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Original Research

# The association between motor and non-motor symptoms in essential tremor patients being evaluated for deep brain stimulation surgery

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ABSTRACT

*Background:* Non-motor symptoms, including depression and cognitive impairment, are common in essential tremor (ET), but associations between these symptoms and tremor are poorly understood.

*Methods:* A retrospective, single-institution, cohort study evaluated 140 patients with ET undergoing evaluation for deep brain stimulation (DBS) surgery. The Fahn-Tolosa-Marin (FTM) or Washington Heights-Inwood Genetic Study of ET (WHIGET) scale was used to grade tremor. Tremor scores were divided into quartiles. Patients underwent clinical neuropsychological evaluations that included a comprehensive cognitive test battery and Beck Depression Inventory-II (BDI-II). Subgroup analysis was performed with groups who met criteria for depression (BDI-II $>$ 14) or overall cognitive impairment ($<$9th percentile on at least two dissimilar cognitive tests). Independent samples t-tests were used for continuous variables and chi square tests for categorical variables. Univariable and multivariable regressions were used to determine relationships between tremor and non-motor scores.

*Results:* Tremor quartile was correlated with language domain performance ($p = 0.044$) but not depression scores. FTM score was associated with BDI-II ($\beta = 0.940$, $p = 0.010$), language ($\beta = -0.936$, $p = 0.012$), and visuospatial domain ($\beta = -0.836$, $p = 0.025$) scores, such that worse tremor was associated with more depression and worse language and visuospatial function. WHIGET score was not associated with any neuropsychological scores on multivariable regression.

*Conclusion:* FTM score was associated with language, visuospatial, and mood symptoms, suggesting a relationship between the severity of these symptom types. Different tremor scores capture different motor symptoms and relationships with nonmotor symptoms.

## 1. Introduction

Essential tremor (ET) is one of the most common tremor disorders, impacting 4–5% of individuals over the age of 65. [1,2] ET is characterized by action and postural tremor and was historically thought to be a purely motor disorder. However, more recently it has been recognized that ET patients also have non-motor symptoms. [3,4] ET patients experience a higher incidence of depression and cognitive impairment than healthy controls, with these symptoms having a significant negative impact on quality of life. [5,6].

The prevalence of depression in ET patients has been reported at 5.4 to 48.4%. [7–9] Depression symptoms are impactful: they are strongly associated with poor quality of life in ET patients. [10] Some studies have suggested that depression may be a primary symptom of ET rather than reactionary to impairment associated with tremor. [11] One previous study found that depression symptoms preceded the onset of motor manifestations in some ET patients. [12] However, a recent *meta*-analysis found that mean depression scores decrease following deep brain stimulation (DBS surgery), suggesting that depression may at least in part be related to motor symptom severity and associated disability in

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ET patients. [13,14] Additionally, another study showed no difference in depression rates between ET and control groups. [15] These conflicting findings are likely at least in part related to the small sample sizes which have limited most previous studies. Further work is needed to better elucidate the relationship between tremor and depression in ET.

ET can also be associated with cognitive impairment. Progressive cognitive changes ranging from mild cognitive impairment to dementia are more prevalent among ET patients than healthy controls. [16] The most commonly affected cognitive domains are executive function and memory. [6] Cognitive impairment may also occur prior to the appearance of motor symptoms in ET patients, [17] suggesting that it may not be directly related to motor symptoms and medications used to treat them. Examining the association between non-motor and motor symptoms in ET is important to help understand disease progression and the etiology of different symptom types. Understanding these relationships is important to help predict disease course and may help guide treatment planning.

Our objective was to investigate the relationship between tremor and non-motor symptoms in essential tremor patients who were being evaluated for deep brain stimulation surgery. By examining the relationships between tremor, depression, and cognition we aim to better understand the risk factors associated with ET non-motor symptoms and relationships between different symptom types.

## 2. Methods

### 2.1. Study design and participants

We performed a retrospective cohort study in patients diagnosed with ET who underwent evaluation for deep brain stimulation (DBS) surgery at our center. As part of their preoperative evaluation all patients underwent motor testing and clinical neuropsychological evaluation. The present study includes patients who underwent evaluation between October 2007 and March 2020. The study was approved by the Vanderbilt Institutional Review Board (IRB 060232) and patients provided written informed consent. Patients in an existing database were screened for eligibility (N =156). Only patients with available comprehensive neuropsychological testing reports were included, resulting in a final sample of 140 patients. Testing results were obtained from the electronic medical record, and data were extracted into a secure REDCap database. [18] The present study followed STROBE reporting guidelines.

### 2.2. Measures and definitions

As part of the standard preoperative workup motor testing was performed to assess tremor severity using either the Fahn-Tolosa-Marin (FTM) or Washington Heights Inwood Genetic Study of Essential Tremor (WHIGET) tremor scale. The scales were performed by physical therapists licensed by the Tennessee board of Physical Therapy and who frequently perform these scales for the purpose of DBS candidacy evaluation. Originally, WHIGET was used for preoperative tremor rating at our institution, but in mid-2016 this was replaced by the FTM scale. The FTM scale consists of three sections with a maximum total score of 144. [19] Part A quantifies tremor of the head and trunk at rest, with posture holding, and with action and intention maneuvers. Part B quantifies action tremors of the upper extremities during writing and pouring liquids. Part C assesses tremor impact on functional disability including impact on speaking, eating, dressing, and hygienic care. The WHIGET scale rates upper-extremity tremors on 6 tests: rest tremor, postural tremor, pouring water, drinking water, using a spoon, finger-to-nose, and spiral drawing. There is a maximum score of 26 for each upper extremity, for a total score of 52. [20] Right, left, and total motor scores were recorded for the purposes of this study. To allow whole-sample analysis, we combined FTM and WHIGET scale scores by grouping total scores on each of these measures into quartiles based on the score distribution within our study sample. A similar method has previously been utilized for analysis of tremor scores obtained using a single scale. [21,22] We then assigned an overall tremor severity score (referred to as 'overall tremor score') to each patient corresponding to the quartile their score fell into.

Clinical neuropsychological evaluations included a comprehensive cognitive test battery that examined function in the domains of attention and working memory, executive function, language, memory, and visuospatial function. These were administered by a licensed clinical neuropsychologist. The individual tests that were analyzed for each domain are listed in Supplementary Table 1. Scores for each test were referenced to age-based norms and converted to z-scores (mean = 0, SD = 1). Per previously published guidelines for diagnosing mild cognitive impairment, patients were classified as "cognitively impaired" if they scored below the 9th percentile on at least two dissimilar neuropsychological tests. [23] As shown in Supplementary Table 1, similar test scores were combined by averaging z-scores. There were at least two individual tests included in each cognitive domain. Composite cognitive domain scores were computed by calculating the mean z-score of dissimilar scores.

During neuropsychological evaluation visits, all patients also completed the Beck Depression Inventory-II (BDI-II), a screening questionnaire quantifying symptoms of depression. Total raw scores range from 0 to 63, with a score of 0–13 indicating minimal depression, 14–19 mild depression, 20–28 moderate depression, and 29–63 severe depression. [24] A BDI-II score ≥14 was used to diagnose depression in the present study.

### 2.3. Statistical analysis

Descriptive statistics were calculated for demographic characteristics, motor scores, and neuropsychological scores (BDI-II and cognitive domain scores). Frequencies were computed for categorical variables and mean (M) ± standard deviation (SD) was calculated for continuous variables. We first examined relationships between motor symptoms and non-motor variables using overall tremor score to quantify tremor. One-way analysis of variance (ANOVA) was used to compare BDI-II and cognitive domain scores between overall tremor quartiles. A Bonferroni post-hoc correction for multiple comparisons was used for all significant ANOVA findings. We also examined the relationship between overall tremor scores, BDI-II, and cognitive domain scores using multivariable regression models, with age and sex as covariates for the model with BDI-II as the dependent variable and sex as a covariate for the models with cognitive domain scores as dependent variables. Age was not included as a covariate in cognitive domain score multivariable regression given that cognitive test z-scores were derived from age-based norms.

We also performed analysis to compare patient subgroups with and without depression and with and without cognitive impairment. Data distribution was assessed for normality using the Shapiro-Wilk test. Means of normally distributed continuous data were compared using independent samples t-tests and those of non-normally distributed data were compared using Mann-Whitney U-tests. We used chi-square tests to compare categorical variables. We also evaluated the relationship between specific tremor scales and nonmotor symptoms. Descriptive analysis detailed cognitive domain and BDI-II scores for the groups of patients tested with FTM and WHIGET tremor scales. Data for this analysis was also evaluated for normal distribution using the Shapiro-Wilk test. Since all variables were normally distributed, chi-squared tests and t-tests were performed to compare demographic and neuropsychological variables between groups. The relationships between FTM and WHIGET scores and BDI-II and cognitive domain scores were assessed using multivariable regression models, with sex and age as covariates for models with BDI-II as the dependent variable, and sex as a covariate for models with cognitive domains as the dependent variable, given that cognitive scores were already age-normed. Statistical significance for all tests was set *a priori* at $\alpha$=0.05, with a Bonferroni correction applied for multiple comparisons. Analyses were performed using IBM SPSS Statistics 27 (IBM, Armonk, NY).

## 3. Results

### 3.1. Overall sample

The mean age of the study population was 65.33 ± 10.85 years, 52% of patients were female, and 89.9% were right-handed (Table 1). Mean BDI-II score was 10.4 ± 7.1. The average z-score for the domain of attention and working memory was −0.49 ± 0.72, executive function was −0.36 ± 0.96, language was −0.39 ± 0.80, memory was −0.39 ± 0.91, and visuospatial processing was 0.17 ± 0.71. Thirty-nine (27.9%) patients met criteria for depression and 86 (61.4%) met criteria for cognitive impairment. Thirty-nine patients (27.9%) had an overall tremor quartile score of 1, 35 (25.0%) had a score of 2, 34 (24.3%) had a score of 3, and 32 (22.9%) had a score of 4. There were no differences in depression scores between overall tremor quartiles (Table 2). Language domain function was significantly different between tremor quartiles ($p$ = 0.044), with post-hoc analysis revealing worse language function for third- compared to second-quartile tremor scores ($p$ = 0.032) (Table 2). There was no association between overall tremor quartiles and depression or cognitive scores on multivariable regression (Supplementary Table 2).

### 3.2. Neuropsychological subgroups

No differences in cognitive measures or overall tremor scores were observed between patients who did or did not have depression (Table 3). Patients with cognitive impairment had worse scores in the domains of attention and working memory, executive function, language, and visuospatial function than cognitively normal patients ($p$ < 0.001 for all) (Table 4). There were no differences in depression or motor scores between patients with and without cognitive impairment (Table 4).

### 3.3. Neuropsychological symptoms and individual tremor scales

We also investigated whether the relationships between tremor and non-motor symptoms were related to the specific scale used to measure tremor. To do this we separated subjects into subgroups according to whether they had been tested with FTM or WHIGET scale. Patients in the FTM group were older than those tested with WHIGET (Supplementary Table 3). The mean total FTM score for patients tested with this scale was 50.4 ± 14.0, and the mean total WHIGET score was 29.0 ± 8.1. There were no differences in BDI-II scores between the two groups (WHIGET group: 10.7 ± 7.1; FTM group: 9.9 ± 7.2), the means of which

**Table 1**
Demographic and Clinical Characteristics of ET Patients.

| | Overall (N = 140) |
|---|---|
| Demographics | |
| Age [Mean (SD)] | 65.3 (11.1) |
| Sex [N (%)] | |
| Female | 75/140 (53.6 %) |
| Handedness [N (%)] | |
| Left | 14/138 (10.1 %) |
| Right | 124/138 (89.9 %) |
| Race [N (%)] | |
| White | 136/140 (97.1 %) |
| Black | 4/140 (2.9 %) |
| Overall Tremor Score [Number of Patients (%)] | |
| 1st | 39/140 (27.9 %) |
| 2nd | 35/140 (25.0 %) |
| 3rd | 34/140 (24.3 %) |
| 4th | 32/140 (22.9 %) |
| Neuropsychological Tests | |
| BDI-II [Mean (SD)] | 10.4 (7.1) |
| Depressed [N (%)] | 39/140 (27.9 %) |
| Attention and Working Memory [Mean (SD)] | −0.49 (0.72) |
| Executive Function [Mean (SD)] | −0.36 (0.96) |
| Language [Mean (SD)] | −0.39 (0.80) |
| Memory [Mean (SD)] | −0.39 (0.91) |
| Visuospatial [Mean (SD)] | 0.17 (0.71) |
| Cognitively Impaired [N (%)] | 86/140 (61.4 %) |

**Table 2**
Mean neuropsychological scores by overall tremor score quartile.

| | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | Statistics |
|---|---|---|---|---|---|
| BDI-II | 10.3 (7.8) | 9.8 (5.5) | 10.2 (8.2) | 11.4 (6.9) | F (3,127) = 0.273, p = 0.845 |
| Number Depressed | 11 (7.9 %) | 9 (6.4 %) | 8 (5.7 %) | 11 (7.9 %) | $\chi^2$ = 0.977, p = 0.807 |
| Attention and Working Memory | −0.47 (0.75) | −0.22 (0.66) | −0.72 (0.69) | −0.59 (0.74) | F(3,68) = 1.560; p = 0.207 |
| Executive Function | −0.19 (0.93) | −0.18 (0.99) | −0.72 (0.94) | −0.40 (0.92) | F(3,63) = 0.963; p = 0.431 |
| Language | −0.44 (0.81) | −0.05 (0.74) | −0.79 (0.57) | −0.32 (0.91) | F(3,70) = 2.838; **p = 0.044** |
| Memory | −0.28 (1.20) | −0.29 (0.71) | −0.73 (1.05) | −0.35 (0.68) | F(3,60) = 0.751; p = 0.526 |
| Visuospatial | −0.24 (0.59) | 0.30 (0.63) | 0.26 (0.68) | −0.10 (0.89) | F(3,60) = 1.153; p = 0.335 |
| Number Cognitively Impaired | 24 (17.1 %) | 21 (15.0 %) | 20 (14.3 %) | 21 (15.0 %) | $\chi^2$ = 0.368, p = 0.947 |

All scores are presented as mean (SD) or count (%).
Bonferroni post-hoc test – Language Domain: 2nd vs 3rd Quartile ($p$ = 0.032).

**Table 3**
Depressed vs Non-Depressed Patients.

| | Depressed (N = 39) | Not depressed (N = 101) |
|---|---|---|
| Demographics | | |
| Age | 63.2 (10.7) | 66.0 (11.5) |
| Sex | | |
| Female | 25/39 (64.1 %) | 50/101 (49.5 %) |
| Handedness | N = 37 | N = 101 |
| Left | 4 | 10 |
| Right | 33 | 91 |
| Neuropsychological Tests | | |
| BDI | 19.4 (4.5)* | 6.6 (3.9) |
| Attention and Working Memory | −0.71 (0.80) | −0.42 (0.70) |
| Executive Function | −0.42 (0.96) | −0.35 (1.00) |
| Language | −0.54 (0.78) | −0.33 (0.81) |
| Memory | −0.52 (0.85) | −0.31 (0.95) |
| Visuospatial | 0.01 (0.78) | 0.23 (0.70) |
| Number of cognitively impaired patients | 24/39 (61.5 %) | 62/101 (61.4 %) |
| Motor Tests | | |
| FTM | | |
| Left | 13.5 (5.0) | 15.40 (4.89) |
| Right | 15.13 (6.58) | 16.14 (4.48) |
| Total | 51.80 (13.69) | 50.86 (13.32) |
| WHIGET | | |
| Left | 13.58 (5.02) | 13.05 (5.32) |
| Right | 15.83 (4.79) | 15.70 (4.26) |
| Total | 29.42 (9.06) | 28.75 (7.83) |
| Overall Tremor Scores | | |
| 1st | 11/39 (28.2 %) | 24/101 (23.8 %) |
| 2nd | 9/39 (23.1 %) | 27/101 (26.6 %) |
| 3rd | 8/39 (20.5 %) | 25/101 (24.8 %) |
| 4th | 11/39 (28.2 %) | 25/101 (24.8 %) |

*$p$-value < 0.001 compared to non-depressed/cognitively impaired counterpart.
All scores are presented as mean(SD) or count(%).

**Table 4**
Cognitively Impaired vs Non-Impaired Patients.

| | Cognitively impaired (N = 86) | Normal cognition (N = 54) |
|---|---|---|
| Demographics | | |
| Age | 64.9 (11.9) | 65.8 (9.7) |
| Sex | | |
| Female | 42/86 (48.8 %) | 33/54 (61.1 %) |
| Handedness | *N = 85* | *N = 53* |
| Left | 6 | 8 |
| Right | 79 | 54 |
| Neuropsychological Tests | | |
| BDI | 10.4 (7.5) | 10.40 (6.7) |
| Number of depressed patients | 24/86 (27.9 %) | 15/54 (27.8 %) |
| Attention and Working Memory | −0.71 (0.61)* | 0.38 (0.34) |
| Executive Function | −0.64 (0.90)* | 0.56 (0.39) |
| Language | −0.65 (0.65)* | 0.55 (0.58) |
| Memory | −0.55 (0.92) | 0.14 (0.62) |
| Visuospatial | 0.05 (0.75)* | 0.56 (0.34) |
| Motor Tests | | |
| FTM | | |
| Left | 14.8 (5.2) | 14.7 (5.6) |
| Right | 15.5 (5.5) | 15.6 (5.4) |
| Total | 50.2 (13.7) | 51.6 (14.4) |
| WHIGET | | |
| Left | 13.5 (5.2) | 13.0 (5.1) |
| Right | 16.4 (4.5) | 15.0 (4.0) |
| Total | 30.0 (8.6) | 28.0 (7.4) |
| Overall Tremor Scores | | |
| 1st | 24/86 (27.9 %) | 15 (29.2 %) |
| 2nd | 21/86 (24.4 %) | 14 (22.9 %) |
| 3rd | 20/86 (23.3 %) | 14 (22.9 %) |
| 4th | 21/86 (24.4 %) | 11 (25.0 %) |

*$p$-value < 0.001 compared to non-depressed/cognitively impaired counterpart.
All scores are presented as mean(SD) or count(%).

both fell into the minimal depression range. The WHIGET group had lower cognitive scores in the domains of attention and working memory (WHIGET group: −0.79 ± 0.66; FTM group: −0.37 ± 0.71; $p = 0.024$), as well as language (WHIGET group: −0.79 ± 0.75; FTM group: −0.23 ± 0.77; $p = 0.006$).

On multivariable regression, total FTM score (β = 0.940, $p = 0.010$) and left FTM score (β = −0.746, $p = 0.004$) were predictive of BDI-II scores, with higher total FTM score and lower left FTM score associated with higher BDI-II scores (Table 5). Total FTM was also associated with language (β = −0.936, $p = 0.012$) and visuospatial (β = −0.836, $p = 0.025$) domain function, such that more severe tremor was associated with worse function in these domains (Table 5). Similarly, right FTM (β = 0.665, $p = 0.015$) and left FTM (β = 0.550, $p = 0.037$) were associated with language and visuospatial domain scores, such that higher right FTM scores were associated with better language function and higher left FTM scores were associated with better visuospatial function (Table 5). WHIGET scores did not predict any neuropsychological variables on multivariable regression (Table 6). To evaluate whether this inverse relationship between left FTM and BDI-II scores was related to tremor severity in non-dominant hand we repeated this analysis with only right-handed patients. Total FTM score (β = 0.865, $p = 0.025$) and left FTM score (β = −0.656, $p = 0.013$) remained predictive of BDI-II scores such that a higher total FTM score or a lower left FTM score was associated with higher BDI-II scores (Supplementary Table 4). Similarly, total FTM (β = −0.909, $p = 0.023$) and right FTM (β = 0.683, $p = 0.018$) were predictive of language function such that a lower total FTM and higher right FTM were associated with higher language scores (Supplementary Table 4). Finally, total FTM (β = −0.927, $p = 0.020$) and left FTM (β = 0.531, $p = 0.050$) were predictive of visuospatial function such that a lower total FTM and higher right FTM were associated with higher visuospatial scores (Supplementary Table 4).

**Table 5**
Relationship between FTM and neuropsychological scores.

| BDI-II | | | | |
|---|---|---|---|---|
| | *β* | SE | t | p |
| Total FTM | 0.940 | 0.177 | 2.695 | **0.010** |
| Left FTM | −0.746 | −0.350 | −3.065 | **0.004** |
| Right FTM | −0.377 | 0.375 | −1.395 | 0.170 |
| Age | −0.336 | 0.134 | −2.467 | **0.018** |
| Sex | 0.278 | 2.317 | 1.705 | 0.095 |
| Attention and Working Memory | | | | |
| | *β* | **SE** | **t** | **p** |
| Total FTM | −0.625 | 0.018 | −1.730 | 0.090 |
| Left FTM | 0.153 | 0.035 | 0.598 | 0.553 |
| Right FTM | 0.355 | 0.039 | 1.323 | 0.192 |
| Sex | −0.421 | 0.236 | −2.553 | **0.014** |
| Executive Function | | | | |
| | *β* | **SE** | **t** | **p** |
| Total FTM | −0.552 | 0.025 | −1.602 | 0.123 |
| Left FTM | 0.091 | 0.046 | 0.375 | 0.710 |
| Right FTM | 0.383 | 0.054 | 1.460 | 0.151 |
| Sex | −0.467 | 0.330 | −2.862 | **0.006** |
| Language | | | | |
| | *β* | **SE** | **t** | **p** |
| Total FTM | −0.936 | 0.020 | −2.628 | **0.012** |
| Left FTM | 0.212 | 0.038 | 0.841 | 0.405 |
| Right FTM | 0.665 | 0.042 | 2.523 | **0.015** |
| Sex | −0.310 | 0.252 | −1.907 | 0.063 |
| Memory | | | | |
| | *β* | **SE** | **t** | **p** |
| Total FTM | −0.534 | 0.023 | −1.537 | 0.122 |
| Left FTM | 0.212 | 0.044 | 0.870 | 0.382 |
| Right FTM | 0.372 | 0.049 | 1.443 | 0.146 |
| Sex | −0.604 | 0.290 | −3.920 | **<0.001** |
| Visuospatial | | | | |
| | *β* | **SE** | **t** | **p** |
| Total FTM | −0.836 | 0.019 | −2.312 | **0.025** |
| Left FTM | 0.550 | 0.037 | 2.151 | **0.037** |
| Right FTM | 0.209 | 0.041 | 0.780 | 0.439 |
| Sex | −0.240 | 0.245 | −1.455 | 0.152 |

## 4. Discussion

In this study we examined the relationship between tremor and non-motor symptoms in patients with ET. We found that overall tremor score was associated with language domain dysfunction. We found that FTM but not WHIGET scores correlated with depression scores. Similarly, FTM was associated with language and visuospatial cognitive scores. Our results increase understanding of the relationship between motor and non-motor symptoms in ET patients.

### *4.1. Association between depression and tremor*

We found that greater depression was associated with worse overall tremor as measured with FTM but not WHIGET. This is consistent with two prior ET studies: one that used FTM scores and found an association with depression [25] and one that used WHIGET scores and did not find an association with depression [26]. This discrepancy may be due to the different features measured by these two scales. WHIGET measures only upper extremity tremor, while FTM quantifies midline, upper, and lower extremity tremor, as well as impact of tremor on functional disability [27]. A previous study found that ET patients with midline tremor exhibited more severe depression and cognitive dysfunction, suggesting that symptoms such as midline tremor captured by FTM but not WHIGET may explain the different relationships between these two scales and depression and cognitive scores [28]. Our study is unique in comparing relationships between these two commonly used measures and suggests that specific tremor rating scale used may impact the relationship between tremor and non-motor symptoms. Interestingly, our analysis found that worse left-sided tremor measured with FTM was associated with lower depression scores. One possible explanation for

**Table 6**
Relationship between WHIGET and neuropsychological scores.

| BDI-II | | | | |
|---|---|---|---|---|
| | β | SE | t | p |
| Total WHIGET | – | – | – | – |
| Left WHIGET | 0.053 | 0.175 | 0.266 | 0.791 |
| Right WHIGET | 0.024 | 0.334 | 0.117 | 0.907 |
| Age | −0.153 | 0.064 | −1.342 | 0.184 |
| Sex | −0.145 | 1.692 | −1.217 | 0.227 |
| Attention and Working Memory | | | | |
| | β | SE | t | p |
| Total WHIGET | – | – | – | – |
| Left WHIGET | −0.218 | 0.048 | −0.597 | 0.559 |
| Right WHIGET | 0.061 | 0.053 | 0.164 | 0.872 |
| Sex | 0.145 | 0.325 | 0.579 | 0.570 |
| Executive Function | | | | |
| | β | SE | t | p |
| Total WHIGET | – | – | – | – |
| Left WHIGET | −1.862 | 0.047 | −3.024 | 0.058 |
| Right WHIGET | 1.698 | 0.096 | 2.559 | 0.056 |
| Sex | −0.221 | 0.314 | −0.838 | 0.426 |
| Language | | | | |
| | β | SE | t | p |
| Total WHIGET | – | – | – | – |
| Left WHIGET | −0.100 | 0.054 | −0.320 | 0.753 |
| Right WHIGET | 0.310 | 0.058 | 1.009 | 0.327 |
| Sex | 0.168 | 0.350 | 0.702 | 0.492 |
| Memory | | | | |
| | Β | SE | t | p |
| Total WHIGET | – | – | – | – |
| Left WHIGET | −0.461 | 0.059 | −1.244 | 0.249 |
| Right WHIGET | 0.099 | 0.068 | 0.264 | 0.798 |
| Sex | −0.313 | 0.459 | −1.001 | 0.346 |
| Visuospatial | | | | |
| | β | SE | t | p |
| Total WHIGET | – | – | – | – |
| Left WHIGET | −0.763 | 0.041 | −1.891 | 0.101 |
| Right WHIGET | 0.386 | 0.045 | 0.953 | 0.372 |
| Sex | 0.001 | 0.302 | 0.001 | 0.998 |

Note: Total WHIGET was removed from the regression due to redundancy, as total WHIGET is the sum of left and right scores.

this finding is that patients with more severe nondominant side tremor have less functional impairment and associated depression [22]. This relationship was also present when we controlled for handedness by examining right handed patients alone, further supporting this interpretation. An alternative explanation is that right brain pathophysiological changes associated with left sided tremor progression are also associated with a feature protective for depression. Importantly, however, depression may be reactive to tremor disability, as previous studies have shown a positive correlation between depression scores and self-reported tremor disability [8]. Further research is required to clarify these relationships.

### *4.2. Association between cognitive functions and tremor*

We found that language domain score was associated with overall tremor score. Language function in those with an overall tremor score of 3 was worse than those with an overall tremor score of 2. We also found an association between total FTM score and language and visuospatial domain scores, such that a higher tremor score was associated with impairment in these cognitive domains. One previous study of 18 ET patients did not find a relationship between individual neuropsychological tests and tremor [29]. However, this negative finding may be due to the fact that only FTM Part A and handwriting scores were utilized in the prior analysis. Additionally, the larger sample size of the present study may allow for a better ability to detect a significant relationship.

ET patients have impairments in multiple cognitive domains including attention, language, verbal memory, and frontal executive functions compared to age-matched controls [30]. Even ET patients with mild tremor can demonstrate cognitive changes such as executive dysfunction and attentional deficits [31]. Cognitive symptoms have also been observed before tremor onset in some ET patients [17]. Several studies have suggested that cognitive symptoms in ET may be associated with cerebellar symptoms [32]. While the underlying pathophysiology of ET is not yet fully understood, it is generally thought to involve cerebellar dysfunction and abnormal oscillatory activity within the cerebello-thalamo-cortical circuit involving motor cortical regions [33,34]. A previous study noted that as tremor progressed over time, the prevalence of cognitive disorders did not change [35], suggesting that cognitive and tremor symptoms may follow different time courses. Cognitive impairments in ET have been linked to disruptions in frontal-subcortical circuits involving the prefrontal cortex, basal ganglia, and thalamus. [36,37].

We found that a higher right FTM tremor score was associated with better language function while higher left FTM score was associated with better visuospatial functioning. The direction of these findings is somewhat surprising given the known lateralization of language and visuospatial functioning: language is function is most frequently dominant in the left hemisphere [38] and visuospatial function is most frequently dominant in the right hemisphere. [39] Patients with ET have decreased functional connectivity in a right-sided visuospatial network compared to healthy controls, which normalizes after thalamic lesioning. [40] Moreover, visual feedback has been shown to worsen tremor, and brain activity changes in a number of regions including right hemisphere visual regions are seen during visual feedback associated tremor worsening and are associated with FTM score [41,42]. One previous study in ET patients who underwent DBS found that higher right thalamic stimulation amplitude was associated with postoperative decline in visuospatial functioning, further supporting a relationship between right brain tremor and visuospatial function circuitry [43]. Another study found that the anterior-posterior location of DBS electrode within the left but not right ventral lateral thalamus was associated with verbal abstraction function in patients with ET who had undergone DBS [44]. More anterior electrode location was associated with worse verbal abstraction function, which the authors suggest is related to thalamic projections to prefrontal language regions. Interestingly, more posterior electrode location was associated with better language function, which the authors suggest may be related to modulation of a cerebellothalamocortical loop involved in language processes. It is possible that the observed relationship between right tremor severity and language function is related to involvement of similar circuitry. Overall, further work is required to clarify the direction of these relationships and how they may be impacted by treatment modalities such as DBS.

Cognitive impairment in patients with movement disorders can have a profound impact on overall quality of life, hinder daily activities, impair work performance, strain interpersonal relationships, and reduce independence [45,46]. Consequently, the overall quality of life for individuals with movement disorders can be significantly affected by cognitive impairment, requiring comprehensive support and management strategies to address both motor and cognitive symptoms. For these reasons, elucidating the association between motor impairment, cognitive impairment, and mood symptoms is paramount in improving the quality of life of ET patients.

In this study, the recruitment strategy focused on patients undergoing DBS surgery. This strategy is likely to have impacted the characteristics of the cohort. Specifically, subjects are likely to have higher severity disease, older age, and less severe depression compared to those in previous studies [3,6], characteristics which may impact our findings. Our findings may have particular relevance for understanding symptom profiles of patients undergoing DBS surgery. Understanding the relationship between tremor and nonmotor symptom severity in this patient population may help to guide patient selection and preoperative counseling as DBS is likely to improve tremor but not nonmotor symptoms. While our results provide an important initial picture of these relationships, further analysis with a larger sample size would allow these relationships to be confirmed and generalized to a more representative ET patient population.

### 4.3. Future directions

Several future directions can help expand understanding of the association between depression, cognition, and motor symptoms in ET patients. Longitudinal studies are essential to determine the temporal relationship between depression and tremor to better understand the causal direction of this association. In addition, future work may examine the relationship between different non-motor symptoms in ET patients. One previous study found that there was no association between depression and memory decline in patients with mild depression scores, but that more severe depressive symptoms were associated with faster memory decline [47]. Other studies have suggested that there may be a distinct clustering of non-motor symptoms more characteristic of ET [26]. Future research should explore these non-motor symptom clusters, potentially uncovering unique patterns within specific ET subtypes. Finally, future studies examining the effect of treatments such as cognitive-behavioral therapy, pharmacotherapy, deep brain stimulation, and focused ultrasound [48] on both motor symptoms and non-motor symptoms in ET patients may also increase our understanding of these relationships and expectations for treatment outcome.

### 4.4. Limitations

The present study has several limitations. The retrospective design of this study has the potential for selection bias, incomplete data, and the inability to establish causal relationships. Future research with larger samples would allow for more robust analyses. Moreover, the study's cross-sectional nature precludes the establishment of temporal relationships between variables, limiting our ability to draw definitive conclusions about causality. Furthermore, this study did not account for education level or the potential influence of medications such as primidone on cognition, due to limitations of data availability related to the study's retrospective design. The FTM and WHIGET scales were used in this study due to institutional practice. One limitation of the FTM scale is that it may not be able to capture as large a range of tremor severity as some other scales, such as the Essential Tremor Rating Assessment Scale (TETRAS), due to a ceiling effect, however it has been shown to have high correlation with TETRAS. [49] Part of our analysis combined scores from two different tremor scales using quartiles of the scores on these different scales. Although tremor quartiles have been utilized in prior studies to categorize motor scores, [21,22] to our knowledge this technique has not previously been used to combine two different tremor scales and requires further validation. However, due to this limitation we additionally analyzed scores from each scale separately. Importantly, all ET patients in our cohort were undergoing evaluation for DBS surgery, likely influencing characteristics of the population including age, tremor severity, and mood. Patients undergoing DBS surgery are likely to be older, have more severe tremor, and may have different levels of depression than the overall ET population. The mean age of the patients in our study was 65 which is older than many other studies and may impact the observed relationships. Further studies are needed to validate our findings in a non-surgical population and determine whether they apply to the general ET population.

## 5. Conclusion

In this retrospective cohort study utilizing a presurgical ET patient database, tremor score was associated with language function. Additionally, total FTM but not WHIGET scores were found to be associated with BDI-II scores. Similarly, FTM scores were associated with language and visuospatial function, while other cognitive domain scores were not associated with tremor scores. These findings increase the understanding of the relationship between tremor and non-motor symptoms in ET patients.

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## CRediT authorship contribution statement

**Anthony E. Bishay:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Daniel R.S. Habib:** Writing – review & editing, Writing – original draft, Data curation. **Alexander T. Lyons:** Writing – review & editing, Writing – original draft, Data curation. **Natasha C. Hughes:** Investigation, Data curation. **Jessica E. Summers:** Data curation. **Kaltra Dhima:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization. **Sarah K. Bick:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2024.03.006.

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