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Mind the Gaps: What We Don't Know About Cognitive Impairment in Essential Tremor

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Abstract

Introduction: Although the hallmark feature of essential tremor (ET) is tremor, there is growing appreciation that cognitive impairment also occurs, including increased prevalence of mild cognitive impairment (MCI) and increased prevalence and incidence of dementia. With emerging knowledge of ET-cognitive impairment, come fundamental questions regarding its course, bases, predictors and clinical outcomes. Studies in the general population and in Parkinson's disease (PD), a related movement disorder, offer a starting point from which to begin filling these clinically important knowledge gaps.

Methods: A PubMed search (June 2018) identified articles for this review.

Results: Much of our knowledge of cognitive impairment in ET is of the *static* condition (e.g., prevalence of cognitive impairment in ET), with nearly no information on its bases, predictors and *dynamics* (i.e., course, and clinical outcomes). In PD, where such data have been published, rates of cognitive decline and conversion to MCI/dementia are higher than in the general population. Predictors of cognitive change in PD and the general population have also been identified, yet they only partially overlap one another.

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Conflict of Interest Statement

The authors declare no conflict of interest.

Conclusion: The predictors and dynamics of cognitive impairment have been investigated fairly extensively in the general population, to a somewhat lesser extent in PD, and are emerging only now in ET. We suggest that longitudinal studies specific to ET are needed, and we outline variables to be considered in these investigations. Increased knowledge of ET-cognitive impairment will facilitate meaningful counseling of patients and their families.

Keywords

essential tremor; cognition; mild cognitive impairment; dementia; risk factors

Introduction

Essential tremor (ET) is among the most prevalent neurological diseases [1]. Although ET had been viewed for many years as an exclusively motor disorder based on its hallmark feature of kinetic tremor [2], there is increasing recognition of non-motor impairments in ET [3, 4]. In particular, clinical studies show that ET patients have poorer cognitive performance than age-matched controls [5–10]. While in many patients the problem is mild, in some it reaches more severe proportions. Results of clinical research are consistent with epidemiological studies demonstrating that ET patients have a higher prevalence of mild cognitive impairment (MCI) than controls [11], and are at increased risk of developing dementia (relative risk [RR] = 1.64 - 1.89) [12, 13]. This converging evidence of the presence of cognitive impairment thus suggests that there is another side to ET [4].

While the past ten years have seen the emergence of a broad range of studies examining cognition in ET [4, 14], our knowledge of whether and how cognitive impairment evolves over time remains surprisingly rudimentary, and there is much that we do not know. The literature in Parkinson's disease (PD) suggests that the rate and predictors of cognitive decline differ in the context of a movement disorder as opposed to the general population. As such, it is important to ascertain ET-specific knowledge about rates of cognitive change, conversion rates, and the factors that predict the course of cognition. Patients with cognitive impairment may also reach a variety of critical endpoints, including admission to a hospital, need for services, or death. The extent to which the presence of cognitive impairment increases risk for these endpoints in ET is unknown. Moreover, little is known about the neuropathological basis of cognitive changes in ET, specifically, the extent to which they represent cerebellar dysfunction or a different pathological process.

Impaired cognition is a growing part of the clinical dialogue in ET, particularly among middle-aged and older ET patients. Despite an outgrowth of scientific studies, as we shall see, there remain important gaps in knowledge. As such, physicians cannot at present meaningfully counsel their ET patients about the extent of the problem, its underlying causes, risk factors, or progression. It is important to identify and then systematically fill our gaps in knowledge, thereby providing data to guide the dialogue between physicians, patients and families in clinical settings.

In this paper, we briefly review the current state of knowledge about cognitive impairment in ET, and then turn our focus to a specific set of clinical and scientific questions regarding cognitive change, its predictors, and its basis that warrant further investigation. To create a

roadmap for this investigation, we briefly review what is known in both the general population and PD, a related movement disorder. A review on ET cannot be written without a relevant context or comparison point, and the brief discussions of the general population and PD are meant to provide a scaffold and relevant framework for the review of ET. That literature is thus viewed as a “gold standard” for the *types of studies* that could be conducted in ET.

Methods

We performed a PubMed search in June 2018 to identify articles for this review. The search field included titles and abstracts. The primary search term was “essential tremor”, and this was crossed with “cognitive” (203 articles), “cognition” (58 articles), “mild cognitive impairment” (17 articles), “dementia” (134), “conversion” (10 articles), and “risk factors” (50 articles). Three similar searches were also conducted. First, the primary search term was “Parkinson disease”, and this was crossed with “cognitive” (1,103 articles), “cognition” (285 articles), “mild cognitive impairment” (154 articles), “dementia” (1,130), “conversion” (84 articles), and “risk factors” (274 articles). Second, the primary search term was “general population”, which was crossed with “cognitive” (2,715 articles), “cognition” (494 articles), “mild cognitive impairment” (101 articles), “dementia” (892), “conversion” (235 articles), and “risk factors” (10,826). Third, the primary search term was “Alzheimer disease”, which was crossed with “cognitive” (4,518 articles), “cognition” (983 articles), “mild cognitive impairment” (1,312 articles), “dementia” (4,729), “conversion” (224 articles), and “risk factors” (670).

Results

General comments

Below, we divide our presentation of results into two primary divisions: “what we do know” and “what we do not know”.

What we do know

Rates of Mild Cognitive Impairment and Dementia in ET—Many studies spanning North America, Europe and Asia document cognitive deficits in ET patients in excess of those seen in age-matched controls [3, 4, 14–17]. These deficits occur not only in older-onset and older ET cases, but also in young ET patients. Thus, a study of 45 young ET patients and 35 age-matched controls (respective mean ages = 24.6 ± 7.2 and 24.8 ± 5.4 years) reported a Montreal Cognitive Assessment (MoCA) score of 25.80 ± 2.76 in ET patients and 28.23 ± 1.69 in controls ($p < 0.001$) [18]. While the cognitive domains most often reported to be affected in ET are those of executive function and memory, deficits are not limited to these domains [4, 19].

Cognitive symptoms in ET also seem to be progressive, and epidemiological studies have shown that prevalent MCI as well as prevalent and incident dementia are more common in ET cases than controls [4, 10–13, 20]. In a study of individuals age 65 and older in Spain, 11.4% of ET cases had dementia vs 6.0% of controls [20]. In a study in New York of individuals age >65 , 25.0% of ET cases had dementia vs 9.2% controls [13]. In prospective,

longitudinal studies, the risk of incident dementia was 1.64 – 1.89 times higher in ET than in age-matched controls [12, 13]. Some data suggest that the risk of dementia is highest in, and perhaps even restricted to, individuals with older age of tremor onset [12, 21].

The timing of the cognitive features of ET relative to that of motor features is also of some interest. While cognitive features certainly occur once the disease (i.e., tremor) is manifest, one study actually reported that the cognitive changes preceded the motor manifestations of ET [22]. The study therefore raised the possibility that there may be a “premotor stage” of disease [23].

When reviewing these studies, it is important to keep in mind that ET patients with cognitive problems are *not simply* older adults with MCI or Alzheimer’s disease that happen to also have ET [24]. Studies reporting the presence of MCI and dementia in ET, for example, compare ET cases to age-matched controls [11, 13, 20] and show a higher prevalence of MCI and dementia in ET, thereby indicating that MCI and dementia are disease-linked and not merely age-linked. By analogy, the cognitive problems in PD are not just “old people” with MCI or dementia who happen to also have PD; there is both clinically and pathologically a separable PD-cognition entity. The same is likely true for ET. That is, ET itself appears to be a risk factor for developing a gradient of cognitive impairments.

Nature and Neuroanatomic Substrates of Cognitive Impairment in ET—

Characterizing the kinds of cognitive changes that occur in ET, and not simply the presence or absence of cognitive impairment, is an important undertaking for at least two reasons. Not only will systematically exploring and documenting heterogeneity in the cognitive presentations of ET facilitate identification and early detection of cognitive deficits, but it will guide investigation of the various potential neuroanatomic substrates and neuropathologies underlying such deficits. Early studies examining cognition in ET, as well as the majority of cognitive studies in ET to date, primarily highlight deficits in executive functioning. For example, individuals with ET have been shown to perform more poorly on tasks assessing theory of mind [25], verbal fluency [26], mental set shifting, inhibition, and problem solving [5], among others. With regard to the severity of the executive dysfunction, and its similarity to that seen in PD, at least two studies [6, 27] have shown comparable levels of executive dysfunction in the two groups, as well as similarly impaired cognitive profiles more broadly in comparison to controls. However, a recent population based study did highlight subtle differences in the two groups; while both groups performed more poorly than controls, the PD group had differentially worse performance on an executive measure (i.e., verbal fluency) than the ET group, and the latter evidenced slower processing speed [26] than the PD group.

Given the documented role of the cerebellum in supporting executive functioning [28, 29], and the known compromise of the cerebellum in ET [30–34], executive deficits in ET have generally been conceptualized as the result of inefficient cerebellar-cortical networks, particularly those projecting to and from the prefrontal cortex [35–40]. Indeed, deterioration in such networks may well underlie executive dysfunction in patients with ET, particularly those who do not progress to dementia. However, cerebellar pathology may be unable to explain the full burden and progression of cognitive impairment seen in ET [14, 16]. In

Rates of Conversion to MCI—In Table 1, we report what is known with respect to annual conversion rates to MCI and dementia across the general population, PD and ET. For the general population, the three studies show remarkably similar annual rates of conversion from cognitively normal to MCI, hovering around 5% (Table 1) [52–54]. For PD, there are three studies, all of which show higher annual rates of conversion to MCI than those in the general population [55–57], ranging from 7.2 – 12.1% (Table 1) [55–57]. Taken together, what can be seen is that the conversion rates to both MCI and dementia are consistently higher among individuals with PD than in the general population.

Currently, the data for conversion to MCI and dementia data in ET are limited both in scope and methodology. There are two studies [13, 58]. In one, 52 patients age >50 were recruited from a Movement Disorder clinic [58]. The dropout rate was high, with only 24 (46.2%) of 52 enrollees completing a second follow-up assessment. Four of 8 (50.0%) with no cognitive impairment at baseline converted to MCI within 2 years (i.e., 25.0% per year) [58]. Aside from the small sample size and the high dropout rate is the fact that the study sampled clinic cases rather than those from the population; hence, conversion rates may have been higher than in a population-based sample, for which conversion rates tend to be considerably lower [59]. In the second study, 1,604 community-dwelling elders in northern Manhattan were enrolled in a prospective cohort study and followed for a mean of 3.8 years; 11.9% of cognitively normal ET cases developed MCI (i.e., 3.1% per year) vs. 10.0% of controls, a difference that was not significant [13]. The study had several limitations, with one of the main ones being that ET diagnoses were assigned based solely on a handwriting sample rather than a detailed neurological examination [13]. In summary, there are two methodologically-limited studies in ET, yielding widely disparate results for annual conversion rates from normal cognition to MCI (25% [58] and 3.1% [13]). There are no further data for ET and no data from studies with longer follow-up (i.e., beyond 3.8 years).

Rates of Conversion to Dementia—For the general population, numerous studies show annual rates of conversion from MCI to dementia that range from 2.6 – 6.3% (Table 1) [59–61]. The lower end of the estimate range, 2.6% (95% CI = 2.3 – 2.9%), was generated by a review of nine long-term community-based studies [59]. The authors noted that the rates were higher in clinical studies from specialist centers where individuals seek treatment for cognitive concerns, as well as in studies with fewer than 5 years of follow-up as those with the most adverse risk profile will tend to progress, dropout or die, leaving a cohort of less vulnerable sufferers (i.e., healthy survivors) to be followed over the longer term [59].

In PD, several studies have examined conversion rates from MCI to dementia (Table 3) [55, 56, 62, 63]. In these studies, rates range from 7.6% to 15.5%, consistently higher than those in the general population. Again, the data for ET are scanty. There is only one study, discussed earlier, which recruited 52 patients > age 50 from a Movement Disorder Clinic [58]. The dropout rate was high, with only 24 (46.2%) completing a second follow-up assessment. Four of 16 (25.0%) with MCI at baseline converted to dementia within 2 years (i.e., 12.5% per year) [58]. As mentioned previously, aside from the small sample size and the high dropout rate, the clinic-based nature of the sample may have resulted in higher conversion rates than seen in the broader ET population [59]. There are no further data (including no data from studies with longer follow-up, i.e., beyond 2 years).

Percentage who convert to dementia if followed for long enough—One issue that is often of importance to patients is the inevitability of dementia. In other words, if followed for long enough, what proportion of a specific group can be expected to develop dementia? In the general population, 22.7% - 35.2% of individuals in the age range of 90 – 105 develop dementia (Table 1) [64, 65]. In PD, the values are higher; in one study of PD cases with a baseline mean age of 73.4 years, 78.2% demented by 8 years [66]. In another study, it was 83% at 20 years of disease (mean age after 20 years = 74 years [67], Table 1). For ET, there are simply no data (Table 1).

Underlying patho-mechanisms for MCI and dementia—While there is obviously a large literature documenting the patho-mechanisms that underlie dementia in both Alzheimer's disease [46, 68, 69] (the most common cause of dementia in the general population) [70] and PD [71–73], there are virtually no clinical-pathological studies in ET. While cognitive impairment in ET may be mediated to some extent by the cerebellar changes seen in ET, an alternate hypothesis is that cognitive impairment and dementia may occur due to other pathological changes that are either concomitant with, or related to, the ET disease process. In one study, the authors compared a group of 40 ET patients that were free of dementia clinically and without Alzheimer's disease on postmortem examination versus a group of 32 controls [74]. The ET patients had a higher Braak neurofibrillary stage than controls; however, Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores for neuritic plaques were similar in patients and controls [74]. The study suggested that ET may predispose individuals to accumulate more widespread cellular tau aggregates, and thus tau could play a central role in the cognitive impairment that can accompany ET [74]. At this juncture, there have been no published clinical-pathological studies of prospectively cognitively well-characterized ET cases in which these cases have come to autopsy.

Predictors of cognitive change and conversion to MCI and dementia—In ET, there are no data on variables which predict rate of cognitive change or conversion to MCI and dementia, other than older age having been identified as a predictor of conversion to dementia [12]. However, the clinical features that predict these cognitive outcomes have been studied extensively in the general population, and to some extent in PD (Table 2), providing specific variables for consideration in ET. In the general population of non-demented individuals, predictors of cognitive change include demographic [75–77], genetic [76], medical [78], subjective cognitive [79], and biologic factors [80–84]. Conversion to MCI has been predicted by many of these variables (Table 2) as well performance on specific cognitive tests [85–88], and aspects of psychological [89, 90] and physical functioning [91–93]. Conversion to dementia has been predicted by both cognitive features [94, 95] as well as a series of non-cognitive features [95–99] (Table 2). In PD, studies have revealed that the predictors of cognitive change and progression to MCI and dementia overlap to some extent with those in the general population [57, 100], but also include a distinctive set of cognitive, neurologic, psychiatric, biologic, and genetic factors that may be disease-specific, as well as factors related to the clinical severity of PD such as duration and stage [57, 100–107].

Predictive utility of cognitive impairment for critical endpoints—Once cognitive impairment sets in, the clinical outlook and prognosis are important to establish. Patients with cognitive impairment may reach a variety of endpoints, including admission to a hospital, institutionalization, and death. They may also arrive at certain medical events (e.g., falls and fractures) and reach the point at which they require certain social and medical assistive services (e.g., home health aide) (Table 3). In Alzheimer’s disease, the primary cause of dementia in the general population, there is an extensive literature examining the extent to which degree of cognitive impairment increases the risk of reaching these additional critical endpoints [108–112] (Table 3). For PD patients with cognitive impairment, there is a similar literature [113–124] (Table 3). For ET, there are no data (Table 3).

Discussion

At present, there are several important and clinically significant gaps in our knowledge of cognitive deficits in ET. Due to the relative absence of long-term, prospective studies, however, there is little or no knowledge of the *dynamic* condition (i.e., rates of decline and diagnostic conversion), its predictors, outcomes, or its underlying pathological mechanisms. We know that the course of cognitive decline and rates of conversion to MCI and dementia are more aggressive in the context of PD than in the general population (Table 1); thus, there is reason to believe that ET patients cannot simply be counseled based on information obtained in the general population. Without ET-specific information, it is difficult to counsel patients and their families meaningfully about their risk of developing these cognitive conditions overall, as well as their individual risks in the setting of their baseline demographic and clinical features. Prospective longitudinal studies are needed to carefully characterize cognition, assign clinical diagnoses, follow individuals over time, and obtain autopsy. Importantly, studies should derive patients outside of specialty centers and follow participants for at least 5 years, as MCI and dementia conversion rates can otherwise be artificially inflated [59].

In addition to insufficient information regarding rate of cognitive decline and conversion to MCI and dementia in ET, we do not yet know the clinical factors that predict these cognitive outcomes.

Finally, there is an extensive literature documenting the patho-mechanisms that underlie dementia in both Alzheimer’s disease [46, 68, 69] and PD [71–73], that offer directions for the clinical-pathological study of ET [74]. One existing study suggested that ET may predispose individuals to accumulate tau aggregates [74]; however, the mechanisms are likely to be multi-factorial, and the role of vascular pathology, Lewy bodies and other pathologies have not been explored.

In conclusion, at present, there is a need for studies to fill these numerous gaps we have outlined above. These studies should include a brain donation at the end of life, thereby allowing investigators to map cognitive patterns on to brain changes.

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- There is growing evidence that cognitive impairment may occur in patients with ET.
- However, numerous clinical and scientific questions still remain.
- There are nearly no data on rate of cognitive decline and conversion to dementia.
- There is nearly no knowledge of pathomechanisms underlying cognitive impairment.
- Absence of these data prevent meaningful counseling of patients and their families.

Table 1.

Rates of Conversion to MCI and Dementia

	General population	Parkinson's disease	Essential tremor
Annual rate of conversion from normal cognition to MCI	5.1% (95% CI = 4.6% - 5.6%) [52] 5.6% (95% CI = 4.6 - 5.6%) [54] 5% (95% CI = 3 - 6%) [53]	9.9% [55] 7.2% [57] 12.1% [56]	25.0% [58] * 3.1% [13] *
Annual rate of conversion from MCI to dementia	2.6% (95% CI = 2.3 – 2.9%) [59] 4.0% [61] 6.3% [60]	10.6% [62] 7.6% [56] 8.9% [55] 15.5% [63]	12.5% [58]
Conversion to dementia if followed for long enough (i.e., cumulative prevalence) or prevalence of dementia in oldest old	22.7% among persons aged 90 – 105 [64] 35.2% in 95 year-olds [65]	78.2% over 8 years [66] 83% over 20 years [67]	No Data

* Only two studies have been conducted, both with major methodological limitations

MCI = Mild Cognitive Impairment. CI = Confidence Interval.

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Table 2.

Predictors of cognitive change and conversion to MCI and dementia

Category	Predictor	Rate of Cognitive Change		Conversion from NC to MCI		Conversion from NC or MCI to Dementia	
		GP	PD	GP	PD	GP	PD
Demographic	Age	[75–77, 125]		[53]		[54, 61, 95, 126, 127]	[128–133]
	Male gender	[134]			[57]	[135]	[136]
	Female gender					[126, 137–139]	
	Education			[140]	[100]		[132, 136, 141]
Medical	Vascular risk	[78]				[126, 142]	
	CAD	[143]					
	Head injury	[144]	[103]			[96, 97]	
	Diabetes Mellitus		[107]			[98, 126, 145, 146]	
	Hypertension		[105]			[99]	
	Estrogen replacement					[147–149]	[150]
	Hyperlipidemia					[126]	
Blood Markers	Serum	[80]	[106]				
	Homocysteine	[82]				[137, 151–153]	[154]
	Plasma β -amyloid					[155, 156]	
	Plasma clusterin					[157, 158]	
	Plasma factor I					[157]	
	Serum miR-206					[159]	
	Terminal complement complex					[157]	
Genetic	APOE E4	[76, 79, 83, 84]	[101]			[160, 161]	
	COMT	[81]	[101]	[162]			
	MAPT H1 haplotype						[163, 164]
	GBA mutation						[136, 165, 166]
Physical	Gait Speed			[167]			
	Body Mass Index			[168, 169]		[168]	
Sensory	Olfactory deficits	[170]	[104]	[91]	[104]	[95, 171, 172]	[173]
	Hearing loss			[92]			
Psychiatric	Depressive Symptoms	[174]		[90]	[57]	[127, 175]	[136]
	Psychotic Symptoms	[176]					[177]
	Thought Disorder		[101]				
	Personality			[89]			
	Visual Hallucinations						[66]
	Excessive Daytime Sleepiness						[132]
Cognition	Memory complaints	[79]		[178]	[179]		

	Memory			[86, 88]	[57]	[52, 180–182]	[62] [183–185]
	Executive Function			[85, 86, 186]	[57]	[94]	[128, 183, 187–190]
	Language			[85, 88]	[191]	[52, 60]	[62]
	Visuospatial Function			[87, 192]	[57]	[52, 94]	[56, 62, 128]
	Attention			[88]			
	Global Cognition					[60, 171, 193] [95]	[136]
	Clock Drawing					[193, 194]	
	Processing Speed						[56]
Neuroimaging	Brain volume			[53]			
Function	CDR Score	[76]					
	Everyday Function			[53, 195–197]		[61, 160]	
	IADLS					[198]	
Family History	Dementia	[76]					
Lifestyle	Lifestyle engagement	[199]					
	Social engagement		[104]				[141]
	Physical Activity			[93]		[137, 200–202]	
	Dietary					[125, 200, 203, 204]	
	Tobacco Use					[126] [137]	[205]
	Alcohol Use					[126]	
	NSAID Use					[206]	
Ascertainment Method	Clinic-based			[53]			
Disease Specific	Levodopa dosage		[101]				[132]
	Changes in gait	NA	[207]				
	REM SBD		[102]				
	Disease duration				[57]		
	UPDRS Score				[57]		[131, 136]
	Hoehn and Yahr Stage				[57, 100]		[100]
	Age of onset					[136, 141, 183]	
	Motor						Motor symptoms [133, 183] Motor phenotype (non-tremor- dominant phenotype) [66, 128, 208]

GP = general population. MCI = mild cognitive impairment. NC = normal cognition. PD = Parkinson’s disease. CAD = Coronary artery disease. APOE = Apolipoprotein E. COMT = Catechol-O-methyltransferase. MAPT = microtubule-associated protein tau. GBA = glucocerebrosidase. CDR = Clinical Dementia Rating. IADLS = Instrumental Activities for Daily Living. NSAID = Nonsteroidal anti-inflammatory drugs. REM SMD = Rapid eye movement sleep behavior disorder. UPDRS = Unified Parkinson’s disease rating scale.

Table 3.

Cognitive Predictors of Critical Endpoints

Endpoints	Alzheimer's disease	PD Dementia	ET Dementia
Institutionalization	Worse cognition [209]	Dementia [113, 114, 116, 119, 121]	No Data
Death	Dementia Severity [120–124]	Dementia [117, 118, 122]	
Higher Medicare expenditures	Dementia severity [210]	Dementia [124]	
Psychiatric features (e.g., psychosis, depressive symptoms)	Greater cognitive impairment [211]	Dementia [115, 121]	
Falls and fractures leading to hospitalization	No Data	Dementia [123]	
Admission to a care home or hospital	Cognition [212]	Dementia [120]	
Home Health Aide Use	Awareness of memory loss [213]	No Data	

PD = Parkinson's disease. ET = Essential Tremor

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