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Depressive symptoms predict memory decline in Essential Tremor

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Abstract

Introduction: Essential tremor (ET), a common movement disorder, is characterized by motor, cognitive and psychiatric symptoms. Depressed mood, a symptom of ET, has historically been viewed as a psychological response to disability. However, depressive symptoms are emerging as a predictor of cognitive decline across several clinical populations. We examined if depressive symptoms predict decline in global cognition, memory, and executive functioning among older adults with ET.

Methods: 125 cognitively normal participants with ET completed three in-person assessments of cognition, mood, and motor symptoms at baseline, 18 months, and 36 months; baseline data were collected from July 2014-July 2016. Depressive symptoms were measured with the Geriatric Depression Scale. Cognitive functioning was measured via a 3–4-hour neuropsychological evaluation. Generalized linear regression models examined depressive symptoms as a predictor of decline in global cognition, executive functioning (EF), and memory.

Results: Participants were grouped according to a median split (GDS <5 versus >=5) due to the bimodal distribution of the data. In unadjusted models, depressive symptoms did not predict change in global cognition ($b = -.002$, $p = .502$) or EF ($b = .000$, $p = .931$), however individuals with GDS >=5 demonstrated faster memory decline in unadjusted ($b = -.008$, $p = .039$) and adjusted models ($b = -.009$, $p = .019$).

Declaration of Interests

Dr. Stephanie Cosentino has provided consultation services to SAGE pharmaceuticals on the development of a literature review examining Essential tremor.

Other authors declare no interests.

Conclusion: The presence of 5 or more depressive symptoms predicted mildly faster memory decline in cognitively normal older adults with ET over 36 months. We discuss potential mechanisms and clinical implications.

Keywords

Essential Tremor; Depression; Cognition; Neurodegeneration

1. Introduction

Essential tremor (ET) is one of the most common adult-onset movement disorders [1]. Diagnosis of ET is based on the presence of a kinetic tremor [2] but, like other movement disorders such as Parkinson's disease (PD) and Huntington's disease (HD), ET is a multi-faceted disease characterized by psychiatric and cognitive symptoms as well [3]. Several studies have indicated that in comparison to controls, patients with ET have more depressive symptoms across the lifespan [4], and older adults are 57% more likely to have Mild Cognitive Impairment (MCI) [5] particularly when tremor begins at or above age 65 years. Furthermore, an approximate 60% increased risk of dementia was found in a population-sample of ET [6]. Determining which older adults with ET are more likely to experience cognitive decline will provide important prognostic information for physicians, patients and families.

Depressed mood may hold particular value as a prognostic indicator of cognitive decline in ET. Depressive symptoms are prominent in older adults with ET [7] and, although such symptoms have historically been viewed as a psychological response to tremor-related disability [8], new evidence suggests that the emergence of depressive symptoms may in fact be a clinical marker of neurodegeneration. Indeed, depressive symptoms have been shown to precede cognitive decline in neurodegenerative disorders such as Alzheimer's disease (AD) [9] and PD [10]. Alongside potential neurodegenerative factors, there may also be other physiological or psychosocial mechanisms by which depressed mood precedes cognitive decline, including disrupted sleep [11] or increased stress [12]. The current prospective, longitudinal study, encompassing comprehensive cognitive assessments at three 18-month intervals, is the first to examine whether depressive symptoms predict cognitive decline in ET. This study examines decline in global cognition, as well as in two specific cognitive domains shown to be commonly impaired in ET, executive function (EF) and memory [13].

An improved understanding of the clinical features which predict cognitive decline in ET will improve patient care and disease prognosis. Moreover, emerging work raises the intriguing possibility that treatment of depressed mood and related psychosocial factors may provide an opportunity to slow future cognitive decline [14].

2. Methods

2.1. Participants

Participants were part of a larger, prospective, longitudinal study (Clinical Pathological Study of Cognitive Impairment in Essential Tremor ["COGNET" NIH NINDS R01

NS086736]) assessing cognition in patients with ET. Study recruitment was performed online through study and International Essential Tremor Foundation websites. Participants who met the following inclusion criteria were recruited: (1) previous diagnosis of ET, (2) aged >=55 years, (3) no history of surgery for the treatment of ET including deep brain stimulation (DBS), (4) agreement to complete study measures, and (5) concurrent enrollment as a brain donor. For purposes of this study, we excluded: (1) cognitive impairment at baseline (i.e., dementia, MCI or other cognitive impairment related to substance use, stroke, or other injuries), and (2) concomitant diagnoses of PD, dystonia, or any non-ET causes of tremor in the study at baseline. Written and signed informed consent was obtained from eligible participants. Study procedures were approved by Yale University, The University of Texas Southwestern Medical Center, and Columbia University Internal Review Boards.

Baseline data for these analyses were collected from July 2014 through July 2016. Participants were seen for a total of three in-person assessments (baseline, 18 months, and 36 months). Cognitive diagnoses (normal, MCI, and dementia) were assigned at each visit during a diagnostic case conference with trained experts (EDH, SC). Neuropsychological tests were selected *a priori* for a diagnosis of MCI, as described previously [13,15]. This study included only those who were diagnosed as cognitively normal at baseline. A total of 201 participants had available longitudinal cognitive data. Of these, 76 were excluded due to: concomitant baseline diagnoses of PD or dystonia (n = 17), missing depression data (n = 7), baseline diagnosis of MCI, dementia, or cognitive impairment related to substance use, stroke, or other injuries (n = 37), and missing data on covariates (n = 15), yielding a total sample of 125 participants (see Table 1 for descriptive statistics).

2.2 Measures

Clinical and demographic information—Demographics including age, sex, education, and race were recorded via self-report as was information regarding participants' current prescribed medications.

Depressive Symptoms—Depressive symptoms were assessed via self-report on the Geriatric Depression Scale (GDS), a brief, 30-item questionnaire that assess a variety of depressive symptoms excluding somatic symptoms of depression (i.e., change in sleep or appetite) as such physical symptoms can be present for a variety of reasons among older adults [16].

Cognitive functioning—To minimize tremor-related disadvantage, the neuropsychological test battery was designed to exclude tests which rely on timed or precise motor-based responses (see Collins et al., 2017 [15] for full battery description). In the current study, along with global cognition, two domain-specific scores were examined as primary outcomes: (1) Executive Function (EF) and (2) memory. The EF domain consisted of the Delis–Kaplan Executive Function System (DKEFS): Verbal Fluency Test, Color-Word Interference, Sorting, and 20-Questions subtests [17] and the Wechsler Adult Intelligence Scale IV (WAIS-IV) Digit Span Backward total score [18]; the reliable digit span (RDS), an embedded measure of performance validity with a cutoff score of 7, was

obtained from the longest string of digits repeated without error over two trials from both the forward and backward conditions [19]. The memory domain comprised the Wechsler Memory Scale Revised (WMS-R): Logical Memory immediate and delayed scores [20], the Wechsler Memory Scale IV (WMS-IV): Verbal Paired Associates immediate and delay scores [21], and the California Verbal Learning Test II (CVLT-II) total recall, long delay, and recognition discriminability scores [22]. The discriminability score, which measures memory storage by eliminating demands on retrieval, is derived from the recognition portion of the test and reflects the number of true- versus false-positive responses [23]. Global cognition included an average z-score of the aforementioned EF and memory tests, alongside measures assessing attention, visuospatial functioning, and language functions. Specifically, the domain of attention included: Oral Symbol Digit Modalities Test [24], and Digit Span Forwards [18]. The domain of visuospatial abilities included the Benton Judgment of Line Orientation [25] and the Benton Facial Recognition Test [26]. Finally, language was assessed via the Boston Naming Test (BNT) [27].

Motor Functioning—Diagnosis of ET was confirmed by a movement disorders neurologist (E.D.L). Tremor severity was rated from a videotaped neurological examination. Based on the neurological examination, diagnoses of ET were confirmed according to diagnostic criteria which require moderate or greater amplitude kinetic tremor during three or more tests, or head tremor in the absence of PD, dystonia, or movement disorder [2].

Total tremor score (higher scores indicate more severe tremor, range 0–36) was calculated based on individual ratings for kinetic and postural tremor (12 items, rated 0–3).

2.3 Data Analysis

Data analysis was performed with SPSS Statistics v. 26. Baseline variables were described using mean and standard deviation for continuous measures, and number and percentage for categorical measures (see Table 1). Raw scores of cognitive assessments were converted to z- scores derived from the mean and SD of baseline cognitive scores of cognitively normal participants. Although individual neuropsychological measures often have published normative scores, the variables which are used to derive these normative scores differ across measures (i.e., while all are adjusted for age, some also adjust for education, and/or gender). Due to these differences, the current study generated within-sample normative scores based on the mean and SD of the cognitively normal participants included in the current study, and adjusted for demographic variables in the statistical models.

Depressive symptoms were dichotomized based on the median split of the sample given the bimodal distribution of such symptoms (see Supplementary Fig. S1): GDS <5 versus >=5. Although a score of 5 is not in the clinically depressed range, scores among those classified as having relatively more depressive symptoms ranged from 5 to 24 [16]. Scores above 5 have been used to define late-life depressive symptomatology [28].

Independent sample t-tests were conducted to examine mean differences in cognition, tremor severity, demographics and clinical information as a function of depressive symptom group. Any participants whose RDS score fell below 7, the performance validity cutoff [19], were excluded from the regression analyses. Chi square analyses were run to examine

significant differences between depressive symptom group and sex and cluster scores. Generalized linear regression models were then conducted to examine the extent to which depressive symptom group at baseline predicted rate of cognitive decline over time. Each model included depressive symptom group (GDS <5 versus >=5) as the predictor, time defined as months from baseline to follow-up visits, and a depressive symptom group*time interaction reflecting differences in rate of change in the cognitive outcome as a function of depressive symptom group. Unadjusted and adjusted models were run separately for each cognitive outcome (EF, memory, and global cognition). Adjusted models included as covariates age, education, sex, total tremor score, and total medications. “Cognitive cluster”, a categorical score reflecting cognitive strengths and weaknesses, was also included as a covariate. Previously described in detail, cluster analysis in this cohort of cognitively normal ET participants identified three overall profiles of cognitive functioning including, relatively low memory scores (Cluster 1), relatively low attention and visuospatial scores (Cluster 2), and high scores in all cognitive domains (Cluster 3); please see Cersonsky et al., 2020 [29] for details regarding clusters. Cluster scores were included as covariates to account for the possibility that baseline differences in cognitive domains, despite being within the normal range, could have relevance for decline in those domains. The false discovery rate (FDR) procedure was utilized as a statistical correction to adjust for multiple comparisons.

3. Results

Baseline demographics and clinical information are described in Table 1. Description of baseline demographics and clinical information as a function of depressive symptom group is presented in Table 2. Independent sample t-tests showed no significant differences in age, education, tremor severity, medications or cognitive performance across these two groups. There was also no difference in the distribution of cognitive clusters between the depressive symptom groups (χ^2= 0.21, p = .901). However, those with GDS >=5 had a higher proportion of females (χ^1) = 4.83, p = .039 (Fisher’s exact test p value).

Generalized linear regression models:

For longitudinal analyses, there were 125 observations at T1, 125 observations at T2, and 117 observations at T3 resulting in a total of 367 observations. Out of the 125 participants, 122 had available data for the computation of the RDS. Out of these, 5 participants fell below the RDS performance validity cut-off (7), thus a total of 8 individuals either didn’t have data to be computed or were confirmed to have invalid data. Analyses were then conducted excluding these participants.

Results from generalized linear regression models are presented in Tables 3–6. Depressive symptom group did not predict change in global cognition (b = −.002, p = .502) or EF (b = .000, p = .931) in either the unadjusted or adjusted models (see Table 3). However, individuals with GDS >=5 evidenced faster memory decline (b = −.008, p =.039). This result remained significant in the adjusted model (b = −.009, p = .019). Several covariates were also found to predict cognitive decline such as cognitive cluster, age and time.

Secondary analyses examined the extent to which depressive symptom group predicted changes in the two primary components of memory, information retrieval (CVLT-Total

Recall) and information storage (CVLT-recognition discriminability). Depressive symptom group did not predict retrieval ($b = -.003$, $p = .622$), but did predict storage in both the unadjusted ($b = -.017$, $p = .004$) and adjusted models ($b = -.018$, $p = .003$) (See Table 4). Global cognition, EF, and overall memory did not survive FDR correction. Memory storage survived FDR correction in the unadjusted model ($p = 0.038$) and neared significance ($p = 0.056$) in the adjusted model.

4. Discussion

Determining which older adults are at greatest risk for cognitive decline has important implications for clinical management, prognosis, and early intervention to delay or slow decline. While older adults with ET have an elevated risk of cognitive decline compared to the general population [6], there is substantial heterogeneity in cognitive functioning in the context of ET [5,6,29]. For example, cognitive change (particularly in domains of executive function and memory [13]) has been observed in ET however, while certain studies suggest that ET is related to cerebellar degeneration [30], there is emerging research on memory deficits suggestive of non-cerebellar disease (i.e., an inability to recognize words from multiple choice occurred only in patients with extra-cerebellar disease [31]). Alongside cognitive change, depression [7] has been observed In ET. Depressive symptoms have been shown to precede memory decline in neurodegenerative disorders such as AD [9] and PD [10]. Thus, the current longitudinal study examined the extent to which depressive symptoms predict global cognitive decline as well as specific decline in executive function and memory among older adults with ET who were cognitively normal at baseline. Results indicated that the presence of at least 5 depressive symptoms at baseline predicted mildly faster memory decline over 36 months, particularly in the ability to store newly learned information. In contrast, depressive symptoms did not predict decline in global cognition or in executive function.

Various mechanisms may link depressive symptoms and memory decline. The first to consider is the impact of physiological and/or psychosocial changes, such as sleep or stress, on memory. Generally, shorter sleep duration has been associated with subsequent cognitive decline [11]. In ET specifically, sleep disturbance is more common as compared to controls [4] and it has been suggested that those with sleep disorders could be at higher risk for dementia over time [32]. Indeed, REM sleep behavior disorder (RBD) has been associated with worse performance on tasks of verbal memory in patients with ET, as compared to ET patients without RBD [32]. Additionally, the impact of stress should be considered. Evidence suggests that chronic stress is associated with reduced hippocampal volume [12] and increased levels of cortisol have been associated with impaired memory performance [12].

Secondly, a neurodegenerative process should also be considered as a possible mechanism linking depressive symptoms to future memory decline for two reasons. First, literature on a variety of neurodegenerative disorders suggests that new-onset mood symptoms in older adults could result from neurodegenerative changes [9,10]. Second, individuals with ET have a disproportionate presence of degenerative postmortem brain changes as compared to control brains [33] and an increased incidence of dementia diagnoses [34].

Interestingly, findings in this study link depressive symptoms to decline in memory storage in particular, an aspect of memory most frequently associated with AD given its reliance on hippocampal function [15]. Taken together, while speculative, it is possible that depressive symptoms could be an early feature of AD-related decline. Ongoing work is incorporating neuropathological examination to better inform the basis of cognitive changes in ET.

There are several clinical implications of the current findings. First is the emphasis on early detection and intervention for depressed mood and its correlated psychosocial factors, such as sleep and stress. Depressed mood is under-recognized in ET [7] and early interventions targeting depressive symptoms may provide an opportunity not only to improve mood, but also perhaps even to impact future cognitive decline [14]. Second, should a neurodegenerative process be unfolding, early detection could inform prognosis and coordination of care.

In summary, this study sought to determine whether depressive symptoms predict cognitive change over 36 months among cognitively normal older adults with ET. Results indicated that the presence of 5 or more depressive symptoms at baseline predicted mildly faster memory decline, but did not predict rate of global cognitive decline or change in executive function. Psychosocial factors and neurodegeneration should be considered as possible mechanisms linking depressive symptoms and memory decline in ET.

Several limitations of this study should be considered. Demographically, this study largely enrolled non-Hispanic White participants, limiting generalizability to other ethnoracial groups. Therefore, it is recommended that a more diverse sample is utilized for future studies. Second, depressive symptoms evaluated at baseline were not coded with regard to their time course and onset (i.e., longstanding versus new onset). Continued follow up of the current cohort will enable examination of new onset depressive symptoms at the second assessment in relation to cognitive decline over subsequent visits. Third, the depression cutoff was based on the median split in this specific cohort, and thus lower than the clinical cut off for depression (9 is commonly used for the GDS [16]). As only 17 participants met the clinical cut off (versus 58 when divided by median split) we did not group participants according to the clinical cutoff. However, it is noted that emerging research suggests that late-life depressive symptomatology is defined as >5/30 on the GDS [28]. Finally, given the relatively small sample, and the nature of the study as primarily a hypothesis generating rather than hypothesis confirming study.

This study also has several strengths. First, ET diagnoses were carefully assigned by a senior neurologist specializing in movement disorders, which allows interpretation of results within the context of a pure ET cohort. Second, diagnoses of normal cognition were assigned by a neuropsychologist and a geriatric psychiatrist during clinical case conferences, which incorporated extensive neuropsychological testing and interviews regarding everyday function. Third, participants were followed at regular intervals with repeat testing across different cognitive domains, allowing for close examination of the cognitive trajectories of various abilities. Ongoing work will ultimately allow for examination of clinical symptoms, longitudinal trajectories, and postmortem neuropathologic diagnoses among this valuable cohort of older adults with ET.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Demographic and Clinical Characteristics

	Mean (SD) / n (%)	Median (sample range)
Age (years)	77.0 (9.5)	77.0 (55 – 95)
Sex/Gender (Male)	45 (36.0)	-
Education (years)	16.0 (2.5)	16.0 (10 – 20)
Race		
White	121 (97%)	-
African American	2 (2%)	-
Other	1 (1%)	-
Number of current prescription medications	5.2 (2.0)	5.0 (0 – 26)
Time (months) in Study	17.29 (14.53)	-
Total tremor score	19.7 (4.0)	20.0 (9.5 – 30)
GDS score	5.9 (5.0)	5.0 (0 – 24)
GDS median split (>5)	58 (46%)	-
Relatively low memory scores (Cluster 1)	55 (44%)	-
Relatively low attention and visuospatial scores (Cluster 2)	30 (24%)	-
High scores across cognitive domains (Cluster 3)	40 (32%)	-
Cognitive *z*-scores		
Global Cognition	0.01 (0.5)	.05 (−1.35 – 1.22)
Memory	−0.01 (0.7)	−.05 (−1.9 – 1.5)
Executive Function	0.01 (0.6)	.09 (−1.7 – 1.38)
RDS cut off ≥ 7	117 (94%)	-

Note. GDS = Geriatric Depression Scale; Cognitive Cluster 1 = relatively low memory scores; Cognitive Cluster 2 = relatively low attention and visuospatial scores; Cognitive Cluster 3 = high scores in all cognitive domains (see [29] for details regarding clusters).

Table 2

Baseline Demographics, Medications and Cognitive Scores by Depressive Symptom Group

	Sample median split <5 Depressive Symptoms	**Sample median split >=5 Depressive Symptoms**	***t* or chi-square**	**CI**	***p*-value**
	M (SD) or %	**M (SD) or %**			
Age (years)	76.3 (1.3)	77.9(1.1)	−0.9	−5.1, 1.7	.331
Education (years)	16.4 (0.3)	15.6 (0.3)	1.6	−0.1, 1.6	.113
Sex/gender (Male)	45.0%	26.0%	**4.8**	-	**.039**
Number of current prescription medications	4.7 (3.9)	5.8 (3.9)	−1.6	−2.5, 0.2	.103
Total tremor score	19.7 (4.9)	20.6 (4.8)	−1.1	−2.7, 0.7	.259
Relatively low memory scores (Cluster 1)	45.0%	43.0%	0.2	-	.901
Relatively low attention and visuospatial scores (Cluster 2)	22.0%	26.0%			
High scores across cognitive domains (Cluster 3)	33.0%	31.0%			
Global Cognition *z*-score	0.0 (0.5)	−0.0 (0.5)	0.8	−0.1, 0.2	.390
Memory *z*-score	−0.0 (0.7)	−0.0 (0.7)	−0.9	−0.3, 0.2	.923
Executive Function *z*-score	0.0 (0.5)	−0.0 (0.6)	1.7	−0.2, 0.3	.085

Note. t = Independent Sample t-test; CI = Confidence intervals of mean differences. Cognitive Cluster 1 = relatively low memory scores; Cognitive Cluster 2 = relatively low attention and visuospatial scores; Cognitive Cluster 3 = high scores in all cognitive domains (see [29] for details regarding clusters).

Table 3

Depressive symptom group predicting Change in Global Cognition, Executive Functioning and Memory

	Global Cognition		***Executive Functioning***		***Memory***	
	B (se)	**p-value**	**B (se)**	**p-value**	**B (se)**	**p-value**
Unadjusted						
Time	−.000 (.002)	.796	−.003 (.002)	.124	**.009 (.002)**	**<.001**
Depressive symptoms (>5)	−.053 (.093)	.564	−.156 (.10)	.135	.063 (.133)	.635
Time x depressive symptoms	−.002 (.003)	.502	.000 (.004)	.931	**−.008 (.004)**	**.039**
Adjusted						
Time	.001 (.002)	.691	−.003 (.002)	.112	**.009 (.002)**	**<.001**
Depressive symptoms (>5)	.036 (.057)	.526	−.016 (.074)	.827	.094 (.106)	.372
Time x depressive symptoms	−.003 (.003)	.378	.000 (.004)	.926	**−.009 (.004)**	**.019**
Age	**−.031 (.004)**	**<.001**	**−.032 (.005)**	**<.001**	**−.028 (.007)**	**<.001**
Male vs. female	.110 (.078)	.156	.142 (.090)	.116	−.198 (.124)	110
Education	−1.991e-05 (.019)	.999	.023 (.022)	.292	.025 (.024)	.301
Cognitive cluster	**.302 (.047)**	**<.001**	**.212 (.054)**	**<.001**	**.440 (.061)**	**<.001**
Total Tremor Score	−.017 (.010)	.083	−.015 (.010)	.139	−.009 (.014)	.516
Number of medications	−.009 (.011)	.387	−.034 (.015)	.024	.00 (.014)	.741

Note: Time = months since baseline. All predictors (depressive symptoms, age, education, sex, cognitive clusters, and medications) were measured at baseline. When adjusted with the false discovery rate procedure, the depressive symptom group no longer predicted change in global cognition, executive functioning, or overall memory.

Table 4:

Depressive symptom group predicting change in Memory Retrieval versus Memory Storage

	Memory Retrieval		***Memory Storage***	
	B (se)	***p*-value**	**B (se)**	***p*-value**
Unadjusted				
Time	**.011 (.005)**	**.016**	**.13 (.004)**	**<.001**
Depressive symptoms (>=5)	.050 (.178)	.778	**.592 (.148)**	**.001**
Time x depressive symptoms	−.003 (.007)	.622	**−.017 (.006)**	**.004** *
Adjusted				
Time	**.013 (.005)**	**.007**	**.135 (.004)**	**<.001**
Depressive symptoms (>=5)	.109 (.164)	.507	**.596 (.181)**	**.001**
Time x depressive symptoms	−.004 (.006)	.477	**−.018 (.006)**	**.003**
Age	**−.036 (.008)**	**<.001**	**−.024 (.007)**	**.001**
Male vs. female	−.177 (.170)	.299	−.245 (.178)	.168
Education	.045 (.033)	.180	.004 (.043)	.920
Cognitive cluster	**.420 (.088)**	**<.001**	**.296 (.100)**	**.003**
Total Tremor Score	−0.001 (.018)	.946	−.007 (.018)	.709
Number of medications	−.014 (.023)	.540	−.012 (.020)	. 553

Note: Time = months since baseline. Depressive symptoms are quantified via self-report on the GDS. Memory retrieval is represented by the CVLT-II total recall score, whilst storage was measured with the CVLT-II recognition discriminability index.

*The use of indicates that results remained significant after correction with the false discovery rate procedure.