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NEW HORIZONS

New horizons in late-onset essential tremor: a pre-cognitive biomarker of dementia?

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Abstract

Essential tremor (ET) is the most common cause of tremor in older adults. However, it is increasingly recognised that 30–50% of ET cases are misdiagnosed. Late-onset ET, when tremor begins after the age of 60, is particularly likely to be misdiagnosed and there is mounting evidence that it may be a distinct clinical entity, perhaps better termed 'ageing-related tremor'. Compared with older adults with early-onset ET, late-onset ET is associated with weak grip strength, cognitive decline, dementia and mortality. This raises questions around whether late-onset ET is a pre-cognitive biomarker of dementia and whether modification of dementia risk factors may be particularly important in this group. On the other hand, it is possible that the clinical manifestations of late-onset ET simply reflect markers of healthy ageing, or frailty, superimposed on typical ET. These issues are important to clarify, especially in the era of specialist neurosurgical treatments for ET being increasingly offered to older adults, and these may not be suitable in people at high risk of cognitive decline. There is a pressing need for clinicians to understand late-onset ET, but this is challenging when there are so few publications specifically focussed on this subject and no specific features to guide prognosis. More rigorous clinical follow-up and precise phenotyping of the clinical manifestations of late-onset ET using accessible computer technologies may help us delineate whether late-onset ET is a separate clinical entity and aid prognostication.

Keywords: late-onset essential tremor, dementia, biomarker, computer vision, ageing-related tremor

Key Points

- Essential tremor (ET) is common in older adults.
- Onset of ET in older adults is associated with cognitive decline, frailty and increased mortality.
- Late-onset ET may be a distinct clinical entity.
- Late-onset ET may be a pre-cognitive biomarker of dementia.
- Smartphone and wearable technologies may help with disease phenotyping.

Introduction

Tremor is defined as an involuntary and rhythmic oscillatory movement of a body part, and may be categorised as rest, postural or kinetic, depending on when it manifests maximally (see Table 1; [1]). Tremor disorders are increasingly common with age and reported to affect approximately 17% of adults ≥64 years [2]; common causes include essential tremor (ET), Parkinson's disease, dystonia, metabolic disorders, drug-induced tremor and enhanced physiological tremor [3].

The most common cause of tremor in older adults is ET [4] but, it is increasingly recognised that ET has a high misdiagnosis rate, especially in older adults [5, 6]. The accuracy of

Table 1. Tremor classification (adapted from [1])

Tremor type	Description	Example
Rest	Tremor occurs in a body part that is at rest and completely supported against gravity	Hands resting on the table
Postural	Tremor is present while voluntarily maintaining a static position against gravity.	Hands outstretched in front of the chest
Kinetic	Tremor occurs during a voluntary movement	Hands reaching toward a cup

clinicians correctly diagnosing ET is only in the range of 50–70%, and it tends to be over-diagnosed rather than missed [7]. Parkinson's disease and dystonic tremor are common causes of erroneous ET diagnoses [5, 6]. Acknowledging this, the 2018 International Movement Disorders Society (MDS) expert consensus statement paper on tremor introduced the term 'ET-Plus' to describe people with ET-like tremor plus additional atypical features such as dystonia, ataxia and cognitive decline. Gait ataxia was previously considered part of the 'typical' ET phenotype but now has been highlighted as an atypical clinical feature [8, 9]. Similarly, an association between cognitive decline and ET was reported in several studies previously [10–12], but is now considered an atypical feature in ET. The MDS recommends that clinicians carefully follow up people with ET-Plus as their diagnoses are particularly likely to be revised over time [13].

Late-onset ET, when tremor begins after the age of 60, may also be considered an atypical form of ET as it has been noted to have associations with frailty and increased risk of dementia [14, 15]. Several internationally renowned tremor experts, such as Gunther Deuschl, have proposed that late-onset ET is a separate clinical entity altogether, and recommended 'ageing-related tremor' (ART) as a more suitable term [16]. The alternative argument is that the differing clinical manifestations may simply reflect markers of physiological ageing, or frailty, superimposed upon ET.

With ageing populations and the growing use of neurosurgical, or irreversible, treatments for long-term ET management, there is a pressing need for clinicians to better understand late-onset ET. For example, high intensity focused ultrasound, gamma knife radiosurgery and deep brain stimulation (DBS) surgery are specialist treatments for ET that are increasingly accessible, including for older adults; however, these may not be suitable in people at high risk of dementia, or, indeed, may be unsuccessful in late-onset ET [17].

Clinicians are thus faced with the challenges of disentangling late-onset ET but have few accessible resources to help them do so. In this article, we will present the emerging theories about late-onset ET and specifically highlight that it may be a pre-cognitive motor biomarker for dementia. In the advent of the 2020 Lancet Commission paper identifying that 40% of dementia cases are attributable to 12 modifiable risk factors [18], we propose that late-onset ET presents clinicians with an opportunity to intensively modify dementia risk factors in a group of older adults that generally still have good cognitive function. There is also evidence that the distribution of tremor in ET (i.e. neck vs upper limbs) and careful measurement of tremor features such as rhythm and frequency may help investigate the underlying pathophysiology and guide prognostication [19]. One strategy to delineate late-onset ET is therefore to precisely phenotype people with ET-like tremors, and in this article we also outline accessible computer technologies that may help with this.

Typical essential tremor

ET may start at any age from adolescence onwards [4] and the prevalence increases from 0.04% in younger adults (20–40 years old) [20], 3.1% in middle age (40–60 years) [21], 5.5% in older adults aged above 65 and 22% in those aged above 95 [4]. Approximately 50% of people with ET have an autosomal-dominant family history of the disorder [22] but despite this, the genetic causes remain somewhat elusive [23].

ET is characterised by a bilateral, symmetrical, upper limb kinetic and/or postural tremor of small amplitude (usually <1 cm) and high frequency, in the range of 8–10 Hz [24, 25]. The amplitude of the kinetic tremor tends to be larger than the amplitude of postural tremor but the frequency is usually the same, suggesting a common central oscillatory circuit drives both tremors [26]. ET may also cause a tremor in the neck, voice and legs [7], but the recent MDS consensus statement emphasises that the diagnosis of ET cannot be made when these tremors are present alone, without a bilateral upper limb tremor [13]. Furthermore, it states at least a three year history of upper limb tremor is required for a confirmed ET diagnosis, and that when symptoms and signs compatible with ET are present but the duration is less than 3 years, the tremor diagnosis should be considered 'indeterminate' [13].

ET characteristically demonstrates alcohol sensitivity [27], with just a small amount of alcohol (usually 1–2 standard drinks) reducing tremor amplitude by 50–70% [28]. The severity of typical ET progresses slowly over decades, with the amplitude slightly increasing and the frequency reducing, and, with ageing, there is a tendency for longstanding ET to also be present at rest [25, 29].

As with other tremor disorders, the diagnosis of ET is made through clinical assessment—gathering evidence of key features such as family history of tremor, alcohol sensitivity and symmetrical upper limb tremor, as well as ascertaining that features of alternative diagnoses such as bradykinesia (Parkinson's disease), action-specific tremor

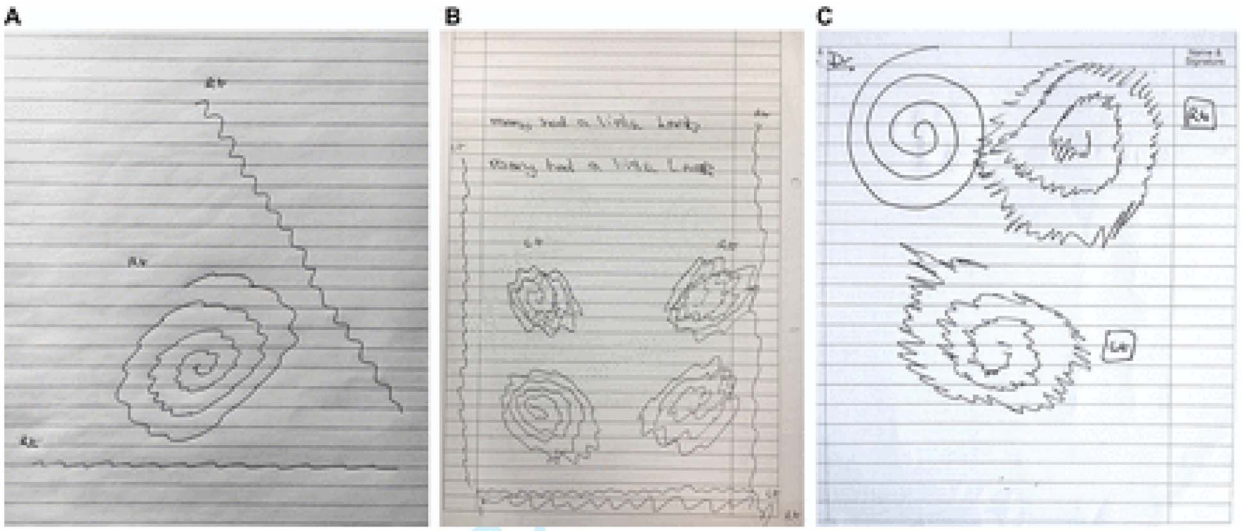

Figure 1. Handwriting and drawing tasks to aid diagnosis of ET. (A) The Archimedes spiral drawing shows a unidirectional tremor axis in the 8–2o'clock direction, suggesting essential tremor, but it is not clear whether the amplitude and frequency are constant. Both straight lines show the frequency to be regular; the line drawn perpendicular to the tremor axis emphasises the amplitude and makes it easier to discern that it is also constant. (B) The handwriting is tremulous and potentially compatible with either essential tremor or dystonic tremor. The spirals show a unidirectional 8–2o'clock axis in the right hand spirals and a 10–4o'clock axis in the left hand, symmetrical in size and severity—all features that point toward essential tremor. However, the regularity of the amplitude and frequency is difficult to determine from the spirals as the severity of the tremor causes the turns to overlap. The straight line drawings demonstrate that the amplitude, frequency and axis are all constant. The left (dominant) handed vertical line has 18 oscillations drawn over 2 s, giving an estimated frequency of 9 Hz. (C) Spiral drawings from a patient with severe essential tremor showing large tremor oscillations with a unidirectional axis, fairly regular amplitude and frequency, and symmetry between the left (lower drawing) and right (upper right drawing) hands (Images and Figure legend reproduced from Alty et al. [29]).

during writing (dystonia) or ataxia (ET-Plus) are not present [25]. Many clinicians supplement standard neurological examination with observation of handwriting, straight line and Archimedes spiral drawing tests to quantify and record aspects of tremor (Figure 1), looking for the typical unidirectional tremor of ET to support clinical acumen [29].

There are currently no routinely available laboratory-supported tests to help with the diagnosis of ET but clinicians with access to neurophysiology assessments sometimes use EMG to objectively quantify tremor frequency as supportive evidence, and to exclude features of dystonia. In one study, for example, EMG recordings could differentiate between parkinsonian tremor and ET with 93% accuracy and mean tremor frequency was a key discriminatory feature [30].

A variety of clinical scales have been devised to help quantify ET, including The Essential Tremor Rating Assessment Scales (TETRAS) [31], the Fahn-Tolosa-Marin (FTM) scale [32] and the Bain and Findley clinical tremor rating scale [33]. However, their use tends to be limited to research settings, and they are only used clinically when 'proof' of effect is required, such as a DBS outcome measure. Most scales take about 10–20 min and clinicians are required to rate severity of tremor on a scale of 0–4 (TETRAS and FTM) or 0–10 (Bain and Findley) for different body parts including voice, neck, face, upper and lower limbs. As all scales rely on the subjective judgement of a clinician, there is a degree of intra- and inter-rater variability [33–35]. In one study of 59 physicians and trained medical personnel, the intra-rater and inter-rater reliability of the FTM scale was 0.54 (i.e. moderate agreement) and 0.10–0.24 (i.e. none to minimal agreement) respectively [34].

Is late-onset ET a separate clinical entity?

For some time, it has been recognised that older adults with ET had an increased risk of cognitive decline; for example, Thawani et al. found that 25% of older adults with ET (mean age 80.9 ± 7.5 years) had prevalent dementia compared to 9.2% of similar aged healthy controls (77.4 ± 6.8 years) and incident dementia rates were twice as high in the ET group: 18.3% of ET patients vs 8.7% of controls [14]. Most older studies, though, did not split participants according to age of tremor onset. More recently, there has been emerging evidence that late-onset ET, generally defined as tremor onset after the age of 60, has particularly strong associations with cognitive decline, compared to older adults with earlier onset [36, 37]. For example, a population-based study in central Spain found that people with late-onset ET (defined as >65 years in this study) were 57% more likely to have cognitive decline compared to age-matched healthy controls [37] whereas, in a study involving 206 ET patients with early-onset of tremor and 3,685 healthy controls, the ET cases were no more likely to have cognitive decline [36].

Table 2. Frailty scores in older adults with ET compared to healthy controls

Items in frailty score	ET $n = 237$ age 75.0 ± 6.9 years	Controls $n = 3{,}903$ age 74.7 ± 6.2 years
Stroke	14 (5.9)	167 (4.3)
Circulatory problems *	98 (41.4)	1,211 (31.0)
Visual problems	124 (52.3)	1,924 (49.3)
Cataracts	82 (34.6)	1,143 (29.3)
Hearing problems*	89 (37.6)	1,126 (28.8)
Osteoarthritis*	163 (69.7)	2,300 (58.9)
Osteoporosis	43 (18.1)	602 (15.4)
Hip fracture	7 (3.0)	130 (3.3)
Cancer	19 (8.0)	254 (6.5)
Anaemia	30 (12.7)	371 (9.5)
Chronic obstructive pulmonary disease*	49 (20.7)	609 (15.6)
Hypertension	128 (54.0)	2,010 (51.5)
Diabetes mellitus	39 (16.5)	629 (16.1)
Heart disease	25 (10.5)	403 (10.3)
Depressive symptoms **	91 (38.4)	833 (21.3)
Number of medications*	2.76 ± 2.12	2.28 ± 1.86
Self-reported limitation in daily activities **	83 (35.0)	731 (18.7)
Going outside alone *	0.27 ± 0.73	0.18 ± 0.64
Travelling out of the neighbourhood, driving, arranging to take a bus*	0.60 ± 1.10	0.42 ± 0.95
Shopping alone for clothes, household necessities or groceries *	0.42 ± 0.91	0.23 ± 0.71

Adapted from [15]. Scores on a 20 Items Frailty Score questionnaire are compared between older adults with ET and controls, where groups were similar in terms of age, gender, education and all other demographic variables. Values are listed as either means ± standard deviation or as numbers of people, with percentages in brackets. Bold items indicate statistically significant group differences denoted by $^{*}P < 0.05$ or $^{**}P < 0.001$.

There is also a growing body of literature showing that late-onset ET is associated with markers of frailty. For example, in Louis et al.'s study of 237 older adults with ET and 3,903 older healthy controls, the mean frailty score was 26.5% higher in the ET group than controls (8.6 ± 5.2 vs 6.8 ± 4.6; $P < 0.001$) and, in those with late-onset ($n = 187$; 8.7 ± 5.1), the frailty score was higher than in those with long-standing ET ($n = 50$; 8.2 ± 5.7) (see Table 2; [15]). Other studies have also found associations with frailty markers including weak grip strength [16], cognitive decline [37] and dementia [38].

Other studies have suggested a different clinical phenotype in late-onset ET, noting a lack of the characteristic alcohol sensitivity [39], more rapid progression [40] and increased mortality risk [16]. For example, in a study of 978 people with ET, the authors observed that 76% of adults with early-onset ET demonstrated alcohol responsiveness (quantified with Archimedes spirals and FTM scales) compared to just 45% of those with late-onset ET [39].

With such growing evidence of different clinical manifestations, the question naturally arises over whether late-onset ET may be a separate clinical entity altogether. Lending support to this idea was a study that found evidence to suggest late-onset ET may have different underlying pathophysiology [41]; the researchers used multi-channel electroencephalography (EEG) to measure cortical brain wave oscillatory patterns and electromyography (EMG) to measure the limb muscle activation oscillations in 10 people with early-onset ET (below 30 years) and 10 people with late-onset ET (defined as >50 years in this study). The coherence between the cortical activity and muscle activity was reduced for patients with late-onset ET, suggesting a difference in oscillating cerebral networks underlying early- and late-onset ET. However, the limited number of participants of a single study warrants replication in larger cohorts to reliably demonstrate a pathophysiological difference.

Further evidence that late-onset ET may be a separate condition comes from Deuschl et al.'s longitudinal Danish cohort study of 2,448 people who were followed up over 11 years [16]. They found that people with late-onset ET had increased mortality compared to people of the same age with early-onset ET. The authors also presented epidemiological evidence to demonstrate that the rates of ET-like tremor developing in older adults is above what would be expected for ET incidence (Figure 2) and proposed using ART to reflect this condition [16].

If late-onset ET, or 'ART', is a separate disorder to ET, it raises the possibility that this group of older adults are at particularly high risk of subsequent dementia. With mounting evidence to support this, we propose that people with late-onset ET should be considered to have a pre-cognitive motor biomarker of dementia. Acknowledging this is a novel view, it would seem pragmatic for clinicians to proactively address modifiable dementia risk factors (such as smoking, hypertension and physical inactivity) in this group, as there is a potential to delay or even prevent cognitive decline. Whilst the 'jury is out' on whether late-onset ET is a separate clinical entity, there would seem to be little to lose from such an approach. The 2020 Lancet Commission paper on dementia prevention highlighted that up to 40% of dementia is attributable to modifiable risk [18], and there is growing body of evidence that people with late-onset ET have at least

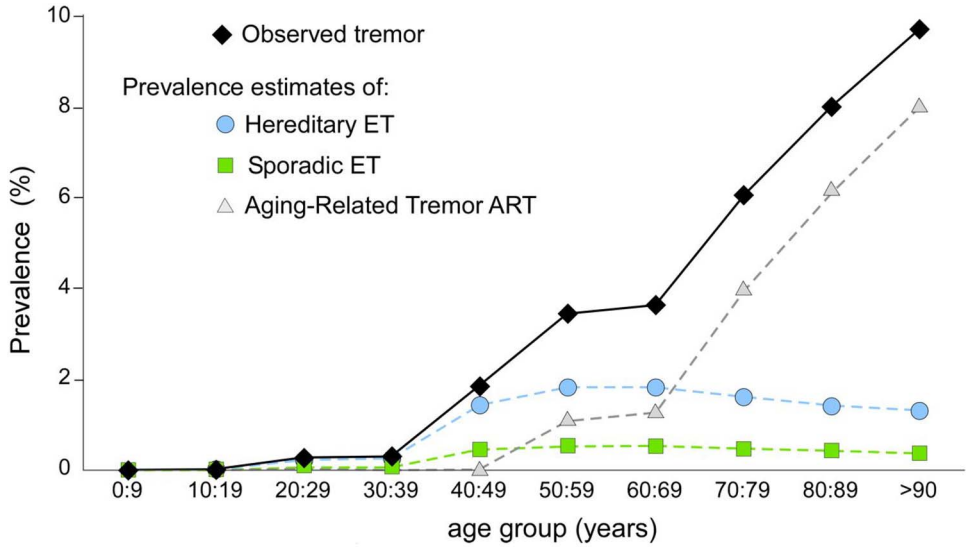

Figure 2. Adapted from Deuschl et al. [16]. A hypothetical model of the prevalence of different tremor disorders across the lifespan. The observed tremor is presented as the black diamonds (from Louis and Ferreira Supplemental Data Fig C. [4]). The prevalence of hereditary ET (blue circles) and sporadic ET (green squares) are estimated from epidemiological studies [42, 43] and the ART (grey triangles) was calculated from subtracting hereditary and sporadic ET estimates from the observed tremor.

as much, if not considerably more than most, to gain from dementia prevention strategies.

Are the manifestations of late-onset ET simply healthy ageing or frailty plus ET?

Although adults with late-onset ET show increased mortality and markers of frailty compared to adults of the same age with early-onset ET, controversies still remain about whether age of onset delineates two separate disorders [44]. Some researchers, including Elan D. Louis, one of the world's leading experts on ET, argues that age of onset is not used to classify other neurological disorders, and points out that, '*patients with late-age of onset of Parkinson's disease are still diagnosed as Parkinson's disease*' [44]. He also outlines that physiological tremor gets worse with increased age too, and this situation is not classified as a new condition [44].

The precise age cut-off when late-onset ET, or 'ART', should be defined is also far from clear. For example, in a study conducted by Hopfner et al. of 673 people with early-onset ET or late-onset ET, a difference in progression severity on Archimedes spiral drawings was spotted between late- and early-onset ET patients but, in this study, they defined 'late onset' as older than 46 years [39]. Such heterogeneity in the definition of 'late-onset' makes it somewhat challenging to draw firm conclusions when comparing study findings.

Probably one of the strongest pieces of evidence that argues against the theory of late-onset being a separate entity, comes from post-mortem studies where the same underlying brain pathology has been found in early- and late-onset ET cases. For example, Kuo et al. found that Purkinje cell counts in the cerebellum and associated pathological changes, were similar between 30 early-onset and 30 late-onset ET cases, where the age cut-off for 'late' onset was defined as 50 [45]. Together, this raises the question of whether the clinical manifestations associated with late-onset ET reflect a spectrum of tremor severity associated with normal ageing, or whether changes associated with ageing or frailty are superimposed on standard ET, rather than late-onset ET being a separate condition.

Can clinically accessible technologies help us disentangle late-onset ET?

There is emerging evidence that the distribution of tremor across different anatomical locations and nuances of tremor features, in late-onset ET may differ from the tremors seen in typical earlier onset cases of ET [19]; furthermore, there is evidence that people with ET who have atypical features (such as rest tremor at onset, or neck tremor rather than limb tremor) may have a more rapid progression [39, 40]. This suggests that more careful phenotyping of late-onset ET may help delineate the disorder. Similar to the thumb tremor observed in 'non-progressive Parkinson's disease' cases a decade or so ago (later identified as 'SWEDDS', or people with 'scans without evidence of dopaminergic deficiency') [46], could it be that certain subtle features of the upper limb tremor, or other associated movement features, of late-onset ET help clinicians with delineation and prognosis? A different pattern of cortical electrical activity has been observed for late-onset ET patients compared to early-onset ET patients, which should prompt us to look more carefully and precisely at the tremor features in late-onset ET; it is not inconceivable that a different profile of frequency, rhythm or amplitude of tremor in certain sub-types of late-onset ET is associated with a more rapid progression, risk of dementia

and mortality. It has certainly been recognised by many tremor experts that ET is probably a syndrome encompassing many different aetiologies rather than one condition, and it thus makes sense to look more carefully at the late-onset ET group to help tease out the 'poor prognosis' indicators [47, 48].

To precisely phenotype 'ET" patients, we can supplement clinical acumen with tools that allow accurate measurements of tremor parameters and motor control (e.g. gait, balance, coordination of hand movements etc). Tracking progression of patients over time will also aid phenotyping and diagnostic accuracy. So far, few clinicians have access (or the time) to objectively measure ET, but with emerging technologies, this may change.

Several groups of researchers have investigated how various technologies may support clinical assessments of ET. High-speed 3D motion capture systems can certainly quantify tremor with high precision [49], but as such techniques are only available in specialised movement laboratories, they will never be appropriate for widespread clinical use. Wearable inertial sensors are a much more accessible method and have been shown to have a position amplitude accuracy of ±0.1 cm and rotation amplitude accuracy within ±0.2 degrees in people with ET [50]. Similar inertial sensors are embedded in smartphones—a tool already in most clinicians' (and patients') pockets. Smartphone and smartwatch accelerometers can record peak tremor frequency in ET just as accurately as laboratory-grade accelerometers but amplitude measures are less reliable [51]. Three-dimensional gyroscopes embedded in smartwatches can measure postural tremor intensity in ET and have been shown to strongly correlate with clinical ratings on the FTM tremor rating scale [52]. The main drawback with these methods, though, is that the weight of the device and concurrent motor command (e.g. patient needs to hold the phone) will likely affect the features of the tremor [53].

Machine learning applied to video recordings of tremor behaviour provides an exciting opportunity to bring precision measurements into the clinic [54]. Tremor frequency can be quantified from smartphone video recordings in ET and PD [54], with an accuracy within 0.5 Hz of an accelerometer. This 'computer vision' method has the advantage that it can be undertaken in clinic using a standard smartphone camera or remotely via a webcam—a particular advantage in the era of telemedicine consultations. Computer vision can also measure tremor in an unloaded limb, i.e. *without* a wearable sensor.

The feasibility and acceptability of using these new technologies clinically in older adults brings some challenges, where smartphone/computer ownership, and access to the Internet is generally less. However, recent research suggests that many older adults, including those with markers of frailty such as cognitive impairment, are increasingly using such technologies. For example, in a study of more than 200 older adults attending a memory clinic in Sydney (including 137 with MCI and 23 with dementia) 91% of participants used smartphones regularly, and 93% had access to the Internet [55]. The increasing rates of smartphone and computer use globally make these technologies accessible for home-based tests, and for those without, the clinician can use their own smartphone in clinic. In summary, several different smartphone tools and computational techniques can already be applied to help clinicians quantify the motor features of ET but they still require a degree of data analysis. If these technologies can be further developed into a 'point and press' smartphone camera tool, for example, there is strong potential to integrate precise quantification of tremor and other movement features into our routine clinical practice.

Conclusion

There is mounting evidence to suggest that late-onset ET is associated with cognitive decline, markers of frailty and increased mortality. This raises the question of whether 'ageing-related tremor' may be a better term, reflecting that late-onset ET may be a separate disorder. However, this is not a universal consensus, and the alternative argument is that the associations of late-onset ET can be explained by the natural ageing process, or markers of frailty simply being superimposed on the phenotype of ET in an older adult. We propose that clinicians should consider late-onset ET as an early biomarker of dementia—providing the opportunity for targeted dementia risk reduction. We will need more studies that quantify the key features of ET to better phenotype a condition that is likely to have numerous aetiologies. Given the use of telemedicine is increasing and that smartphones are becoming ubiquitous across all societies, embedded computer vision technologies may hold the key to a low cost, accessible method to quantify ET. Such advanced technologies may unlock the door to precisely assess tremor for all patients, and help us understand more about late-onset ET.

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