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Daytime sleepiness and nighttime sleep quality across the full spectrum of cognitive presentations in essential tremor

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Abstract

There is increasing evidence that essential tremor (ET) is a complex and heterogeneous disorder with nonmotor features including cognitive deficits and sleep problems. We are unaware of a study that has examined sleep deficits in ET across the full spectrum of cognitive presentations. Cross-sectional (baseline) data on self-reported nighttime sleep dysfunction and excessive daytime sleepiness were collected using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) in 96 ET cases enrolled in a prospective study. Cases underwent a

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Conflict of interest statement

The authors declare no conflict of interest.

Author roles

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comprehensive neuropsychological assessment, and were classified as ET with normal cognition (ET-NC), ET with mild cognitive impairment (ET-MCI), and ET with dementia (ET-D). PSQI scores did not significantly differ across the three ET cognitive groups ($p = 0.22$). ESS scores were highest (more daytime sleepiness) in the ET-MCI group, followed by the ET-D and ET-NC groups, respectively ($p = 0.016$). We examined sleep dysfunction across the cognitive spectrum in ET. We demonstrate for the first time that excessive daytime sleepiness is greater in ET-MCI than ET-NC. Unpredicted low ESS scores in the dementia group raises two possibilities: a self-report bias related to cognitive impairment and/or the possibility that currently undefined pathological heterogeneity in ET may map onto multiple presentations of non-motor deficits.

Keywords

Essential tremor; Cognition; Sleep; Dementia; Clinical

1. Introduction

In recent years, traditional views of essential tremor (ET) as a monosymptomatic and ‘benign’ tremor disorder have given way to awareness of a more complex and heterogeneous disease with nonmotor features [1–6], including mild sleep and cognitive deficits. While it is a distinct disorder, Parkinson’s disease (PD) shares both motor and nonmotor features with ET, though these are often milder in ET. Although mixed [1,4,5,7], there is some evidence that both excessive daytime sleepiness and nighttime sleep quality scores in ET fall intermediately between PD and normal controls [1,5], suggesting that a mild form of sleep dysregulation may be present in ET.

Indeed, pathological studies have identified Lewy bodies in the locus coeruleus of some patients with ET [6,8], and this brainstem nucleus has been implicated in the maintenance of normal sleep patterns [9,10].

In general, there is a well-established and widely accepted deleterious effect of poor sleep on cognition; furthermore, it is likely a bidirectional relationship [11]. However, this relationship has not been formally assessed in ET despite the presence of a mild form of sleep dysregulation as well as a reported twofold risk of developing dementia in elderly onset ET patients [12]. In PD, excessive daytime sleepiness in the absence of nighttime sleep dysfunction was associated with deficits in attention and working memory, executive functioning, memory, and visuospatial functioning, across the cognitive spectrum from normal cognition to dementia [13]. That this sleepiness was observed in the absence of nighttime sleep dysfunction suggests a neuropathological basis, rather than a mere secondary symptom of hyposomnia. It is possible that this pattern of excessive daytime sleepiness and cognitive deficits result from a similar underlying pathology. Whether these same findings in PD apply to ET is unknown; there are no similar studies in ET. With regards to ET, the pathology is likely heterogeneous [14–16]. It is possible that pathological heterogeneity in ET could map onto multiple presentations of non-motor deficits. For this reason, it is important to study sleep deficits in ET across the full spectrum of cognitive presentations. We are not aware of any studies that have done this to date.

The data used for these analyses were derived from a prospective, clinical-pathological study of cognition in ET that utilized a comprehensive neuropsychological battery and represented patients with a wide range of cognitive presentations, from normal cognition to dementia. In this study, which used baseline data, we cross-sectionally examined the relationships between excessive daytime sleepiness, nighttime sleep quality, and cognition in ET. Based on the similarities between ET and PD, and recently-published findings in PD [13], our *a priori* hypothesis was that excessive daytime sleepiness, but not nighttime sleep dysfunction, would be greatest in ET patients with dementia (ET-D), followed by those with mild cognitive impairment (ET-MCI) and those with normal cognition (ET-NC) (i.e., as there is in PD, there would be a dissociation between daytime sleepiness, nighttime sleep quality and cognition, and that daytime sleepiness would be greatest in the group with dementia).

2. Methods

2.1. Cases

One hundred ET cases were recruited into the Clinical-pathological Study of Cognition in Essential Tremor (COGNET; August 2014–October 2015, NIH R01 NS086736). Cases had been diagnosed by their local neurologist as having ET and diagnoses were confirmed after enrollment based on a detailed history and videotaped neurological examination reviewed by a senior neurologist specializing in movement disorders (EDL) who applied reliable and valid diagnostic criteria, as described below.

2.2. Collection of demographic and clinical data

Upon enrollment, all cases provided informed written consent approved by the Institutional Review Boards of both Columbia University and Yale University. Cases were evaluated in person by a trained tester who administered structured clinical questionnaires that elicited demographic and clinical information.

During the evaluation, all current medications were recorded. It is important to consider the effects of medication on sleep as well as cognition. First, as in a previous sleep study [7], a “graded medications with sleep effects” score was carefully assigned to each case with regards to medications and their potential effects on sleep quality (1 = case takes one or more medications that increases drowsiness; 0 = case either takes no medications with sleep effects or case simultaneously takes a combination of medications that stimulate wakefulness and increase drowsiness; -1 = case takes one or more medications that stimulate wakefulness). Second, the number of cases taking sleep medication (medication whose sole purpose is to facilitate sleep) in each group was determined. In addition, the number of cases taking cognition enhancing medication (medication whose sole purpose is to enhance cognition or prevent cognitive decline, e.g., memantine) was determined.

Height and weight of each case were collected via self-report. Body mass index (BMI) was calculated by dividing weight (kilograms) by the square of height (meters).

2.3. Sleep evaluation

Sleep quality was evaluated using two self-administered, validated and widely-used measures: the Epworth Sleep Scale (ESS) [17] and the Pittsburgh Sleep Quality Index (PSQI) [22]. The ESS is a self-report measure that assesses the likelihood that an individual might doze off in eight common situations. Each situation is graded on a scale from 0 to 3 (maximum score, 24 = greatest daytime sleepiness). As in prior studies [1,13,17], an ESS score ≥ 10 was used as an indicator of greater than normal levels of daytime sleepiness. The PSQI assesses a variety of nighttime sleep issues, which are then converted into seven sleep components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, medication use for sleep, and daytime dysfunction) and translated into a global PSQI score (maximum score, 21 = worst sleep quality). As in prior studies [18], a PSQI score > 5 was used as an indicator of poor nighttime sleep quality.

To address the possibility that the cases may under-perceive their sleep symptoms, we used the Bed Partner/Roommate section of the PSQI to determine whether informants reported nighttime sleep dysfunction that cases did not. These sleep dysfunctions included the following items: loud snoring, long pauses or breaths between sleep, legs twitching or jerking during sleep, episodes of disorientation or confusion during sleep, and an “other restlessness” category. The total number of these disturbances was used for analyses.

2.4. Videotaped neurological examination and confirmation of ET diagnoses

As in our previous studies [7], each case underwent a videotaped neurological examination, which included a detailed assessment of postural tremor, five tests for kinetic tremor, and the motor portion of the Unified Parkinson’s Disease Rating Scale (UPDRS) [19], excluding an assessment of rigidity. A senior movement disorders neurologist reviewed all videotaped examinations. Severity of postural and kinetic tremors were rated (0–3), resulting in a total tremor score (range 0–36 [maximum]), a measure of the severity of the action tremor. Based on the videotaped examination, the senior movement disorders neurologist confirmed ET diagnoses using published diagnostic criteria (moderate or greater amplitude kinetic tremor on ≥ 3 tests, or head tremor, in the absence of PD or dystonia).

2.5. Neuropsychological evaluation

The neuropsychological evaluation included a comprehensive cognitive battery, a semi-structured interview with a close family member or friend informant, and clinical impressions of the case’s general cognitive function and functional abilities as reported by a trained tester. The cognitive battery included individual tests that were not dependent on efficient motor functioning, and which were grouped into the following cognitive domains: Attention and working memory (Digit Span subtest from the Wechsler Adult Intelligence Scale-III (WAIS; [20]), Symbol-Digit Modalities test [21]), executive function (Delis-Kaplan Executive Function System [22] subtests Verbal Fluency, Color Word Interference, Sorting, and Twenty Questions), language (The Boston Naming Test [23] and the Multilingual Aphasia Examination Token subtest [24]), memory (California Verbal Learning Test-II [25], Verbal Paired Associates subtest from the Wechsler Memory Scale (WMS; [26]), and the Logical Memory subtest A from the WMS-Revised Edition [27]), visuospatial abilities (Judgment of Line Orientation [28], Benton Facial Recognition [29], and the Visual

Puzzles subtest of the WAIS-IV [30]), global cognition (Mini Mental State Examination (MMSE; [31]), Montreal Cognitive Assessment (MoCA; [32])), and premorbid intellectual functioning (Wechsler Scale of Adult Reading (W-TAR; [33–34])).

The Geriatric Depression Scale (GDS) [35] was chosen to assess depression; this scale minimizes the influence of somatic symptoms on the total depression score. Informants (when available) provided reports of the cases' everyday functioning.

2.6. Cognitive classification

ET cases were classified into cognitive groups (ET-NC, ET-MCI, ET-D) through a consensus conference (neuropsychologist SC; neuropsychiatrist EH; neurologist EDL) using data from the semi-structured interviews with the patient and informant, and clinical and neuropsychological data. Clinical Dementia Rating (CDR) scores [36] were assigned based on the examiner's interview and impression of the patient as well as informant report when available. Raw scores for cognitive tests were transformed to z scores based upon published normative data from healthy, cognitively intact controls, matched for age, education, and gender/ethnicity when possible. Impairment on neuropsychological tests was demonstrated by z scores of -1.5 on at least two neuropsychological tests (either two tests in the same domain or one impaired test in two different domains).

ET-MCI diagnoses were based on criteria set forth by Peterson [37] and consisting of both impairment on testing as described above and functional deficit as reported by the participant or an informant (CDR of 0.5). Subjective memory complaint was not a requirement for the study or for the diagnoses. Cases with test impairment and CDR score 1 were considered demented (ET-D). Cases with a CDR score < 0.5 and no test impairment or impairment on only one test were considered ET-NC.

2.7. Final case selection

Four cases who had brain surgery to treat their tremor (1 focused ultrasound, 3 deep brain stimulation) were excluded from analyses due to limited available literature regarding the potential adverse cognitive and sleep effects of these treatments. The final sample comprises 96 ET cases.

2.8. Statistical analyses

Statistical analyses were performed using SPSS (Version 21; Chicago, Illinois). We compared the ET cognitive groups by demographic and clinical variables. Our initial testing compared the three ET cognitive groups; if a difference was detected, then we compared ET-D to ET-NC and ET-MCI to ET-NC. In several analyses, we ordered the groups (e.g., ET-NC, ET-MCI, ET-D) and used the Jonckheere-Terpstra test to assess for an ordinal progression in a variable (e.g., age). We then assessed the clinical correlates of sleep test scores. We used chi-square tests, Student's *t*-tests, analysis of variance, and Pearson's correlation coefficients when variables were normally distributed. For measures that were not normally distributed, non-parametric approaches were used (e.g. Mann-Whitney test, Kruskal-Wallis test, Spearman's rho). ESS and PSQI scores were not normally distributed. To test our hypothesis, (sleep test scores differ across cognitive groups), we performed

Mann-Whitney tests using continuous sleep scale scores and Chi-square tests using dichotomously coded sleep scores based on established cutoffs for both measures (ESS score ≥ 10 , PSQI score > 5) [17,18], indicating clinically significant levels of daytime sleepiness and impaired nighttime sleep quality, respectively. In logistic regression models (forward approach) examining the association between cognitive diagnosis (ET-NC, ET-MCI, ET-D) and ESS score (ESS ≥ 10) or PSQI score (PSQI > 5) as the dependent variable, we conservatively adjusted for variables that were associated with either the cognitive diagnosis or specific sleep test score at a $p < 0.10$ level. Hence, the selection of confounding variables differed slightly for each sleep test score. When ESS was the dependent variable, we included ET-NC and ET-MCI. We also examined the PSQI component subscores across the three ET cognitive groups using Kruskal-Wallis tests. Statistical significance was set at $\alpha = 0.05$, unless otherwise stated.

3. Results

3.1. Case characteristics

There were 96 ET cases (67 ET-NC, 16 ET-MCI, and 13 ET-D, Table 1). The cognitive groups were similar in numerous demographic and clinical respects (e.g., education, race, see Table 1 for p values > 0.05). As expected, cognitive features differed across the three groups and cognition enhancing medication use was lowest in the ET-NC group (Table 1). The ET-D and ET-MCI groups were older than the ET-NC group, and the ET-D group had higher total tremor scores than the other groups. Antidepressant medication use was greatest in the ET-D group.

3.2. Clinical correlates of sleep test scores

The ESS score co-varied either marginally or significantly with several variables (BMI and GDS score, Table 2). The PSQI score covaried either marginally or significantly with age, total prescription medications, medication with sleep effects score, BMI, MMSE scores and GDS scores (Table 2).

3.3. Sleep scale test scores

The mean $\pm$ standard deviation [median] ESS score of the entire cohort was 6.7 ± 6.0 [4.3]. The PSQI score of the entire cohort was 5.9 ± 5.0 [3.9]. Of the sample, 29 (30.2%) had an ESS score ≥ 10 , signifying poor nighttime sleep quality, and 23 (24.0%) had a PSQI score > 5 , signifying excessive daytime sleepiness. The ESS and PSQI scores were not significantly correlated with one other (Spearman's $r = 0.14$, $p = 0.91$). This lack of association persisted even after the ET cases were stratified by cognitive diagnosis (data not shown).

The ESS score was 6.1 ± 4.0 [5.0] in ET-NC, 10.1 ± 5.0 [10.0] in ET-MCI, and 6.8 ± 2.9 [6.0] in ET-D (Kruskal-Wallis test = 8.320, $p = 0.016$, Table 3); the ET-MCI cases had scores that were higher than each of the other two groups (Table 3). An ESS score ≥ 10 was observed in 13 (19.4%) ET-NC cases, 9 (56.3%) ET-MCI cases, and 1 (7.7%) ET-D cases ($\chi^2 = 10.48$, $p = 0.005$, Table 3).

The PSQI score was 6.4 ± 4.1 [5.0] in ET-NC, 5.5 ± 4.1 [4.0] in ET-MCI, and 4.4 ± 3.4 [3.5] in ET-D, a difference that did not achieve statistical significance ($p = 0.22$). A PSQI score > 5 was observed in 23 (34.3%) ET-NC cases, 3 (18.8%) ET-MCI cases, and 3 (23.1%) ET-NC cases ($p = 0.36$). We examined the seven component scores of the PSQI and analyses revealed a weak, yet significant difference only in sleep duration, with ET-NC reporting the shortest sleep duration, followed by ET-MCI and ET-D, respectively (Table 4), although this difference did not remain significant after correcting for multiple comparisons ($\alpha = 0.007$). Given the number of comparisons ($n = 7$), however, this difference was of questionable significance.

We next considered the role of potential confounding factors. In a logistic regression analysis that adjusted for age, total tremor score, cognition enhancing medication, antidepressant use, BMI and GDS score, cognitive diagnosis (ET-MCI vs. ET-NC) was associated with ESS score (odds ratio = 4.34, 95% confidence interval = 1.11–16.92, $p = 0.03$). In a logistic regression analysis that adjusted for age, total tremor score, antidepressant use, cognition enhancing medication use, total number of prescription medications, medication with sleep effects score, BMI and GDS score, cognitive diagnosis (ET-NC, ET-MCI, ET-D) was not associated with PSQI score ($p = 0.582$).

3.4. Informant reports of case sleep symptoms

To address the possibility that the cases may under-perceive their sleep symptoms, we used the Bed Partner/Roommate section of the PSQI to determine whether informants reported nighttime sleep dysfunction that cases did not. These include the following items: loud snoring, long pauses or breaths between sleep, legs twitching or jerking during sleep, episodes of disorientation or confusion during sleep, and an “other restlessness” category. In a Spearman’s correlation, the total number of these disturbances was not related to the total PSQI score, $r = 0.2$, $p = 0.88$, suggesting that informants and patients did not reliably agree or disagree on the presence of sleep disturbances.

4. Discussion

To our knowledge, this study is the first to examine nighttime sleep quality and daytime sleepiness across the full spectrum of cognition that is observed in patients with ET. Based on the similarities between ET and PD, and recently-published findings in PD [13], our *a priori* hypothesis was that excessive daytime sleepiness, but not nighttime sleep dysfunction, would be greatest in ET patients with dementia (ET-D), followed by those with mild cognitive impairment (ET-MCI) and those with normal cognition (ET-NC) (i.e., as there is in PD, there would be a dissociation between daytime sleepiness, nighttime sleep quality and cognition, and that daytime sleepiness would be greatest in the group with dementia). As hypothesized, nighttime sleep dysfunction as measured by PSQI scores did not statistically differ across the ET cognitive groups. While excessive daytime sleepiness scores differed across groups, it did not do so precisely in the way we had hypothesized. ESS scores were highest in the ET-MCI group, and similar across ET-NC and ET-D groups, and the proportion of cases reporting clinically significant levels of excessive daytime sleepiness (ESS ≥ 10) followed a similar pattern.

ESS and PSQI scores were not correlated even after stratifying data by cognitive diagnosis. A study using a community sample of older adults found a weak correlation ($r = 0.16$, $p = 0.03$) between the measures that was eliminated by removing the 'Daytime Dysfunction' sub-scale scores of the PSQI [38], and another study of patients referred to a sleep laboratory also found a weak correlation ($r = 0.13$, $p = 0.05$) [39], although they did not report whether it persisted without the above mentioned subscale. Although the ESS and the PSQI measure different aspects of sleep symptoms, intuitively nighttime sleep dysfunction should result in excessive daytime sleepiness; the absence of a strong relationship in these studies may be due to other, individual health factors affecting the regulation of arousal.

Alterations in nighttime sleep architecture, including shorter sleep duration, are associated with both age and cognitive impairment in patients with PD [40] as well as those without PD [41–43]. Older adults frequently report dissatisfaction with their sleep quality, and up to 50% of older adults report disturbed sleep, though there are often comorbid medical or psychiatric contributors. More relevant to the current results is that excessive daytime sleepiness is a widely accepted correlate of cognitive impairment and dementia [41–43], and has previously been reported in patients with ET relative to matched controls [7]. However, its association or dissociation with certain cognitive subtypes of ET has not been examined previously.

There are several potential explanations for our findings. First, there is some concern about the validity of using self-report sleep measures in individuals with cognitive impairment [44]. Indeed, under-perception of daytime napping as measured by multiple sleep latency tests has been associated with lower scores on both the ESS and a measure of global cognition in Alzheimer's disease [45]. Thus, one explanation for our findings could be that there is a valid excess of daytime sleepiness in ET-MCI when compared with ET-NC, yet that those with ED-D under-report the extent of their excessive daytime sleepiness. An alternative explanation, which is not mutually exclusive, is that there is phenotypic heterogeneity within ET. Clinical features appear to manifest differently across ET patients, with some developing head tremor, PD, or dementia, while others do not, leading to speculation that the contemporary clinical entity ET may actually represent several disease entities [14]. It is possible that some varieties of this disorder are associated with excessive daytime sleepiness whereas others are not, and that the former track more with the co-occurrence of mild cognitive dysfunction that is less likely to progress to dementia. This is discussed further below. Finally, it is conceivable that the small sample size of the ET-D group ($n = 13$) provided insufficient power to detect a difference in daytime sleepiness in that group. This reflects the *a priori* design of the study, as we administered neuropsychological assessments to 96 ET subjects and later classified them into cognitive groups. While sample size is certainly a concern, the means of the ET-D and ET-NC group were virtually identical (Table 3), suggesting that a mere increase in sample size (i.e., increased enrollment) would not likely have resulted in a clinically meaningful difference between those two groups. Nonetheless, the possibility certainly remains.

As noted above, it is likely that ET may actually represent several disease entities (i.e., that there are likely to be several disorders that fall under the title "ET") and that some varieties of this disorder are associated with excessive daytime sleepiness whereas others are not. The

classification of potential ET symptom clusters into discrete clinical entities requires further clinical and pathological study. Several methods of classification have been proposed, including age of onset [46], familial history, and neuropathological features [47].

Our findings should be interpreted in the context of several limitations. First, as it was a cross-sectional investigation, we are unable to make inferences about temporal relations and potential causal relationships between sleep and cognitive deficits in ET. Second, although our measures were commonly used measures of sleep dysfunction, they are likely susceptible to self-report bias in individuals with cognitive impairment. We attempted to corroborate nighttime sleep dysfunction with informant reports and found no significant relationship. Although the questions on the informant and patient sections of the PSQI are slightly different, we would have expected at least a weak correlation indicating that at least both parties were aware of sleep difficulty; the lack of this relationship suggests that there may be a large discrepancy in the perception of the existence of sleep dysfunction. Future work should also compare case and informant measures of excessive daytime sleepiness. Self-report bias may be minimized in future work by also using objective measures, such as actigraphy for nighttime sleepiness and multiple sleep latency tests for excessive daytime sleepiness. While the enrollment of a control group would have provided additional useful information, the design of our study was identical to that of Goldman et al. [13], who administered the ESS and PSQI to a group of PD patients with a range of cognitive deficits and who did not enroll a control group. Hence, the current work is parallel to that presented in a related disorder, PD, and provides valid information about the associations between sleep dysfunction and cognitive dysfunction within the setting of ET. Finally, while it is possible that some of our ET cases may have had Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), which can present on rare occasion as isolated action tremor, several studies have shown that the proportion of ET patients harboring expanded FMR1 alleles is very low [48,49], and is no greater than that seen in control samples. While the present study did not utilize genetic testing, we expect that the proportion of our sample having FXTAS is negligible.

This study also had several strengths. These included the prospective design, the enrollment and consensus diagnosis of ET cases with a wide range of cognitive presentations from normal cognition through to dementia, our use of a comprehensive neuropsychological examination with the ability to capture subtle deficits that may be missed by global cognitive screens, and our evaluation of multiple possible contributors to either cognition or sleep, including medication, BMI, age, and depression.

The association between sleep dysfunction and cognitive decline has been well-established and widely accepted. Sleep dysfunction, including nighttime sleep disturbances and excessive daytime sleepiness, has been associated with a variety of physical and psychological morbidities. The current findings raise several issues surrounding the assessment of non-motor symptoms of ET, namely potential self-report inaccuracies related to cognitive impairment and the possibility that currently undefined pathological heterogeneity may map onto multiple presentations of non-motor deficits. Despite these limitations in interpretation, our findings demonstrate for the first time that reported excessive daytime sleepiness is greater in ET-MCI than ET-NC.

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Abbreviations

ET	essential tremor
PD	Parkinson's disease
ET-NC	ET with normal cognition
ET-MCI	ET with mild cognitive impairment
ET-D	ET with dementia
ESS	Epworth Sleepiness Scale
PSQI	Pittsburgh Sleep Quality Index
UPDRS	Unified Parkinson's Disease Rating Scale
GDS	Geriatric Depression Scale
CDR	Clinical Dementia Rating Scale
MMSE	Folstein Mini Mental State Examination

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Table 1

Demographic and clinical characteristics of 96 ET cases.

	ET-NC, n = 67	ET-MCI, n = 16	ET-D, n = 13	p-Value
<i>Demographic variables</i>				
Age (years)	79.9 ± 9.1	84.5 ± 7.0 ^{1a}	87.2 ± 6.4 ^{1a}	0.007^a 0.003^b
Male gender	20 (29.9)	8 (50.0)	6 (46.2)	0.79 ^c
Education (years)	15.9 ± 2.8 [16.0]	15.0 ± 2.5 [15.0]	14.8 ± 2.7 [16.0]	0.21 ^d
White race	63 (94.0)	16 (100.0)	13 (100.0)	0.79 ^c
<i>Tremor duration and severity</i>				
Tremor duration (years)	35.6 ± 20.4 [31.5]	38.8 ± 22.4 [37.5]	48.8 ± 25.3 [25.0]	0.22 ^d
Total tremor score	21.2 ± 5.9 [21.0]	21.3 ± 6.4 [20.8]	25.2 ± 8.1 [25.0] ^{3a,4b}	0.04^d 0.06^b
<i>Overall health, health habits, and medications</i>				
Smoker in lifetime	33 (49.3)	5 (31.2)	6 (46.2)	0.43 ^c
Cigarette pack years ^g	12.2 ± 17.9 [0.0]	14.7 ± 27.8 [0.0]	4.3 ± 6.8 [0.0]	0.46 ^d
Current smoker	4 (6.0)	0 (0.0)	0 (0.0)	0.41 ^c
Total prescription medications	5.5 ± 4.8 [4.0]	5.3 ± 3.0 [5.0]	8.1 ± 6.2 [6.0]	0.20 ^d
Medications with sleep effects score ^h	0.2 ± 0.6 [0.0]	0.5 ± 0.7 [1.0]	0.0 ± 0.7 [1.0]	0.16 ^d
Sleep medication	18 (26.9)	2 (12.5)	2 (15.4)	0.60 ^c
Antidepressant use	5 (8.3)	1 (6.3)	5 (38.5)	0.01^c
Cognition enhancing medication	2 (3.3)	3 (23.1)	3 (23.1)	0.03^c
BMI (kg/m ²)	25.5 ± 5.1 [24.0]	26.4 ± 3.9 [25.9]	22.8 ± 6.2 [23.6]	0.34 ^d
<i>Cognitive and neuropsychological features</i>				
Attention/working memory domain score	-0.13 ± 0.77	-0.97 ± 0.49 ^{1a}	-0.76 ± 1.83 ^{1a}	0.002^a <0.001^f
Executive function domain score	0.55 ± 1.71 [0.41]	-0.39 ± 0.67 [-0.39] ^{3a}	-1.19 ± 0.87 [-0.88] ^{3a,4a}	<0.001^d <0.001^f
Language domain score	0.17 ± 0.52	-0.29 ± 0.64 ^{1a}	-0.79 ± 0.78 ^{1a,2b}	<0.001^a <0.001^f
Memory domain score	0.03 ± 0.72	-1.44 ± 0.76 ^{1a}	-2.13 ± 0.54 ^{1a,2a}	<0.001^a <0.001^f
Visuospatial domain score	0.74 ± 0.84	0.39 ± 0.76	-0.25 ± 1.20 ^{1a,2b}	0.002^a 0.003^f
MMSE score	28.6 ± 2.7 [29.0]	27.3 ± 2.3 [27.5] ^{3a}	23.7 ± 3.9 [23.0] ^{3a,4a}	<0.001^d <0.001^f
GDS score	6.8 ± 5.4 [6.0]	7.8 ± 6.4 [6.0]	8.7 ± 6.9 [7.0]	0.85 ^d

Values are mean ± standard deviation [median] or number (percentage). Significant values are bold.

BMI = body mass index (kg/m²), ET-D = essential tremor dementia, ET-MCI = essential tremor mild cognitive impairment, ET-NC = essential tremor normal cognition, GDS = Geriatric Depression Scale, MMSE = Folstein Mini Mental State Examination.

^aAnalysis of variance comparing the 3 groups.

^bJonckheere-Terpstra test comparing the 3 groups

^cChi-square test comparing the 3 groups.

^dKruskal Wallis test comparing the 3 groups.

^eMann-Whitney test comparing the 2 groups.

^fStudent *t*-test comparing the 2 groups.

^gCigarette pack years included data on both smokers and non-smokers.

^hEach case was assigned one of the following three values: 1 = case takes one or more medications that increases drowsiness; 0 = case either takes no medications with sleep effects or case simultaneously takes a combination of medications that stimulate wakefulness and increase drowsiness; -1 = case takes one or more medications that stimulate wakefulness.

^{1a}Significantly different from ET-NC ($p < 0.05$) using Student *t*-test.

^{2a}Significantly different from ET-MCI ($p < 0.05$) using Student *t*-test.

^{2b}Marginally different from ET-MCI ($p < 0.10$) using Student *t*-test.

^{3a}Significantly different from ET-NC ($p < 0.05$) using Mann-Whitney test.

^{4a}Significantly different from ET-MCI ($p < 0.05$) using Mann-Whitney test.

^{4b}Marginally different from ET-MCI ($p < 0.10$) using Mann-Whitney test.

Table 2

Association between demographic and clinical characteristics and ESS or PSQI test scores.

	Correlation with ESS score or mean $\pm$ standard [median] deviation ESS score	p-Value	Correlation with PSQI score or mean $\pm$ standard deviation [median] PSQI score	p-Value
<i>Demographic variables</i>				
Age (years) ^a	r = -0.06	0.59	r = -0.26	0.03
Gender ^b				
Male	7.4 $\pm$ 4.3 [7.0]	0.20	5.6 $\pm$ 3.7 [4.5]	0.59
Female	6.4 $\pm$ 4.3 [5.5]		6.2 $\pm$ 4.2 [4.5]	
Years of education ^c	r = 0.01	0.95	r = 0.06	0.64
<i>Tremor duration and severity</i>				
Tremor duration ^c	r = -0.01	0.96	r = 0.08	0.53
Total tremor score ^c	r = -0.14	0.19	r = -0.02	0.88
<i>Overall health, health habits, and medications</i>				
Smoker in lifetime ^b				
Smoker	7.0 $\pm$ 4.4 [6.0]	0.64	6.4 $\pm$ 4.6 [4.0]	0.79
Non-smoker	6.6 $\pm$ 4.3 [6.0]		5.6 $\pm$ 3.5 [5.0]	
Cigarette pack years ^{c,f}	r = 0.06	0.58	r = 0.08	0.50
Current smoking status ^b				
Smoker	7.0 $\pm$ 4.6 [6.0]	0.88	9.0 $\pm$ 7.2 [7.0]	0.39
Non-smoker	6.8 $\pm$ 4.4 [6.0]		5.8 $\pm$ 3.8 [5.0]	
Total prescription medications ^c	r = 0.16	0.17	r = 0.24	0.06
Medication with sleep effects score ^{c,d}	r = 0.03	0.79	r = 0.23	0.08
Antidepressant use ^b				
Yes	7.1 $\pm$ 4.6 [8.0]	0.53	6.2 $\pm$ 3.7 [5.5]	0.66
No	6.6 $\pm$ 4.2 [6.0]		5.8 $\pm$ 4.0 [4.0]	
Cognition enhancing medication use ^b				
Yes	5.4 $\pm$ 3.9 [6.0]	0.61	7.5 $\pm$ 6.4 [5.0]	0.50
No	6.6 $\pm$ 3.9 [6.0]		4.8 $\pm$ 3.0 [4.0]	
BMI (kg/m ²) ^a	r = 0.21	0.05	r = 0.21	0.07
<i>Cognitive and neuropsychological features</i>				
Attention/working memory domain score ^a	r = -0.14	0.21	r = 0.10	0.93
Executive function domain score ^c	r = -0.16	0.14	r = 0.12	0.32
Language domain score ^a	r = -0.003	0.98	r = 0.07	0.52
Memory domain score ^a	r = -0.12	0.28	r = 0.22	0.65
Visuospatial domain score ^a	r = -0.06	0.56	r = -0.22	0.06
MMSE scores ^c	r = 0.07	0.49	r = 0.33	0.005
GDS scores ^c	r = 0.19	0.08	r = 0.44	<0.001

	Correlation with ESS score or mean $\pm$ standard deviation ESS score	p-Value	Correlation with PSQI score or mean $\pm$ standard deviation [median] PSQI score	p-Value
<i>Sleep environment</i>				
Bed partner status ^e				
Partner in same bed	7.7 $\pm$ 4.7 [7.0]	0.49	5.9 $\pm$ 4.1 [6.0]	0.92
Partner in same room, different bed	9.5 $\pm$ 0.7 [9.5]		5.0 $\pm$ 1.4 [5.0]	
Partner in another room	8.0 $\pm$ 4.6 [8.0]		7.0 $\pm$ 4.5 [5.0]	
No bed partner or roommate	6.5 $\pm$ 4.0 [6.0]		5.8 $\pm$ 4.1 [4.0]	

Data are means $\pm$ standard deviation [median] or Spearman's rho (r). Significant values are bold.

BMI = body mass index (kg/m²), ESS = Epworth Sleep Scale, GDS = Geriatric Depression Scale, MMSE = Folstein Mini Mental State Examination, PSQI = Pittsburgh Sleep Quality Index.

^aPearson's correlation (r).

^bMann-Whitney test.

^cSpearman's rho (r).

^dEach case was assigned one of the following three values: 1 = case takes one or more medications that increases drowsiness; 0 = case either takes no medications with sleep effects or case simultaneously takes a combination of medications that stimulate wakefulness and increase drowsiness; -1 = case takes one or more medications that stimulate wakefulness.

^eKruskal-Wallis test.

^fCigarette pack years included data on both smokers and non-smokers.

Table 3

Sleep scale results by ET cognitive group.

	ET-NC, n = 65	ET-MCI, n = 16	ET-D, n = 13	p-Value
ESS	6.1 ± 4.0 [5.0]	10.1 ± 5.0 [10.0] ¹	6.8 ± 2.9 [6.0] ²	0.016^a
ESS 10	13 (19.4)	9 (56.3) ³	1 (7.7) ⁴	0.005^b
PSQI	6.4 ± 4.1 [5.0]	5.5 ± 4.1 [4.0]	4.4 ± 3.4 [3.5]	0.22 ^a
PSQI >5	23 (34.3)	3 (18.8)	3 (23.1)	0.36 ^b
Informant reported sleep disturbance ⁵	13 (52.0)	2 (40.0)	2 (40.0)	0.81 ^b

Data are mean ± standard deviation [median] or n (%). Significant values are bold.

ESS = Epworth Sleepiness Scale, ET-NC = essential tremor normal cognition, ET-MCI = essential tremor mild cognitive impairment, ET-D = essential tremor dementia, PSQI = Pittsburgh Sleep Quality Index.

^aKruskal-Wallis test comparing the 3 groups.

^bChi-square test comparing the 3 groups.

¹Significantly different from ET-NC ($p < 0.05$) using Mann-Whitney test.

²Significantly different from ET-MCI ($p < 0.05$) using Mann-Whitney test.

³Significantly different from ET-NC using Chi-square test.

⁴Significantly different from ET-MCI using Chi-square test.

⁵Reports of one or more sleep disruptions (see Section 2). Data from a sample of approximately 30% of each cognitive group (25 ET-NC, 5 ET-MCI, 5 ET-D).

Table 4

Component scores of PSQI for the ET cognitive groups.

	ET-NC, n = 65	ET-MCI, n = 16	ET-D, n = 13	p-Value
Component 1: Subjective sleep quality	0.9 ± 0.8 [1.0]	0.6 ± 0.8 [0.0]	0.5 ± 0.8 [0.0]	0.09 ^a
Component 2: Sleep latency	1.0 ± 0.9 [1.0]	1.1 ± 0.9 [1.0]	0.7 ± 0.7 [1.0]	0.66 ^a
Component 3: Sleep duration	0.8 ± 0.8 [1.0]	0.5 ± 0.9 [0.0]	0.2 ± 0.4 [0.0]	0.03^{a,b}
Component 4: Sleep efficiency	0.8 ± 1.1 [0.0]	1.2 ± 1.4 [1.0]	0.9 ± 1.3 [0.0]	0.47 ^a
Component 5: Sleep disturbance	1.3 ± 0.6 [1.0]	1.1 ± 0.3 [1.0]	1.0 ± 0.0 [1.0]	0.11 ^a
Component 6: Use of sleep medication	0.8 ± 1.2 [0.0]	0.4 ± 0.9 [0.0]	0.4 ± 0.9 [0.0]	0.28 ^a
Component 7: Daytime dysfunction	0.7 ± 0.7 [1.0]	1.1 ± 0.5 [1.0]	1.0 ± 0.0 [1.0]	0.24 ^a

Data are mean ± standard deviation [median]. Significant values are bold.

^aKruskal-Wallis test comparing the 3 groups.^bAfter adjustment for multiple comparisons ($\alpha = 0.007$), this is no longer significant.