[b]
Years since last hospitalization	15.3 ± 12.9 [12.0]	12.6 ± 15.0 [6.0]	**0.03**[a]
Vitamin B12 supplements or thyroid medication	20 (12.8)	5 (6.9)	0.26[b]
Beck Depression Inventory	4.5 ± 4.7 [3.5]	3.9 ± 4.2 [3.0]	0.38[a]
Total tremor score	6.8 ± 2.3 [6.5]	6.5 ± 2.6 [6.5]	0.35[a]
MoCA Score	27.13 ± 2.44 [28.0]	27.42 ± 1.52 [27.0]	0.97[a]
MoCA Score < 23	5 (3.2)	0 (0.0)	0.18[b]
MoCA Score < 24	11 (7.1)	2 (2.7)	0.23[b]
MoCA Score < 25	18 (11.5)	3 (4.1)	0.09[b]
MoCA Score < 26	34 (21.8)	5 (6.9)	**0.004**[b]
MoCA Score < 27	47 (30.1)	18 (24.7)	0.43[b]

Table 2B. Participants age ≥60

Demographic and Clinical Features	FD-ET (N = 79)	Co (N = 46)	Significance
Age (years)	66.1 ± 7.3 [64]	65.5 ± 4.9 [64]	0.69[a]
Female gender	50 (63.3)	12 (26.1)	< **0.001**[b]
Education (years)	17.1 ± 2.6 [18]	16.4 ± 2.8 [16]	0.16[a]
White race	77 (97.5)	46 (100)	0.53[b]
English language	78 (98.7)	35 (97.2)	1.00[b]
Current cigarette smoker	0 (0.0)	0 (0.0)	1.00[b]
Total CIRS Score	4.8 ± 3.1 [5.0]	4.6 ± 3.4 [4.0]	0.56[a]
Number of prescription medications	2.6 ± 2.6 [2.0]	3.2 ± 3.1 [3.0]	0.31[a]
Takes medication with potential cognitive side effects	5 (6.3)	5 (13.9)	0.50[b]
Years since last hospitalization	14.9 ± 13.5 [11.0]	11.1 ± 16.2 [4.0]	**0.01**[a]
Vitamin B12 supplements or thyroid medication	9 (11.4)	2 (4.4)	0.33[b]
Beck Depression Inventory	4.2 ± 3.8 [4.0]	4.2 ± 4.6 [3.0]	0.68[a]
Total tremor score	7.1 ± 2.5 [6.5]	6.6 ± 2.8 [6.5]	0.23[a]
MoCA Score	26.73 ± 2.52 [27]	27.28 ± 1.43 [27]	0.49[a]
MoCA Score < 23	4 (5.1)	0 (0.0)	0.30[b]
MoCA Score < 24	8 (10.1)	1 (2.2)	0.15[b]
MoCA Score < 25	12 (15.2)	2 (4.4)	0.08[b]
MoCA Score < 26	22 (27.9)	2 (4.4)	**0.001**[b]
MoCA Score < 27	30 (38.0)	13 (28.3)	0.33[b]

Table 2C. Participants age ≥70

Demographic and Clinical Features	FD-ET (N = 26)	Co (N = 12)	Significance
Age (years)	74.4 ± 5.8 [73.5]	71.9 ± 3.3 [71.0]	0.35[a]
Female gender	15 (57.7)	2 (16.7)	**0.03**[b]
Education (years)	16.38 ± 2.50 [16]	17.5 ± 3.56 [16.5]	0.36[a]
White race	25 (96.2)	12 (100)	1.00[b]
English language	26 (100)	12 (100)	1.00[b]
Current cigarette smoker	0 (0.0)	0 (0.0)	1.00[b]
Total CIRS Score	5.4 ± 2.7 [5.0]	6.0 ± 4.1 [5.5]	0.81[a]
Number of prescription medications	3.1 ± 2.7 [3.0]	4.7 ± 4.4 [3.0]	0.39[a]
Takes medication with potential cognitive side effects	0 (0.0)	2 (16.7)	0.09[b]
Years since last hospitalization	16.0 ± 15.3 [10.0]	8.4 ± 16.9 [2.0]	**0.01**[a]
Vitamin B12 supplements or thyroid medication	4 (15.4)	1 (8.3	1.00[b]
Beck Depression Inventory	3.9 ± 3.1 [3.5]	3.1 ± 3.6 [2.50]	0.28[a]
Total tremor score	7.4 ± 2.7 [6.8]	6.9 ± 3.7 [6.5]	0.49[a]
MoCA Score	25.65 ± 2.94 [26]	26.4 ± 1.00 [26.5]	0.40[a]
MoCA Score < 23	3 (11.5)	0 (0.0)	0.54[b]
MoCA Score < 24	4 (15.4)	0 (0.0)	0.29[b]
MoCA Score < 25	5 (19.2)	1 (8.3)	0.64[b]
MoCA Score < 26	12 (46.2)	1 (8.3)	**0.03**[b]
MoCA Score < 27	16 (61.5)	6 (50.0)	0.73[b]

All values represent means ± standard deviation [median] or number (percentage).
Values in bold are significant.
For some variables, < 5% of values are missing.
Abbreviations: Cumulative Illness Rating Scale (CIRS), Controls (Co), FD-ET (First-degree relatives of ET cases), Montreal Cognitive Assessment (MoCA).
[a] Mann-Whitney test.
[b] Chi-square or Fisher's exact test.

Table 3
Clinical correlates of MoCA in 229 participants.

Demographic and Clinical Features	MoCA Score ≥ 26 (n = 190)	MoCA < 26 (n = 39)	Significance
Age (years)	59.7 ± 7.3 [59.0]	63.4 ± 10.3 [61.0]	p = 0.06[a]
Female gender	104 (54.7)	19 (48.7)	p = 0.60[b]
Education (years)	16.6 ± 2.8 [16.0]	16.5 ± 2.3 [16.0]	p = 0.91[a]
White race	187 (98.4)	37 (94.9)	p = 0.20[c]
English language	187 (98.4)	38 (97.4)	p = 0.53[b]
Current cigarette smoker	2 (1.1)	0 (0.0)	p = 1.00[b]
Total CIRS Score	4.2 ± 3.2 [4.0]	4.6 ± 3.7 [4.0]	p = 0.84[a]
Number of prescription medications	2.3 ± 2.5 [2.0]	2.5 ± 2.4 [2.0]	p = 0.49[a]
Takes medication with potential cognitive side effects	13 (7.9)	3 (7.7)	p = 0.74[b]
Years since last hospitalization	14.2 ± 17.8 [6.0]	13.3 ± 12.1 [12.5]	p = 0.69[a]
Vitamin B12 supplements or thyroid medication	21 (11.1)	4 (10.3)	p = 1.00[b]
Beck Depression Inventory	4.3 ± 4.7 [3.0]	4.5 ± 4.2 [4.0]	p = 0.81[a]
Total tremor score	6.8 ± 2.3 [6.5]	6.7 ± 3.0 [6.25]	p = 0.77[a]

All values represent means ± standard deviation [median] or number (percentage).
Values in bold are significant.
For some variables, < 5% of values are missing.
[a] Mann-Whitney test.
[b] Chi-square or Fisher's exact test.
Abbreviations: Cumulative Illness Rating Scale (CIRS), Montreal Cognitive Assessment (MoCA).

these different cut-offs; of note however, in 12 of 15 such comparisons approximately three to six-times as many FD-ET cases than controls performed below the cutoffs (Table 2).

We next assessed the correlates of our dichotomous MoCA variable in our core sample of participants. Lower MoCA score was marginally correlated with older age (p = 0.06), but there were no other correlates (Table 3).

In an initial logistic regression model of our core sample in which low MoCA (< 26) was the dependent variable, FD-ET were 3.79 times more likely to have a low MoCA than were Co (95% CI = 1.42–10.14, p = 0.008). In an initial multivariate logistic regression model, we adjusted for age, gender, education, and CIRS score; in our core sample, FD-ET were 4.83 times more likely to have a low MoCA than were Co (95% CI = 1.68–13.88, p = 0.003). Using this same model for participants 60 and older, FD-ET were 12.28 times more likely to have a low MoCA than were Co (95% CI = 2.45–61.62, p = 0.002). In another multivariate logistic regression model, we adjusted for number of medications, use of a medication that could interfere with cognitive ability, and years since last hospitalization, and FD-ET were 4.70 times more likely to have a low MoCA than were Co (95% CI = 1.58–14.00, p = 0.006). For participants 60 and older, FD-ET were 11.94 times more likely to have a low MoCA than Co (95% CI = 2.28–69.98, p = 0.004).

We performed two additional analyses. First, to gauge possible neurocognitive effects of vitamin B12 deficiency or thyroid dysfunction, we excluded 25 participants who took vitamin B12 or thyroid medications. In our core sample of participants 50 and older, 31 of 136 (22.8%) FD-ET vs. only 4 of 68 (5.9%) Co had a MoCA score < 26 (Fisher's exact test, p = 0.003). We also analyzed a randomly selected subset of our core sample (146 participants), which contained the same number of age and gender-matched FD-ET and Co (i.e., 73 in each group). For participants 50 and older, 21 of 73 (28.8%) FD-ET vs. 5 of 73 (6.9%) Co had a MoCA score < 26 (Fisher's exact test p = 0.001). For participants 60 and older, 15 of 37 (40.5%) vs. 2 of 46 (4.4%) Co had a MoCA score < 26 (Fisher's exact test p < 0.001).

4. Discussion

We performed a global cognitive screen (i.e., MoCA) in 229 individuals, comparing FD-ET to Co of comparable age. None self-reported tremor or met criteria for ET on examination. We hypothesized that a higher proportion of FD-ET might exhibit cognitive deficits than Co. Despite a comparable mean MoCA score across groups, a larger proportion of FD-ET demonstrated scores that were consistent with cognitive impairment than did Co. This difference persisted when exploring different age cut-offs; it was also apparent, though not

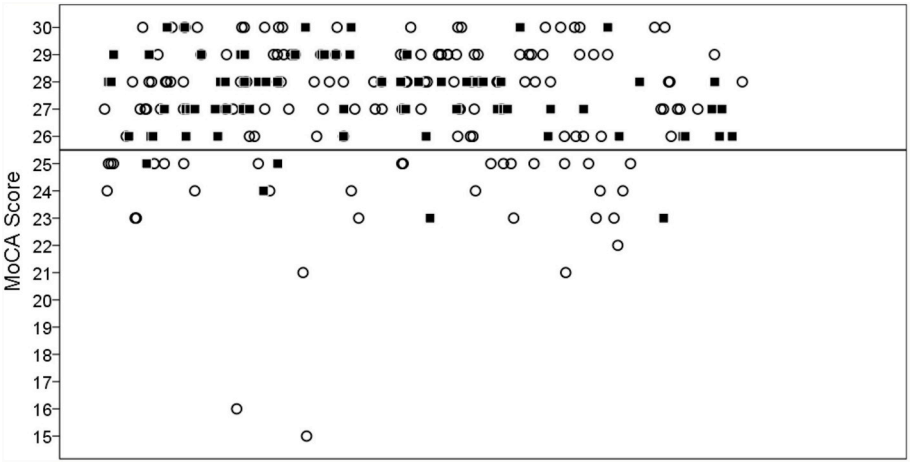

Fig. 1. MoCA score in FD-ET and Co (229 participants).
Open circles indicate FD-ET and black boxes indicate Co. MoCA scores < 26 appear below the horizontal bar. Several data points overlap, appearing as one.

statistically significant, with the use of different MoCA cut offs.

Scores on the MoCA can be used to stratify individuals as cognitively impaired based on a defined cutoff score. It is important to note that a score below the cutoff is consistent with mild cognitive impairment, although it is not in itself sufficient to diagnose mild cognitive impairment [18].

In our core sample (mean age = 60 years), 21.8% of FD-ET vs. 6.8% of Co had scores that were consistent with mild cognitive impairment (Table 1). Among our participants age 70 and older, these values rose to 46.2% and 8.3% (Table 2C). In a study of 55 bariatric surgery candidates 65 years and older (mean age = 68.2 ± 2.6 years), 22% fell below a score of 26 [26]. In a study of 45 patients with severe chronic obstructive pulmonary disease and 50 controls (mean respective ages = 68.4 ± 8.7 vs. 67.4 ± 8.8 years), mild cognitive impairment was found in 36% and 12% respectively [27]. The frequency of mild cognitive impairment that is usually reported in population-based studies is on the order of 3–19% [27,28]. Thus, our results suggest that mild cognitive impairment is a possible endophenotype trait for ET.

One may ask how the MoCA scores of our FD-ET compare to those of patients with ET and related neurological disorders. This is an interesting issue but a difficult one to address for ET. For example, studies that have used the MoCA have either enrolled subjects that are far younger than our FD-ET (e.g., 30 ET patients with mean age = 48.7 ± 7.4 years had a mean MoCA score of 25.2 ± 2.2) [29] or far older than our FD-ET (e.g., 199 ET cases with mean age = 78.6 ± 9.6 years had a mean MoCA score of 24.6 ± 3.9) [30]. There is some comparable literature in PD. In a study of 72 cognitively normal PD cases with a mean age (64.5 ± 8.4 years) that was only a few years older than that of our FD-ET (60.1 ± 8.3 years), the mean MoCA score was 26.7 ± 2.1, which is slightly lower than that of our FD-ET (27.13 ± 2.44) [31].

These results have several implications. First, using a family study design for the first time, our results strengthen the scientific notion that cognitive difficulties are a disease-associated feature of ET [2,3,32]. Second, they raise the possibility that such cognitive difficulty may be an endophenotype for ET and, third, they strengthen the notion that there may be a pre-tremor phase of illness in ET [5,6]. The results are also in line with those of our previous studies in which we showed that first-degree relatives have a greater burden of subclinical (i.e. “mild”) tremor than controls [33], and more problems with balance, albeit mild, than controls [11].

One concern is whether some of our FD-ET may have had manifest ET. For several reasons, this is unlikely. First, no FD-ET reported tremor during a 12-item tremor screening questionnaire [14]. Second, no FD-ET had received a diagnosis of ET by a treating physician. Third, no FD-ET met diagnostic criteria for ET or borderline ET based on a detailed neurological examination reviewed by a senior movement disorders neurologist [23]; indeed, their total tremor scores were very low and well-within the range of what has been reported in normal controls of similar age and their scores were no different from those of Co (Table 1).

There are several limitations of this work. First, although our sample size had > 80% power for our primary analysis, the number of Co was < 100 and in some analyses (e.g., restricting sample to those age ≥70 and using different MoCA cut points), the sample sizes became very small. Future studies should enroll larger numbers of subjects. Second, we used a global screening instrument for cognitive impairment; future studies should use a more detailed neuropsychological evaluation to assess whether there are specific areas of cognition that differ between FD-ET and Co. Nonetheless, it is remarkable that even with a simple screening measure, as we used, a clear difference between groups was observable. This suggests that more in-depth testing would likely uncover a plentitude of differences. Third, we did not assess whether the participants self-reported cognitive difficulties and future studies should do so. Fourth, one question is whether relatives of ET cases have a greater burden of white matter lesions or other structural lesions on brain imaging that could have contributed to the their lower MoCA scores. This was not a brain imaging study. Hence, we are not able to directly address this. We know of no published data on this topic (i.e., prevalence of white matter or other structural lesions among relatives of ET cases) either. This, though, is a worthwhile goal for future work. The study also had a number of strengths. First, the question we address is novel and has wide ranging implications for clinical care of FD-ET. Second, the family study design has not been employed in this setting. Third, more than 200 participants were enrolled and each received a standardized evaluation. Fourth, we carefully collected data on numerous potential confounding factors (e.g., age, education, burden of medical co-morbidity) and were able to show that these did not account for the difference seen in our two groups. Finally, all enrollees underwent a detailed in-person assessment, which included a videotaped neurological examination, which was examined by a senior movement disorders neurologist.

5. Conclusions

In summary, more FD-ET performed in the cognitively impaired range on the MoCA scores than did controls. These data provide additional support for the scientific notion that cognitive difficulties are a disease-associated feature of ET, may serve as an endophenotype, and may represent a pre-tremor phase of illness in ET.

Conflicts of interest

None of the authors has any conflicts of interest.

Authors' contributions

Conception and design of study; analysis and interpretation of data; drafting/editing manuscript; final approval of work (J.H.M.).

Acquisition of data; drafting/editing manuscript; final approval of work (R.H., A.D.C., R.H.).

Conception and design of study; interpretation of data; drafting/editing manuscript; final approval of work (P.F.L., S.C.).

Conception and design of study; analysis and interpretation of data; drafting/editing manuscript; final approval of work (E.D.L.).

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