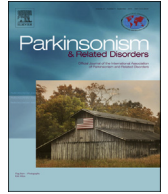




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## Non-motor symptoms in essential tremor: A review of the current data and state of the field

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### ABSTRACT

**Background:** The motor features of essential tremor (ET) include its hallmark element, kinetic tremor, yet non-motor features are increasingly being recognized as an accompanying part of what was previously viewed as a solely motor disorder. Given the evolving state of the ET field with respect to these non-motor features, the purpose of this manuscript is to critically review the current data.

**Methods:** A PubMed search was conducted on July 1, 2015. The term “essential tremor” was crossed in sequential order with 13 additional search terms (e.g., “cognitive”, “dementia”, “depression”). The total number of unique hits was 322.

**Results:** Numerous studies seem to substantiate the presence of a range of non-motor features occurring in excess in ET cases compared to age-matched controls. These comprise cognitive features (including a full spectrum from mild cognitive difficulty through to frank dementia), psychiatric (including depression, apathy, anxiety, and personality characteristics), sensory (hearing and possibly olfactory abnormalities), and other non-motor features (e.g., sleep dysregulation). Emerging evidence suggests that some of these features could be primary disease features that pre-date motor features of ET.

**Conclusions:** The presence of numerous non-motor features in ET is increasingly evident. The biological basis of these features deserves additional study.

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## 1. Introduction

The motor features of essential tremor (ET) include its hallmark element, kinetic tremor, as well as a range of other tremors (i.e., postural, intention, rest), a gait disorder, and problems with coordination and motor timing [1], each of which may be present as well. Mild dystonia may occur in advanced cases, although this point remains controversial.

Non-motor are increasingly being recognized as an accompanying feature of what was previously viewed as a solely motor disorder [2]. These may be classified into several distinct domains: cognitive [3], psychiatric [2], sensory [4] and other (sleep disturbance [5]). The presence of such features should come as no surprise, as non-motor features commonly accompany and seem to be a clear phenotype that coexists alongside the motor features of a

wide range of other disorders of involuntary movement [6]. For many of these disorders, they are regarded as a core, but variable, component of the clinical phenotype [6].

Given the evolving state of the ET field with respect to these non-motor features, the purpose of this manuscript is to critically review the current data.

## 2. Methods

A PubMed search was conducted on July 1, 2015. The term “essential tremor” was crossed in sequential order with 13 additional search terms, restricting the searches to human subject studies and those which contained the two terms in the title or abstract. The second search terms (and number of search hits) were: “cognitive” (112), “dementia” (91), “Alzheimer’s” (33), “cognition” (21), “MCI” (2), “olfaction” (14), “smell” (13), “hearing” (15), “non-motor” (27), “sleep” (28), “depression” (81), “anxiety” (52), and “personality” (23). The total number of unique hits was 322.

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### 3. Results

#### 3.1. Cognitive

Numerous studies, spanning North America, Europe and Asia, document cognitive deficits in ET patients in excess of those seen in age-matched controls [3]. These deficits occur not only in older-onset and older ET cases, but also in young ET patients - in a study in Turkey of 45 young ET patients and 35 age-matched controls (mean ages =  $24.6 \pm 7.2$  vs.  $24.8 \pm 5.4$  years), the Montreal Cognitive Assessment (MoCA) score was  $25.80 \pm 2.76$  in ET and  $28.23 \pm 1.69$  in controls ( $p < 0.001$ ) [7]. The cognitive features also seem to be progressive, and epidemiological studies have shown that mild cognitive impairment (MCI) as well as prevalent and incident dementia are more common in ET cases than controls [3]. Furthermore, one study noted that the cognitive changes preceded the motor manifestations of ET [8]. While the cognitive domains most reported to be affected are those of executive function and memory, the deficits are not limited to these domains. Although the presence of a cerebellar cognitive syndrome has been well documented in the literature, and involvement of the cerebellum could explain some portion of the observed cognitive dysfunction in ET, it does not explain the full burden of MCI and dementia seen in ET, and these are likely of a neurodegenerative nature [3].

#### 3.2. Psychiatric

A number of psychiatric features have been associated with ET. These include depression, apathy, anxiety, and personality characteristics.

##### 3.2.1. Depression

Many studies have demonstrated that ET patients have more depressive symptoms and perhaps even a higher prevalence of depression than controls. In a study of 50 ET cases and 50 controls in India, Hamilton Depression Rating Scale scores were significantly higher in ET than controls ( $p < 0.001$ ) [9]. Greater tremor severity was associated with higher depression scores ( $r = 0.53$ ,  $p < 0.01$ ), suggesting that depressive symptoms may be a secondary response to tremor [9]. In a study of 45 ET cases and 35 controls in Turkey, Beck Depression Inventory scores were significantly higher in ET cases ( $p < 0.001$ ), and the percentage of cases who had moderate and severe depression (Beck Depression Inventory scores  $\geq 20$ ) was 35.5%, compared with 5.8% in controls [7]. In a study of 60 ET cases and 22 controls in Korea, cases had higher Montgomery–Asberg Depression Rating Scale scores (i.e., more depressive symptoms) ( $p = 0.02$ ) [10]. A study of 37 ET cases and 34 controls was performed in Italy, and a psychiatric evaluation, including the Structured Clinical Interview (SCID-I) for Axis-I disorders, was conducted by two trained psychiatrists [11]. SCID-I showed that Axis-I psychiatric disorders, mainly depressive disorders, were more frequent in ET cases (54.1%) than controls (23.5%) ( $p < 0.01$ ), with depressive disorders being present in 27.0% of ET cases and 8.8% of controls ( $p = 0.07$ ) [11].

There is some preliminary evidence that the specific depressive features seen in ET patients may differ from those of controls. In a study of 61 depressed ET cases vs. 112 depressed controls in China, depressive symptoms were assessed using the Montgomery–Asberg Depression Rating Scale [12]. Patients with ET experienced a specific profile of depressive symptoms that differed from the depressed patients without ET - depressed patients with ET experienced significantly less severe subjective experience of depression, lack of interest and feelings of guilt and significantly more concentration difficulties and loss of energy than depressed patients without ET [12].

Moving beyond cases ascertained from clinics, a study of depressive symptoms in a largely untreated population-dwelling sample of ET cases demonstrated that depressive symptoms were over-represented in ET; in that study, 89 ET cases living in the Mersin province, Turkey were matched to 89 controls from the same population [13]. Hamilton Depression Scale scores were higher in ET cases than controls ( $p = 0.003$ ) and, among ET cases, these scores were correlated with tremor severity ( $r = 0.24$ ,  $p = 0.03$ ) [13].

Aside from being a secondary response to tremor, one study suggests that the mood disorder of ET may be a primary feature of the underlying disease [14] - in a population-based prospective study in central Spain, the authors demonstrated that baseline self-reported depression was associated with increased risk of incident ET (adjusted relative risk = 1.78,  $p = 0.018$ ).

At present, the biological basis for depression in ET is not known, but the possibility that it could be both a primary and a secondary feature of ET, suggests that the mechanisms could be heterogeneous and complex.

##### 3.2.2. Apathy

Apathy (i.e., decreased goal-directed activity), has frequently been observed in Parkinson's disease (PD), indicating that it may accompany some movement disorders. In one study, the Apathy Evaluation Scale was administered to 79 ET cases, comparing them to 20 dystonia cases, 39 PD cases and 80 controls [15]. The Apathy Evaluation Scale score was higher in ET, dystonia, and PD cases than controls (all  $p \leq 0.04$ ), and analyses stratified by presence/absence of depressive symptoms indicated the presence of a group of apathetic but non-depressed ET cases, indicating that features of apathy occurred independent of depressive symptoms. Further studies are needed, and the mechanistic basis for the observed increased features of apathy are not known.

##### 3.2.3. Anxiety

Numerous studies have demonstrated that ET cases have more anxiety than matched controls, with this anxiety being viewed as a psychiatric response to their tremor. In a study of 45 ET cases and 35 controls in Turkey, Beck Anxiety Scale scores were significantly higher in cases ( $p < 0.001$ ), and the percentage of patients with moderate and severe anxiety levels (Beck Anxiety Scale score  $\geq 16$ ) was 71.1% vs. only 20.0% in controls [7]. Hamilton Anxiety Rating Scale scores were also significantly higher in 50 ET cases than 50 controls in India ( $p < 0.001$ ) [9]. In ET, the anxiety may take specific forms, with social phobia being one of the most common. A study of 88 ET cases and 84 controls in New York included the social phobia module of the Structured Clinical Interview for DSM-IV Axis I Disorders, and current social phobia was present in 14.8% of ET cases vs. 3.6% of controls ( $p = 0.01$ ) [16]. The anxiety in ET also seems to accompany relatively milder cases ascertained directly from the population. Thus, in a study in New York [17], 37 community-dwelling ET cases were compared to 37 community-dwelling controls; Hamilton Anxiety Rating Scale scores were approximately three times higher in the former. A population-based study in Turkey of 89 ET cases, most of whom had mild ET and who had not been diagnosed previously, reported that the mean Hamilton Anxiety Rating Scale score was approximately twice as high in ET cases than matched controls ( $p < 0.001$ ) [13].

##### 3.2.4. Personality characteristics

Most movement disorders (e.g., PD, Huntington's disease) are neuropsychiatric in nature, with patients often, but not always, exhibiting a certain personality profile, and ET may be no exception. Several studies in New York examined the personality profile of ET cases using the Tridimensional Personality Questionnaire, which

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