The cognitive side of essential tremor: what are the therapeutic implications?

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Abstract: While essential tremor (ET) has traditionally been categorized as a pure motor disease, cross-sectional and longitudinal studies of cognition in ET have demonstrated that these patients may have cognitive dysfunction. Recent epidemiological studies demonstrate an association between ET (particularly with onset after age 65) and increased risk for cognitive impairment and dementia. Although existing studies have generally conceptualized cognitive changes in ET as consistent with a 'frontosubcortical' or 'corticocerebellar' profile, results from these same studies suggest that cognitive impairment in ET may in fact be heterogeneous. Furthermore, the underlying mechanisms remain uncertain. Cognitive changes could be a byproduct of the cerebellar dysfunction of ET itself; alternately, they may be a feature of concomitant neurodegenerative diseases that have been associated in several studies with ET, including Alzheimer's disease, Parkinson's disease or progressive supranuclear palsy. While the study of cognitive dysfunction in ET has received research attention in recent years, the results of these studies have not been translated into the clinical domain and clinical practice. This review first summarizes the current literature on the potential relationships between ET and cognitive change. We then suggest areas of further clinical evaluation and treatment; these suggestions are directed at physicians caring for ET patients who may demonstrate or complain of cognitive impairment. As we discuss, clinicians should ideally screen ET patients for possible signs or symptoms of cognitive impairment in addition to assessing for psychiatric comorbidity and quality of life. These recommendations are in contrast to most current clinical practice, which does not routinely include such assessment among ET patients. To our knowledge, there have been no pharmacotherapeutic trials to date of any agent for cognitive change associated with ET. We believe that studies for this indication are now called for. Future efforts in this direction will also need to take into account the pathobiology of cognitive changes in ET, which itself is an area that is ripe for future investigations.

Keywords: clinical, cognition, essential tremor

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Introduction

Essential tremor (ET) traditionally has been categorized as a pure motor disease. However, cross-sectional and longitudinal studies have increasingly demonstrated that ET may be associated with cognitive impairment or dementia in a subsection of patients [Kim *et al.* 2009; Frisina *et al.* 2009; Lombardi *et al.* 2001; Higginson *et al.* 2008; Gasparini *et al.* 2001; Troster *et al.* 2002; Lacritz *et al.* 2002; Benito-Leon *et al.* 2006a, 2006b, 2011; Louis *et al.* 2010a; Bermejo-Pareja *et al.* 2007; Thawani *et al.* 2009]. This association does not appear to be accounted for by medication side effects [Lombardi *et al.* 2001; Higginson *et al.* 2008] or psychiatric symptoms [Li *et al.* 2011], and may be related to cognitive changes associated with ET itself; alternately, it may be associated with concomitant neurodegenerative diseases that themselves have been reported to be associated with ET, including Alzheimer's disease (AD), Parkinson's disease (PD), Lewy body dementia (DLB) or progressive supranuclear palsy (PSP). This review summarizes the current literature on the potential relationships between ET and cognitive change, and suggests areas of further

evaluation and treatment of ET patients with cognitive impairment.

Current literature on the relationships between ET and cognitive change

Association of ET with cognitive dysfunction

Studies on cognition in ET have predominantly assessed two areas: the integrity of various neuropsychological abilities, particularly executive functioning [Kim *et al.* 2009; Frisina *et al.* 2009; Lombardi *et al.* 2001; Higginson *et al.* 2008; Gasparini *et al.* 2001; Sahin *et al.* 2006; Schwartz *et al.* 1999; Passamonti *et al.* 2011] and the extent to which patients with ET are at increased risk for mild cognitive impairment (MCI) or dementia [Benito-Leon *et al.* 2006b; Bermejo-Pareja *et al.* 2007; Thawani *et al.* 2009].

Evaluation of cognitive symptoms and neuropsychological deficits related to ET stem from early cognitive studies of cerebellar dysfunction. Beginning in the mid to late 1980s and early 1990s, observational studies described cognitive dysfunction related to cerebellar degeneration or stroke. Kish and colleagues described difficulties with concept formation, learning of paired associates and cognitive slowing in patients with olivopontocerebellar atrophy [Kish *et al.* 1988]. Patients with cerebellar cortical atrophy were found to have impaired executive function demonstrated by increased planning time on the Tower of Hanoi Test [Grafman *et al.* 1992], and by poor performance on tests of fluency and the initiation/ perseveration subtest of the Mattis Dementia Rating Scale [Appollonio *et al.* 1993]. Visual spatial deficits were described following excision of left cerebellar hemisphere tumors [Wallesch and Horn 1990], as well as in the setting of chronic phenytoin intoxication [Botez *et al.* 1985], and after left superior cerebellar artery territory infarction [Botez-Marquard *et al.* 1994]. Linguistic processing was impaired in patients with right cerebellar infarction, with symptoms including agrammatism [Silveri *et al.* 1994] and impaired linguistic error detection [Fiez *et al.* 1992].

These clinical observations were reinforced by functional neuroimaging experiments showing cerebellar activation by nonmotor tasks [Allen *et al.* 1997; Fiez and Raichle, 1997] and by behavioral studies [Schmahmann, 1996] that indicated involvement of the cerebellum in cognitive processing and emotion. Together, clinical and imaging findings led to a designation of the 'cerebellar cognitive affective syndrome', which included impairments in executive function (including planning, set-shifting, abstract reasoning, verbal fluency and working memory), often with perseveration or inattention, visual spatial disorganization and impaired visual spatial memory, and difficulties with language production including dysprosodia, agrammatism and mild anomia [Schmahmann and Sherman, 1998; Akshoomoff *et al.* 1997; Hallet and Grafman, 1997; Molinari *et al.* 1997; Desmond and Fiez, 1998; Rapoport *et al.* 2000].

As the cerebellothalamocortical basis of tremor in ET began to be defined in the late 1990s and early 2000s [Middleton and Strick, 2000a, 2000b, 2001; Montgomery *et al.* 2000; Deuschl *et al.* 2000; Singer *et al.* 1994], the possibility of cerebellum-influenced cognitive impairment in ET also began to be considered. Given the deficits outlined in the cerebellar cognitive affective syndrome, it was expected that cognitive changes in ET might include changes in executive function, abstract reasoning, verbal fluency, working memory, attention, visual spatial skills, and language. Two initial studies evaluated the effect of thalamic deep brain stimulation (DBS) on verbal fluency, verbal recall and quality of life in ET [Troster *et al.* 1999; Lucas *et al.* 2000] and demonstrated improvement in recall and quality of life and variable results in verbal fluency following DBS. However, Gasparini and colleagues were the first to publish findings concerning neuropsychological function in ET. Utilizing cognitive measures to evaluate frontal lobe function, the researchers compared the average neuropsychological test scores of small groups of patients with ET and a family history of ET (n = 15), patients with ET and a family history of PD (n = 12), patients with PD (n = 15), and healthy controls (n = 15) [Gasparini *et al.* 2001]. Relative to the healthy control group, the group with ET and a family history of ET demonstrated poorer performance on a task involving conceptualization and set-shifting [Wisconsin Card Sorting Test (WCST)] and on an inhibition task (Stroop task interference condition), but not on another executive function task assessing planning (Tower of London). The group with ET but a family history of PD demonstrated impairments on the same tasks, as well as on a letter fluency task (FAS). The ET group with a family history of PD generally performed more like PD than did the ET

with family history of ET group. The authors hypothesized that these findings might occur if ET and PD represented points on a spectrum of motor disorders with executive cognitive dysfunction. Into such a continuum, cognitive impairment among ET patients with a family history of ET *versus* ET patients with a family history of PD might occur by intermediate degrees, similar to each other but different from either individuals without neurological disease or PD-only patients. They concluded that further studies on larger sample groups were warranted to investigate the cognitive profile of ET to provide a better understanding of its relationship with PD. Utilizing a broader range of neuropsychological tests, Lombardi and colleagues found that, relative to normative test values, 18 ET patients undergoing evaluation for surgical treatment of tremor demonstrated impaired semantic fluency [Lombardi *et al.* 2001]. Furthermore, when patients' actual scores were compared with their own expected scores given their estimated intelligence quotient (IQ), the patients also showed impairments in letter fluency, visual confrontation naming, verbal recall, and working memory and attention. While ET patients in this study also demonstrated difficulty with WCST, they demonstrated strengths on other executive measures of conceptualization (including matrix reasoning and similarities) and on visuospatial tasks including facial matching and the Hooper visual organization task. In summary, these initial findings provided preliminary evidence that ET might compromise performance on some, but not all, measures of attention and executive function and may also incorporate non-executive abilities.

Over the past decade, numerous studies have continued the neuropsychological evaluation of cognition in patients with ET. For the sake of conciseness, these study findings, including numbers of cases *versus* controls as well as the specific cognitive domains evaluated and neuropsychological batteries utilized, are summarized in Table 1. All studies used either self-established [Lombardi *et al.* 2001; Duane and Vermilion, 2002] or previously published standardized criteria for diagnosis of ET [Fahn *et al.* 1993; Louis *et al.* 1998; Salemi *et al.* 1994; Bain *et al.* 2000]. In addition, other neurological conditions that could mimic ET, such as PD, were specifically evaluated and potential participants with these symptoms were excluded [Kim *et al.* 2009; Frisina *et al.* 2009; Lombardi *et al.* 2001; Higginson *et al.* 2008; Gasparini *et al.* 2001; Lacritz *et al.* 2002; Benito-Leon *et al.* 2006a; Sahin *et al.* 2006; Schwartz *et al.* 1999; Passamonti *et al.* 2011; Duane and Vermilion, 2002]. There were certain limitations to some studies. While numbers of cases and controls were limited in most individual studies (the exception being the study by Benito-Leon and colleagues, with 232 cases and 696 controls [Benito-Leon *et al.* 2006a]), when taken as a whole, overall participant numbers are robust. In addition, while most studies either excluded potential participants with psychiatric comorbidities or medications that could impact cognition [Higginson *et al.* 2008; Gasparini *et al.* 2001; Passamonti *et al.* 2011], or controlled for these conditions [Benito-Leon *et al.* 2006a], other studies did not [Duane and Vermilion, 2002].

Evaluating the results as presented in Table 1, it is apparent that over the past decade many studies have evaluated multiple cognitive domains for evidence of cognitive change in patients with ET. Over time, studies have become increasingly complex and sophisticated in the cognitive batteries that they include for cognitive assessment. As a result, many areas of cognition have been comprehensively assessed in ET patients. Most studies demonstrated that patients with ET have clear evidence of cognitive impairment. The majority of studies evaluating executive functioning (seven out of nine) have found deficits in this area, as manifested by low scores on tests such as the WCST [Passamonti *et al.* 2011], Stroop Test [Gasparini *et al.* 2001; Troster *et al.* 2002; Lacritz *et al.* 2002] Frontal Assessment Battery [Passamonti *et al.* 2011], verbal fluency tests [Kim *et al.* 2009; Frisina *et al.* 2009; Lombardi *et al.* 2001; Higginson *et al.* 2008; Gasparini *et al.* 2001; Troster *et al.* 2002; Lacritz *et al.* 2002; Sahin *et al.* 2006], and the Similarities [Lombardi *et al.* 2001] subtest of the Wechsler Adult Intelligence Scales (WAIS). Deficits in working memory (e.g. WAIS Digit Span forward [Kim *et al.* 2009; Frisina *et al.* 2009; Lombardi *et al.* 2001; Higginson *et al.* 2008] and backward, and the WAIS symbol search [Higginson *et al.* 2008] and letter–number sequencing tests [Lombardi *et al.* 2001]), verbal fluency (letter fluency [Kim *et al.* 2009; Frisina *et al.* 2009; Lombardi *et al.* 2001; Gasparini *et al.* 2001; Troster *et al.* 2002; Lacritz *et al.* 2002; Benito-Leon *et al.* 2006a; Sahin et al 2006] and semantic fluency (animal naming) [Kim *et al.* 2009; Frisina *et al.* 2009; Lombardi *et al.* 2001; Higginson *et al.* 2008; Troster *et al.* 2002] and

Table 1. Results of neuropsychological evaluation studies in patients with ET.

	Schwartz *et al.* (1999)	Gasparini *et al.* (2001)	Lombardi *et al.* (2001)	Duane and Vermilion, (2002)	Lacritz *et al.* (2002)	Troster *et al.* (2002)	Benito-Leon *et al.* (2006a)	Sahin *et al.* (2006)	Higginson *et al.* (2008)	Frisina *et al.* (2009)	Kim *et al.* (2009)	Passamonti *et al.* (2011)
(Cases) [Controls]	(23) [25]	(27) [15]	(18) [–]	(55) [–]	(13) [–]	(101) [–]	(232) [696]	(16) [16]	(24) [21]	(34) [–]	(34) [33]	(15) [15]
Global cognitive function												
MMSE (or similar test)			=		=	=	++			+	++	=
Calculated IQ							=					
Clock drawing test								=				
Attention and working memory												
Digit span forward (WAIS)			++	=				=	++		++	=
Digit span backward			++					=	++		++	=
Spatial span forward (WMS)			=									
Spatial span backward			=									
Symbol search (WAIS)									+			
Letter–number sequencing (WAIS)			++									
Picture completion (WAIS)			=						++			
Trail Making Test Part A		=					++	=				
Brief test of attention (working memory)						++						
Visual attention (several tests)				++								
Executive functions												
Stroop test		++			++	++		+				
WCST		++	++	=	++	=		=				
Tower of London		=										
Tower of Hanoi								=				
Go-No-Go test											=	
Ruff total design					++							
Frontal assessment battery												+

Table 1. (Continued)

	Schwartz *et al.* (1999)	Gasparini *et al.* (2001)	Lombardi *et al.* (2001)	Duane and Vermilion, (2002)	Lacritz *et al.* (2002)	Troster *et al.* (2002)	Benito-Leon *et al.* (2006a)	Sahin *et al.* (2006)	Higginson *et al.* (2008)	Frisina *et al.* (2009)	Kim *et al.* (2009)	Passamonti *et al.* (2011)
Modified card sorting test												=
Matrix reasoning (WAIS)			=						=			
Similarities (WAIS)			=						+			
Memory												
CVLT relayed recall			+		=	++		=				
CVLT Delayed recognition			=		=	++		+				
Logical memory recall (WMS)						=	+		+			
Hopkins Verbal Learning Free Recall											++	
Hopkins Verbal Learning Delayed Recall											++	
Hopkins Verbal Learning Recognition											=	
Figural memory (WMS)						=						
Faces (WMS)									+			
Rey Complex Figure Immediate Recall											=	
Rey Complex Figure Delayed Recall				=							=	
Rey Complex Figure Recognition											++	
WMS: visual reproduction, % retention					++							
RAVLT (immediate recall)				=			+					=
RAVLT (delayed recall)				=			+					+

(Continued)

Table 1. (Continued)

	Schwartz *et al.* (1999)	Gasparini *et al.* (2001)	Lombardi *et al.* (2001)	Duane and Vermilion, (2002)	Lacritz *et al.* (2002)	Troster *et al.* (2002)	Benito-Leon *et al.* (2006a)	Sahin *et al.* (2006)	Higginson *et al.* (2008)	Frisina *et al.* (2009)	Kim *et al.* (2009)	Passamonti *et al.* (2011)
Language												
Letter fluency		++	++		+	++	++	++	=		++	=
Semantic fluency (animal naming)			++		=	++	=		++		++	
Vocabulary (WAIS)			=									
BNT			+		=	++		=	+		++	
Language comprehension (Token Test)												+
Visuospatial												
Benton facial recognition test			=			++		+				
Benton line orientation test								+				
Rey Complex Figure Copy				=				=			=	
Block designs (WAIS)					=			=	++			
Hooper visual organization test			=			++		=				
Judgment of Lines Orientation												=
Visual recognition deficits					+	+		+			=	
Mood												
Depression			+	++	+				+			=
BDI												=
HAM-A (anxiety)												=
Motor												
Grooved Pegboard						++						
Self-designed visuomotor tracking test	+											

Key

= p value not significant ($p > 0.05$)

+ $p \leq 0.05$

++ $p \leq 0.001$

not assessed in given study

BDI, Beck Depression Inventory; BNT, Boston Naming Test; CVLT, California Verbal Learning Test; ET, essential tremor; HAM-A, Hamilton Anxiety Rating Scale; IQ, intelligence quotient; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; WAIS, Wechsler Adult Intelligence Scales; WCST, Wisconsin Card Sorting Test WMS; Wechsler Memory Scale.

verbal recall (e.g. California Verbal Learning Test (CVLT) [Lombardi *et al.* 2001; Troster *et al.* 2002], Wechsler Memory Scale (WMS) Logical Memory Test [Higginson *et al.* 2008; Benito-Leon *et al.* 2006a] and the Hopkins Verbal Learning Test Free and Delayed Recall [Kim *et al.* 2009]) might also be best conceptualized as executive deficits. However, impairment has also been reported on tasks that generally have low executive demands in areas including global cognition: Mini-Mental State Examination (MMSE) [Kim *et al.* 2009; Frisina *et al.* 2009]); language (e.g. Boston Naming Test [Kim *et al.* 2009; Frisina *et al.* 2009; Lombardi *et al.* 2001; Higginson *et al.* 2008; Troster *et al.* 2002]); verbal recognition (e.g. CVLT [Troster *et al.* 2002; Sahin *et al.* 2006], WMS Logical Memory Test [Higginson *et al.* 2008; Benito-Leon *et al.* 2006a] and the Hopkins Verbal Learning Test [Kim *et al.* 2009]); and visual spatial function (e.g. Benton facial recognition test [Troster *et al.* 2002; Sahin *et al.* 2006], Benton line orientation test [Sahin *et al.* 2006], WAIS Block Design [Higginson *et al.* 2008] and the Hooper Visual Organization Test [Troster *et al.* 2002; Duane and Vermilion, 2002]).

The biological basis for the cognitive dysfunction associated with ET is unclear, although a number of mechanisms may be responsible. It has been hypothesized that cognitive deficits are mediated through cerebellar, thalamic and frontal connections that are compromised in ET [Kim *et al.* 2009; Troster *et al.* 2002; Sahin *et al.* 2006]. Much of the literature supports that ET is a disorder of cerebellar dysregulation, including the presence of intention tremor [Leegwater-Kim *et al.* 2006; Louis *et al.* 2009b], gait ataxia [Singer *et al.* 1994; Stolze *et al.* 2001], oculomotor abnormalities [Helmchen *et al.* 2003] and problems with dysrhythmia and motor learning [Trillenberg *et al.* 2006; Avanzino *et al.* 2009; Bares *et al.* 2010; Farkas *et al.* 2006; Shill *et al.* 2009; Kronenbuerger *et al.* 2007]. In addition, postmortem studies in ET have indicated the presence of a variety of structural and degenerative changes in the cerebellum, including increased number of Purkinje cell axonal swellings ('torpedoes') [Louis *et al.* 2007b; Axelrad *et al.* 2008], increased number of displaced or heterotopic Purkinje cells [Kuo *et al.* 2011], reduction in number of Purkinje cells in some studies [Axelrad *et al.* 2008] and hypertrophy of basket cell processes ('hairy baskets') [Erickson-Davis et al 2010]. Moreover, DBS surgery in ET targets the specific thalamic nucleus (i.e. ventral intermediate) that is the cerebellar receiving area, providing further support for pathway dysregulation in ET. More recently, the presence of dysregulated cerebellar pathways in ET has been supported by neuroimaging findings, including functional magnetic resonance imaging (MRI) [Bucher *et al.* 1997], positron emission tomography [Jenkins *et al.* 1993; Wills *et al.* 1994; Colebatch *et al.* 1990], ^{1}H magnetic resonance spectroscopic imaging [Louis *et al.* 2002; Pagan *et al.* 2003], diffusion tensor imaging [Shin *et al.* 2008; Klein *et al.* 2011; Nicoletti *et al.* 2010], voxel-based morphometry [Benito-Leon *et al.* 2009; Quattrone *et al.* 2008] and studies using other automated volumetric methods [Cerasa *et al.* 2009] which demonstrate the presence of functional, metabolic and structural abnormalities in the cerebellum of ET patients.

The idea that cognitive impairment in ET may reflect the distal effects of cerebellar changes *via* cerebellothalamocortical or cerebellothalamofrontal networks [Kim *et al.* 2009; Troster *et al.* 2002; Sahin *et al.* 2006] is consistent with a growing literature documenting the role of the cerebellum in facilitating psychological, cognitive and learning activities [Lombardi *et al.* 2001; Schmahmann and Sherman, 1998; Middleton and Strick, 2000a; Watson, 1978; Peterburs *et al.* 2010]. In addition, many reports of neuropsychological performance in patients with ET have highlighted a pattern of attentional and executive dysfunction that is analogous to that observed in neurodegenerative diseases affecting subcortical white matter [Schmidtke and Hull, 2002; Traykov *et al.* 2002; Tierney *et al.* 2001; Doddy *et al.* 1998; Lafosse *et al.* 1997] and basal ganglia structures [Troster *et al.* 2002; Lundervold *et al.* 1994; Pillon *et al.* 1995; Cummings, 1998].

While cognitive impairment in ET may be mediated by the processes or pathways specifically involved in the disease, an alternate hypothesis is that some cases of ET may also manifest a spectrum of neurodegenerative diseases, including AD, DLB, PD or Parkinson Plus Disorders. As a result, associated cognitive impairment and dementia actually may occur as a result of these concomitant neurodegenerative diseases (i.e. 'ET plus') [Louis, 2005b]. Although existing studies have generally conceptualized cognitive changes in ET as consistent with a 'frontosubcortical' or 'corticocerebellar' profile, results from these same studies suggest that cognitive impairment in ET

may in fact be heterogeneous, with a subset of changes uncharacteristic of cerebellar pathology. For example, three out of five studies that have evaluated verbal recognition memory (a measure of memory storage rather than retrieval) document impairment in patients with ET [Kim *et al.* 2009; Lombardi *et al.* 2001; Troster *et al.* 2002; Lacritz *et al.* 2002; Sahin *et al.* 2006]. This cognitive deficit is generally not a component of cerebellar cognitive syndromes [Neau *et al.* 2000; Daum and Ackermann, 1997] or of frontosubcortical impairment in dementia [Schmidtke and Hull. 2002; Traykov *et al.* 2002; Tierney *et al.* 2001; Doddy *et al.* 1998; Lafosse *et al.* 1997; Lundervold *et al.* 1994; Pillon *et al.* 1995; Cummings, 1998]. Rather, recognition deficits reflect a primary amnestic syndrome that is a classic sign of hippocampal dysfunction [Beyer *et al.* 2013; Deweer *et al.* 1995; Manns *et al.* 2003] and a cardinal feature of AD [Remy *et al.* 2005; Lekeu *et al.* 2003; Hamilton *et al.* 2004; Pillon *et al.* 1993]. Moreover, while language and visual spatial deficits in ET may be accounted for by disruptions in cerebellocortical networks, it may also be the case that such deficits reflect local changes in the temporal and parietal cortex consistent with early AD.

Association of late-onset ET with risk for MCI and dementia

This latter hypothesis is further supported by recent epidemiological studies demonstrating an association between ET (especially with onset after age 65) and risk for dementia. A series of papers from the Neurological Disorders in Central Spain (NEDICES) study examined the associations between ET and cognitive dysfunction [Benito-Leon *et al.* 2006a; Louis *et al.* 2010b], prevalent MCI [Benito-Leon *et al.* 2011], and both prevalent and incident dementia [Benito-Leon *et al.* 2006b; Bermejo-Pareja *et al.* 2007]. ET cases were gathered from three communities in central Spain and all participants were 65 years of age or older. The investigators used a population-based case–control study design matching patients with ET and controls for age, gender, education, depressive symptoms and medications that could potentially affect cognition. The neuropsychological battery tested global cognitive performance, executive function, memory and pre-morbid intelligence. Subjects were also asked whether they suffered from forgetfulness or depression. The investigators demonstrated that ET cases performed less well than controls on neuropsychological testing, particularly on tests of memory and executive abilities, and a larger proportion of cases reported forgetfulness [Benito-Leon *et al.* 2006a; Louis *et al.* 2010b] Moreover, cross-sectional analyses revealed that ET with tremor onset after age 65 was associated with an increased odds of MCI [adjusted odds ratio (OR) = 1.57, 95% confidence interval (CI) 1.03–2.38, $p = 0.03$], whereas cases with tremor onset prior to age 65 years and controls were equally likely to have MCI (adjusted OR = 0.73, 95% CI 0.34–1.57, $p = 0.43$) [Benito-Leon *et al.* 2011]. These study subjects were then followed longitudinally for a mean of 3.2 years, and the rate of cognitive decline appeared to be faster in ET cases with tremor onset after 65 years of age than in controls [Louis *et al.* 2010a]. The same study demonstrated an association between ET with onset after 65 years of age and prevalent dementia [Benito-Leon *et al.* 2006b] (adjusted OR = 1.70, 95% CI 1.04–2.76, $p = 0.03$), as well as incident dementia [Bermejo-Pareja *et al.* 2007] over a mean follow-up duration of 3.2 years [relative risk (RR) = 1.98, 95% CI 1.14–3.45, $p = 0.01$).

A second prospective, population-based study of elders (study enrollment age ≥65 years but ET age of onset unknown) was conducted in northern Manhattan, New York [Thawani *et al.* 2009] and demonstrated similar results. In cross-sectional analyses, 31 of 124 (25.0%) ET cases had prevalent dementia *versus* 198 of 2161 (9.2%) controls (adjusted OR = 1.84, 95% CI 1.13–2.98, $p = 0.01$). In prospective analyses, 17 of 93 (18.3%) ET cases *versus* 171 of 1963 (8.7%) controls developed incident dementia [adjusted hazard ratio (HR) = 1.64, 95% CI 0.99–2.72, $p = 0.055$). Thus, in a second population-based study of elders, ET was associated with both increased odds of prevalent dementia and increased risk of incident dementia.

In both the New York [Thawani *et al.* 2009] and Spanish studies [Benito-Leon *et al.* 2006b; Bermejo-Pareja *et al.* 2007], the majority of ET cases who developed incident dementia carried clinical diagnoses of probable AD, making this a likely etiology of their cognitive symptoms. Postmortem studies in different study groups also suggest that there may be an increase in Alzheimer-type changes in the ET brain (i.e. neurofibrillary tangles and neuritic plaques) [Louis *et al.* 2007b], providing further support for this etiologic hypothesis.

Cortical Lewy bodies have not been a prominent feature of ET pathology in most studies [Louis *et al.* 2007b; Shill *et al.* 2008]. However, one group recently described a subset of ET patients whose postmortem examination revealed an anatomically restricted manifestation and distinctive pattern of DLB (with many Lewy bodies in the locus ceruleus, rare Lewy bodies in the substantial innominata and dorsal vagal nuclei, and rare or absent Lewy bodies in the substantia nigra), which has not been observed in patients with subclinical or clinically manifest PD [Louis *et al.* 2005]. This raises the question as to whether a proportion of ET cases might have forms of DLB; however, the role that Lewy body pathology may play in cognitive change, MCI, or dementia in patients with ET has yet to be investigated prospectively or in large epidemiologic studies.

Neurodegenerative diseases traditionally categorized as Parkinson Plus Disorders may also play a role in cognitive impairment in ET. Our group recently reported an evaluation of 89 ET patients prospectively collected at the ET Centralized Brain Repository over the course of its first 9 years [Louis *et al.* 2013]. Of this group, 11 (12.4%) ET patients were found to have postmortem changes consistent with PSP. PSP is a syndrome characterized by supranuclear palsy, postural instability and some degree of Parkinsonism in many patients; it may also be characterized by dementia. Five patients in our group had cognitive complaints later in life and four of these individuals were diagnosed by their treating physician as having had dementia. The latency from onset of ET to dementia ranged from 5 to 47 years. The prevalence of PSP in this ET sample was larger than the population prevalence of PSP (0.001–0.00655%), and was also 2–5 times the proportion of normal cases with incidental PSP reported in two prior autopsy series [Shill *et al.* 2008; Rajput *et al.* 2004]. In a Canadian ET postmortem series, two out of 20 (10%) ET patients were also reported to have had PSP, which is a value that is similar to the 11 out of 89 (12.4%) reported above [Rajput *et al.* 2004], but given the small numbers (n = 2 with ET + PSP), the authors did not draw attention to this possible connection. In an Arizona ET postmortem series, one out of 24 (4.2%) had PSP [Shill *et al.* 2008]; however, this study specifically excluded subjects with ET and PD as well as ET with dementia. These findings raise the question of what proportion of ET patients who develop what is presumed during life to be concomitant PD or AD actually have PSP. This is particularly important when speaking about cognitive change in ET, as executive impairment is a notable feature of PSP [Williams and Lees, 2009; Litvan *et al.* 1996] and thus may account for some instances of ET patients with cognitive impairment.

Association of ET with psychiatric disorders

Psychiatric issues such as depression and anxiety, personality changes, social phobias and low measures of subjective health status or health-related quality of life are all frequently observed in patients with ET [Li *et al.* 2011; Miller *et al.* 2007; Siddiqui *et al.* 2009; Louis, 2005a, 2010a; Poewe *et al.* 1990; Lorenz *et al.* 2006; Chatterjee *et al.* 2004; Louis *et al.* 2007a, 2008; Ozel-Kizil *et al.* 2008; Findley, 2004; Galvin, 2009; Woods *et al.* 2008; Dogu *et al.* 2005]. Some studies have estimated that as many as 30% of patients with ET have mild depressive symptoms [Lorenz *et al.* 2006]. Depression in ET may have different clinical manifestations than in patients with primary affective disorders, in that patients with ET are more likely to report concentration difficulties and fatigue [Li *et al.* 2011]. Although the association between psychiatric issues and ET is documented in many studies, more information is needed regarding their initiation and evolution. Traditionally, psychiatric symptoms have been regarded as occurring in response to debilitating neurological symptoms in ET [Chatterjee *et al.* 2004]. However, other evidence suggests that depression might occur before the motor symptoms of ET manifest; in such situations this psychiatric disorder cannot be a secondary response to disability [Louis, 2010a; Louis *et al.* 2007a; Dogu *et al.* 2005]. The pathophysiological basis of depression and anxiety in patients with ET is currently unknown and awaits prospective studies. Importantly, however, depression does not appear to account for cognitive deficits in ET [Li *et al.* 2011].

Therapeutic implications

Implications for patient care: assessment and counseling

A variety of studies demonstrate that patients with ET are at increased risk for cognitive deficits. Specifically, those with tremor onset at age 65 or older are at increased risk for MCI (OR = 1.57, 95% CI 1.03–2.38, *versus* controls) [Benito-Leon

et al. 2011] with a faster rate of cognitive decline once impairment has occurred [Louis *et al.* 2010a]. Similarly, individuals with ET are also at increased risk for prevalent dementia (OR = 1.70–1.84 *versus* controls) [Bermejo-Pareja *et al.* 2007; Thawani *et al.* 2009], and incident dementia (RR = 1.64–1.98 *versus* controls) [Bermejo-Pareja *et al.* 2007; Thawani *et al.* 2009], with the most frequent presumed etiology being concomitant AD [Louis *et al.* 2009b].

What are the therapeutic implications of these findings? To begin with, clinicians should consider routinely assessing ET patients (particularly those with older age of onset) for possible signs or symptoms of cognitive impairment. Briefly, such an interview could include an assessment of the patient's ability to recall recent events and appointments, and their ability to independently conduct somewhat complex tasks such as management of finances, driving and housework. Ancillary interviews of close friends or family members for their opinions of the patient's cognition should also be strongly considered. Clinician initiation of this discussion may assist many patients with ET and their families who are reluctant to volunteer such information spontaneously. Patients who are experiencing cognitive difficulties may have uncertainty about the meaning of their problems, and an informed and open discussion with an educated practitioner can allay some of their anxieties. These suggestions are in contrast to current clinical practice, which does not routinely include such assessment of ET patients and which may further judge evidence of such cognitive decline, if detected, to be inconsequential or related to normal aging or medication side effects [Tolosa and Molineuvo, 2010].

If concerns are raised during the clinician interview with the patient or family members, additional follow-up steps may be taken. For example, psychometric screening tests such as the Montreal Cognitive Assessment (MoCA) [Nasreddine *et al.* 2005] take approximately 10 minutes to administer in an office environment and can help the clinician to assess a patient's cognitive performance and to track the clinical evolution of these cognitive deficits over time. The MoCA has been shown to have excellent specificity and sensitivity for detecting MCI and dementia, and for tracking cognitive change over time, outperforming the MMSE in these regards [Dong *et al.* 2012; Freitas *et al.* 2013]. The Addenbrooke's Cognitive Examination Revised (ACE-R) [Mioshi *et al.* 2006] has also been shown to be particularly useful in the detection of cognitive impairment in individuals with movement disorders [Bak *et al.* 2005]. The ACE-R, designed to be a more thorough cognitive screening tool than the MMSE, includes six subscores evaluating orientation, attention, memory, verbal fluency, language and visuospatial functioning. The ACE-R has high sensitivity and specificity for the diagnosis of dementia in PD using a cutoff score of 83 [Reyes *et al.* 2009], and more recent work has shown it to be a highly useful screen for the diagnosis of MCI in PD using a cutoff score of 89 [McColgan *et al.* 2012]. Moreover, performance on aspects of the ACE-R, particularly the verbal fluency subscore, has been shown to inform the differential diagnosis of Parkinsonian syndromes including PD, PSP and corticobasal degeneration (CBD) [Rittman *et al.* 2013]. Examination of performance across ACE-R subscores may also provide preliminary information regarding the profile of cognitive impairment and the extent to which patients present with primary deficits in executive function *versus* memory. However, individuals who demonstrate cognitive deficits on screening should be referred for more extensive neuropsychological evaluations through a neuropsychologist to determine the extent of cognitive limitations and to more comprehensively examine whether the pattern of deficits is consistent with a known neurodegenerative etiology such as AD, PD, DLB or PSP.

While neuroimaging methods have been used to support the diagnosis of several cognitive neurodegenerative diseases, no such studies to date have evaluated the use of specific neuroimaging tests to investigate the nature of cognitive changes in ET. It may be possible to use functional imaging such as fluorodeoxyglucose positron emission tomography (FDG-PET) and single photon emission computed tomography (SPECT) to determine whether some ET patients also have AD pathology, particularly if the patient's cognitive profile is supportive of this possibility; however, specific studies have not yet been performed to evaluate this potential association. While ^{123}I-2β-carbometoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane (^{123}I-FP-CIT) scans for the dopamine transporter have demonstrated the capacity to distinguish ET and healthy controls from patients with PD, DLB and PSP based on reduced levels of dopamine active transporter (DAT) in the latter conditions [Roselli *et al.* 2010], they cannot

distinguish ET from healthy controls. As a result, future studies are needed to specifically examine these different imaging indications.

There are many potential functional aspects to cognitive impairment and the evaluation of cognitive performance would allow clinicians to proactively identify areas of potential cognitive and functional difficulty [Kronenbuerger *et al.* 2009; Louis *et al.* 2010a]. In a recent population-based study, lower cognitive test scores in ET were associated with more self-reported functional difficulty, indicating that cognitive deficits in ET seem to have functional consequences [Louis, 2010c]. This was supported by a second study which demonstrated that Minimum Data Set Activities of Daily Living Section (MDS-ADL) scores were significantly correlated with overall cognitive level (as assessed by the MMSE) but not with motor disability among patients with ET. Overall, these findings highlight that the cognitive aspects of ET may be more functionally disabling than the hallmark motor features. If areas of cognitive functional difficulty are identified, modifications for daily cognitive tasks can be discussed with the patient and his or her family to identify means of assistance or reassignment of difficult tasks to others.

The clinician should keep in mind that functional difficulties that seem out of proportion to any underlying cognitive impairment may be a sign of a co-occurring mood disturbance. Thus, clinicians should consider assessing these patients for quality of life and depression [Louis, 2010c; Louis *et al.* 2010a], as standard treatment with selective serotonin reuptake inhibitors (SSRIs) or other antidepressant regimens is available and effective in patients with ET.

Potential pharmacotherapies for cognitive complaints in ET

To our knowledge, there have been no clinical trials to date of any agent for cognitive change associated with ET. As a result, studies for this indication are needed. Given that many of these patients with ET demonstrate impairment in attention and memory, it may make sense for trials of cholinesterase inhibitors such as donepezil, galantamine and rivastigmine to be conducted. Memantine, an *N*-methyl-D-aspartic acid (NMDA) receptor antagonist used for treatment of moderate to severe AD has been investigated in studies for its anti-tremor effects in animals [Iseri *et al.* 2011] and in humans [Handforth *et al.* 2010]. While animal studies showed that memantine had a neuroprotective effect on cerebellar and inferior olivary neurons [Iseri *et al.* 2011], human studies indicate that the average effect of memantine on tremor was mild or not significant except for a small subset of patients for whom memantine conferred meaningful tremor benefit [Handforth *et al.* 2010]. It should be noted that while the beneficial effect of memantine on tremor was primarily noted at higher dosages (i.e. 30–40 mg/day), adverse events were also more common at higher doses and included dizziness, somnolence and fatigue [Handforth *et al.* 2010]. Cognition was not studied as an endpoint in either of these studies.

Further study recommendations

Future studies are needed to better characterize the cardinal neuropsychological features of ET to aid in accurate clinical diagnoses and appropriately categorize patients for inclusion in clinical treatment trials. Additional case-control and longitudinal studies are needed to examine the potential relationships between ET and the mechanisms contributing to cognitive, personality and psychological change. Autopsy studies and genetic susceptibility studies are also critical for exploration of potential common biologic and genetic pathways between ET and neurodegenerative diseases associated with cognitive impairment such as AD, PD, DLB and PSP. Neuroimaging studies present another modality for examining these potential relationships. Finally, once these patterns and relationships are better characterized, clinical trials could examine the potential utility of cholinesterase inhibitors and memantine for treatment of cognitive impairment in ET.

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The authors declare no conflicts of interest and no competing financial interests in preparing this article.

References

Akshoomoff, N., Courchesne, E. and Townsend, J. (1997) Attention coordination and anticipatory control. *Int Rev Neurobiol* 41: 575–598.

Allen, G., Buxton, R., Wong, E. and Courchesne, E. (1997) Attentional activation of the cerebellum independent of motor involvement. *Science* 275: 1940–1943.

Appollonio, I., Grafman, J., Schwartz, V., Massaquoi, S. and Hallett, M. (1993) Memory in patients with cerebellar degeneration. *Neurology* 43: 1536–1544.

Avanzino, L., Bove, M., Tacchino, A., Ruggeri, P., Giannini, A., Trompetto, C. *et al.* (2009) Cerebellar involvement in timing accuracy of rhythmic finger movements in essential tremor. *Eur J Neurosci* 30: 1971–1979.

Axelrad, J., Louis, E., Honig, L., Flores, I., Ross, G., Pahwa, R. *et al.* (2008) Reduced Purkinje cell number in essential tremor: a postmortem study. *Arch Neurol* 65: 101–107.

Bain, P., Brin, M., Deuschl, G., Elble, R., Jankovic, J., Findley, L. *et al.* (2000) Criteria for the diagnosis of essential tremor. *Neurology* 54: S7.

Bak, T., Rogers, T., Crawford, L., Hearn, V., Mathuranath, P. and Hodges, J. (2005) Cognitive bedside assessment in atypical parkinsonian syndromes. *J Neurol Neurosurg Psychiatry* 76: 420–422.

Bares, M., Lungu, O., Husarova, I. and Gescheidt, T. (2010) Predictive motor timing performance dissociates between early diseases of the cerebellum and Parkinson's disease. *Cerebellum* 9: 124–135.

Benito-Leon, J., Alvarez-Linera, J., Hernandez-Tamames, J., Alonso-Navarro, H., Jimenez-Jimenez, F. and Louis, E. (2009) Brain structural changes in essential tremor: voxel-based morphometry at 3-Tesla. *J Neurol Sci* 287: 138–142.

Benito-Leon, J., Louis, E. and Bermejo-Pareja, F. & Neurological Disorders in Central Spain Study Group (2006a) Population-based case-control study of cognitive function in essential tremor. *Neurology* 66: 69–74.

Benito-Leon, J., Louis, E., Bermejo-Pareja, F. and Neurological Disorders in Central Spain Study Group (2006b) Elderly-onset essential tremor is associated with dementia. *Neurology* 66: 1500–1505.

Benito-Leon, J., Louis, E., Mitchell, A. and Bermejo-Pareja, F. (2011) Elderly-onset essential tremor and mild cognitive impairment: a population-based study (NEDICES) *J Alzheimers Dis* 23: 727–735.

Bermejo-Pareja, F., Louis, E., Benito-Leon, J. and Neurological Disorders in Central Spain Study Group (2007) Risk of incident dementia in essential tremor: a population-based study. *Mov Disord* 22: 1573–1580.

Beyer, M., Bronnick, K., Hwang, K., Bergsland, N., Tysnes, O., Larsen, J. *et al.* (2013) Verbal memory is associated with structural hippocampal changes in newly diagnosed Parkinson's disease. *J Neurol Neurosurg Psychiatry* 84: 23–28.

Botez, M., Gravel, J., Attig, E. and Vezina, J. (1985) Reversible chronic cerebellar ataxia after phenytoin intoxication: possible role of cerebellum in cognitive thought. *Neurology* 35: 1152–1157.

Botez-Marquard, T., Leveille, J. and Botez, M. (1994) Neuropsychological functioning in unilateral cerebellar damage. *Can J Neurol Sci* 21: 353–357.

Bucher, S., Seelos, K., Dodel, R., Reiser, M. and Oertel, W. H. (1997) Activation mapping in essential tremor with functional magnetic resonance imaging. *Ann Neurol* 41: 32–40.

Cerasa, A., Messina, D., Nicoletti, G., Novellino, F., Lanza, P., Condino, F. *et al.* (2009) Cerebellar atrophy in essential tremor using an automated segmentation method. *AJNR Am J Neuroradiol* 30: 1240–1243.

Chatterjee, A., Jurewicz, E., Applegate, L. and Louis, E. (2004) Personality in essential tremor: further evidence of non-motor manifestations of the disease. *J Neurol Neurosurg Psychiatry* 75: 958–961.

Colebatch, J., Findley, L., Frackowiak, R., Marsden, C. and Brooks, D. (1990) Preliminary report: activation of the cerebellum in essential tremor. *Lancet* 336: 1028–1030.

Cummings, J. (1988) The dementias of Parkinson's disease: prevalence, characteristics, neurobiology, and comparison with dementia of the Alzheimer type. *Eur Neurol* 28(Suppl. 1): 15–23.

Daum, I. and Ackermann, H. (1997) Neuropsychological abnormalities in cerebellar syndromes – fact or fiction? *Int Rev Neurobiol* 41: 455–471.

Desmond, J. and Fiez, J. (1998) Neuroimaging studies of the cerebellum: language, learning and memory. *Trends Cogn Sci* 2: 355–362.

Deuschl, G., Wenzelburger, R., Loffler, K., Raethjen, J. and Stolze, H. (2000) Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. *Brain* 123: 1568–1580.

Deweer, B., Lehericy, S., Pillon, B., Baulac, M., Chiras, J., Marsault, *et al.* (1995) Memory disorders in probable Alzheimer's disease: the role of hippocampal atrophy as shown with MRI. *J Neurol Neurosurg Psychiatry* 58: 590–597.

Doddy, R., Massman, P., Mawad, M. and Nance, M. (1998) Cognitive consequences of subcortical magnetic resonance imaging changes in Alzheimer's disease: comparison to small vessel ischemic vascular dementia. *Neuropsychiatry Neuropsychol Behav Neurol* 11: 191–199.

Dogu, O., Louis, E., Sevim, S., Kaleagasi, H. and Aral, M. (2005) Clinical characteristics of essential tremor in Mersin, Turkey – a population-based door-to-door study. *J Neurol* 252: 570–574.

Dong, Y., Lee, W., Basri, N., Collinson, S., Merchant, R., Venketasubramanian, N. and Chen, C. (2012) The Montreal Cognitive Assessment is superior to the Mini-Mental State Examination in detecting patients at higher risk of dementia. *Int Psychogeriatr* 24: 1749–1755.

Duane, D. and Vermilion, K. J. (2002) Cognitive deficits in patients with essential tremor. *Neurology* 58: 1706; author reply 1706.

Erickson-Davis, C., Faust, P., Vonsattel, J., Gupta, S., Honig, L. and Louis, E. (2010) 'Hairy baskets' associated with degenerative Purkinje cell changes in essential tremor. *J Neuropathol Exp Neurol* 69: 262–271.

Fahn, S., Tolosa, E. and Marin, C. (1993) Clinical rating scale for tremor. In: Jankovic, J. and Tolosa, E. (eds.), *Parkinson's Disease and Movement Disorders*, Williams and Wilkins, Baltimore, MD, pp. 271–280.

Farkas, Z., Szirmai, I. and Kamondi, A. (2006) Impaired rhythm generation in essential tremor. *Mov Disord* 21: 1196–1199.

Fiez, J., Petersen, S., Cheney, M. and Raichle, M. (1992) Impaired non-motor learning and error detection associated with cerebellar damage. A single case study. *Brain* 115: 155–178.

Fiez, J. and Raichle, M. (1997) Linguistic processing. *Int Rev Neurobiol* 41: 233–254.

Findley, L. (2004) Expanding clinical dimensions of essential tremor. *J Neurol Neurosurg Psychiatry* 75: 948–949.

Freitas, S., Simoes, M., Alves, L. and Santana, I. (2013) Montreal Cognitive Assessment: validation study for mild cognitive impairment and Alzheimer's disease. *Alzheimer Dis Assoc Disord* 27: 37–43

Frisina, P., Tse, W., Halbig, T. and Libow, L. (2009) The pattern of cognitive-functional decline in elderly essential tremor patients: an exploratory-comparative study with Parkinson's and Alzheimer's disease patients. *J Am Med Dir Assoc* 10: 238–242.

Galvin, J. (2009) When a tremor is not just a tremor: cognitive and functional decline in essential tremor, a more complex disorder than we thought. *J Am Med Dir Assoc* 10: 218–220.

Gasparini, M., Bonifati, V., Fabrizio, E., Fabbrini, G., Brusa, L., Lenzi, G. *et al.* (2001) Frontal lobe dysfunction in essential tremor: a preliminary study. *J Neurol* 248: 399–402.

Grafman, J., Litvan, I., Massaquoi, S., Stewart, M., Sirigu, A. and Hallett, M. (1992) Cognitive planning deficit in patients with cerebellar atrophy. *Neurology* 42: 1493–1496.

Hallett, M. and Grafman, J. (1997) Executive function and motor skill learning. *Int Rev Neurobiol* 41: 297–323.

Hamilton, J., Salmon, D., Galasko, D., Delis, D., Hansen, L., Masliah, E. *et al.* (2004) A comparison of episodic memory deficits in neuropathologically-confirmed Dementia with Lewy bodies and Alzheimer's disease. *J Int Neuropsychol Soc* 10: 689–697.

Handforth, A., Bordelon, Y., Frucht, S. and Quesada, A. (2010) A pilot efficacy and tolerability trial of memantine for essential tremor. *Clin Neuropharmacol* 33: 223–226.

Helmchen, C., Hagenow, A., Miesner, J., Sprenger, A., Rambold, H., Wenzelburger, R. *et al.* (2003) Eye movement abnormalities in essential tremor may indicate cerebellar dysfunction. *Brain* 126: 1319–1332.

Higginson, C., Wheelock, V., Levine, D., King, D., Pappas, C. and Sigvardt, K. (2008) Cognitive deficits in essential tremor consistent with frontosubcortical dysfunction. *J Clin Exp Neuropsychol* 30: 760–765.

Iseri, P., Karson, A., Gullu, K., Akman, O., Kokturk, S., Yardymoglu, M. *et al.* (2011) The effect of memantine in harmaline-induced tremor and neurodegeneration. *Neuropharmacology* 61: 715–723.

Jenkins, I., Bain, P., Colebatch, J., Thompson, P., Findley, L., Frackowiak, R. *et al.* (1993) A positron emission tomography study of essential tremor: evidence for overactivity of cerebellar connections. *Ann Neurol* 34: 82–90.

Kim, J., Song, I., Shim, Y., Park, J., Yoo, J., Kim, Y. *et al.* (2009) Cognitive impairment in essential tremor without dementia. *J Clin Neurol* 5: 81–84.

Kish, S., el-Awar, M., Schut, L., Leach, L., Oscar-Berman, M. and Freedman, M. (1988) Cognitive deficits in olivopontocerebellar atrophy: implications for the cholinergic hypothesis of Alzheimer's dementia. *Ann Neurol* 24: 200–206.

Klein, J., Lorenz, B., Kang, J., Baudrexel, S., Seifried, C., van de Loo, S. *et al.* (2011) Diffusion tensor imaging of white matter involvement in essential tremor. *Hum Brain Mapp* 32: 896–904.

Kronenbuerger, M., Gerwig, M., Brol, B., Block, F. and Timmann, D. (2007) Eyeblink conditioning is impaired in subjects with essential tremor. *Brain* 130: 1538–1551.

Kronenbuerger, M., Konczak, J., Ziegler, W., Buderath, P., Frank, B., Coenen, V. *et al.* (2009) Balance and motor speech impairment in essential tremor. *Cerebellum* 8: 389–398.

Kuo, S., Erickson-Davis, C., Gillman, A., Faust, P., Vonsattel, J. and Louis, E. (2011) Increased number of heterotopic Purkinje cells in essential tremor. *J Neurol Neurosurg Psychiatry* 82: 1038–1040.

Lacritz, L., Dewey, R., Jr., Giller, C. and Cullum, C. (2002) Cognitive functioning in individuals with 'benign' essential tremor. *J Int Neuropsychol Soc* 8: 125–129.

Lafosse, J., Reed, B., Mungas, D., Sterling, S., Wahbeh, H. and Jagust, W. (1997) Fluency and memory differences between ischemic vascular dementia and Alzheimer's disease. *Neuropsychology* 11: 514–522.

Leegwater-Kim, J., Louis, E., Pullman, S., Floyd, A., Borden, S., Moskowitz, C. *et al.* (2006) Intention tremor of the head in patients with essential tremor. *Mov Disord* 21: 2001–2005.

Lekeu, F., Van der Linden, M., Degueldre, C., Lemaire, C., Luxen, A., Franck, G. *et al.* (2003) Effects of Alzheimer's disease on the recognition of novel *versus* familiar words: neuropsychological and clinico-metabolic data. *Neuropsychology* 17: 143–154.

Li, Z., Xie, M., Tian, D., Li, J., Zhang, J., Jiao, L. *et al.* (2011) Characteristics of depressive symptoms in essential tremor. *J Clin Neurosci* 18: 52–56.

Litvan, I., Agid, Y., Calne, D., Campbell, G., Dubois, B., Duvoisin, R. *et al.* (1996) Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 47: 1–9.

Lombardi, W., Woolston, D., Roberts, J. and Gross, R. (2001) Cognitive deficits in patients with essential tremor. *Neurology* 57: 785–790.

Lorenz, D., Schwieger, D., Moises, H. and Deuschl, G. (2006) Quality of life and personality in essential tremor patients. *Mov Disord* 21: 1114–1118.

Louis, E. (2005a) Behavioral symptoms associated with essential tremor. *Adv Neurol* 96: 284–290.

Louis, E. (2005b) Essential tremor. *Lancet Neurol* 4: 100–110.

Louis, E. (2010a) Essential tremor as a neuropsychiatric disorder. *J Neurol Sci* 289: 144–148.

Louis, E. (2010b) Essential tremor: evolving clinicopathological concepts in an era of intensive post-mortem enquiry. *Lancet Neurol* 9: 613–622.

Louis, E. (2010c) Functional correlates of lower cognitive test scores in essential tremor. *Mov Disord* 25: 481–485.

Louis, E., Babij, R., Ma, K., Cortés, E. and Vonsattel, J. (2013) Essential tremor followed by progressive supranuclear palsy: postmortem reports of 11 patients. *J Neuropathol Exp Neurol* 72: 8–17.

Louis, E., Benito-Leon, J., Bermejo-Pareja, F. and Neurological Disorders in Central Spain Study Group (2007a) Self-reported depression and anti-depressant medication use in essential tremor: cross-sectional and prospective analyses in a population-based study. *Eur J Neurol* 14: 1138–1146.

Louis, E., Benito-Leon, J., Bermejo-Pareja, F. and Neurological Disorders in Central Spain Study Group (2008) Philadelphia Geriatric Morale Scale in essential tremor: a population-based study in three Spanish communities. *Mov Disord* 23: 1435–1440.

Louis, E., Benito-Leon, J., Vega-Quiroga, S., Bermejo-Pareja, F. and Neurological Disorders in Central Spain Study Group (2009a) Antihypertensive agents and risk of Parkinson's disease, essential tremor and dementia: a population-based prospective study (NEDICES) *Neuroepidemiology* 33: 286–292.

Louis, E., Benito-Leon, J., Vega-Quiroga, S., Bermejo-Pareja, F. and Neurological Disorders in Central Spain Study Group (2010a) Faster rate of cognitive decline in essential tremor cases than controls: a prospective study. *Eur J Neurol* 17: 1291–1297.

Louis, E., Benito-Leon, J., Vega-Quiroga, S., Bermejo-Pareja, F. and Neurological Disorders in Central Spain Study Group (2010b) Cognitive and motor functional activity in non-demented community-dwelling essential tremor cases. *J Neurol Neurosurg Psychiatry* 81: 997–1001.

Louis, E., Faust, P., Vonsattel, J., Honig, L., Rajput, A., Robinson, C. *et al.* (2007b) Neuropathological changes in essential tremor: 33 cases compared with 21 controls. *Brain* 130: 3297–3307.

Louis, E., Ford, B., Lee, H., Andrews, H. and Cameron, G. (1998) Diagnostic criteria for essential tremor: a population perspective. *Arch Neurol* 55: 823–828.

Louis, E., Frucht, S. and Rios, E. (2009b) Intention tremor in essential tremor: Prevalence and association with disease duration. *Mov Disord* 24: 626–627.

Louis, E., Honig, L., Vonsattel, J., Maraganore, D., Borden, S. and Moskowitz, C. (2005) Essential tremor associated with focal nonnigral Lewy bodies: a clinicopathologic study. *Arch Neurol* 62: 1004–1007.

Louis, E., Rios, E. and Rao, A. (2010c) Tandem gait performance in essential tremor: clinical correlates and association with midline tremors. *Mov Disord* 25: 1633–1638.

Louis, E., Shungu, D., Chan, S., Mao, X., Jurewicz, E. and Watner, D. (2002) Metabolic abnormality in the cerebellum in patients with essential tremor: a proton magnetic resonance spectroscopic imaging study. *Neurosci Lett* 333: 17–20.

Lucas, J., Rippeth, J., Uitti, R., Shuster, E. and Wharen, R. (2000) Neuropsychological functioning in a patient with essential tremor with and without bilateral VIM stimulation. *Brain Cogn* 42: 253–267.

Lundervold, A., Karlsen, N. and Reinvang, I. (1994) Assessment of 'subcortical dementia' in patients with Huntington's disease, Parkinson's disease, multiple sclerosis and AIDS by a neuropsychological screening battery. *Scand J Psychol* 35: 48–55.

Manns, J., Hopkins, R. and Squire, L. (2003) Semantic memory and the human hippocampus. *Neuron* 38: 127–133.

McColgan, P., Evans, J., Breen, D., Mason, S., Barker, R. and Williams-Gray, C. (2012) Addenbrooke's Cognitive Examination Revised for mild cognitive impairment in Parkinson's disease. *Mov Disord* 27: 1173–1177.

Middleton, F. and Strick, P. (2000a) Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res Brain Res Rev* 31: 236–250.

Middleton, F. and Strick, P. (2000b) Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. *Brain Cogn* 42: 183–200.

Middleton, F. and Strick, P. (2001) Cerebellar projections to the prefrontal cortex of the primate. *J Neurosci* 21: 700–712.

Miller, K., Okun, M., Fernandez, H., Jacobson, C., Rodriguez, R. and Bowers, D. (2007) Depression symptoms in movement disorders: comparing Parkinson's disease, dystonia, and essential tremor. *Mov Disord* 22: 666–672.

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R. and Hodges, J. R. (2006) The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry* 21: 1078–1085.

Molinari, M., Leggio, M., Solida, A., Ciorra, R., Misciagna, S., Silveri, M. *et al.* (1997) Cerebellum and procedural learning: evidence from focal cerebellar lesions. *Brain* 120: 1753–1762.

Montgomery, E., Jr., Baker, K., Lyons, K. and Koller, W. (2000) Motor initiation and execution in essential tremor and Parkinson's disease. *Mov Disord* 15: 511–515.

Nasreddine, Z., Phillips, N., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I. *et al.* (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 53: 695–699.

Neau, J., Arroyo-Anllo, E., Bonnaud, V., Ingrand, P. and Gil, R. (2000) Neuropsychological disturbances in cerebellar infarcts. *Acta Neurol Scand* 102: 363–370.

Nicoletti, G., Manners, D., Novellino, F., Condino, F., Malucelli, E., Barbiroli, B. *et al.* (2010) Diffusion tensor MRI changes in cerebellar structures of patients with familial essential tremor. *Neurology* 74: 988–994.

Ozel-Kizil, E., Akbostanci, M., Ozguven, H. and Atbasoglu, E. (2008) Secondary social anxiety in hyperkinesias. *Mov Disord* 23: 641–645.

Pagan, F., Butman, J., Dambrosia, J. and Hallett, M. (2003) Evaluation of essential tremor with multi-voxel magnetic resonance spectroscopy. *Neurology* 60: 1344–1347.

Passamonti, L., Novellino, F., Cerasa, A., Chiriaco, C., Rocca, F., Matina, M. *et al.* (2011) Altered cortical-cerebellar circuits during verbal working memory in essential tremor. *Brain* 134: 2274–2786.

Peterburs, J., Bellebaum, C., Koch, B., Schwarz, M. and Daum, I. (2010) Working memory and verbal fluency deficits following cerebellar lesions: relation to interindividual differences in patient variables. *Cerebellum* 9: 375–383.

Pillon, B., Blin, J., Vidailhet, M., Deweer, B., Sirigu, A., Dubois, B. *et al.* (1995) The neuropsychological pattern of corticobasal degeneration: comparison with progressive supranuclear palsy and Alzheimer's disease. *Neurology* 45: 1477–1483.

Pillon, B., Deweer, B., Agid, Y. and Dubois, B. (1993) Explicit memory in Alzheimer's, Huntington's, and Parkinson's diseases. *Arch Neurol* 50: 374–379.

Poewe, W., Karamat, E., Kemmler, G. and Gerstenbrand, F. (1990) The premorbid personality of patients with Parkinson's disease: a comparative study with healthy controls and patients with essential tremor. *Adv Neurol* 53: 339–342.

Quattrone, A., Cerasa, A., Messina, D., Nicoletti, G., Hagberg, G. E., Lemieux, L. *et al.* (2008) Essential head tremor is associated with cerebellar vermis atrophy: a volumetric and voxel-based morphometry MR imaging study. *AJNR Am J Neuroradiol* 29: 1692–1697.

Rajput, A., Robinson, C. A. and Rajput, A. H. (2004) Essential tremor course and disability: A clinicopathologic study of 20 cases. *Neurology* 62: 932–936.

Rapoport, M., van Reekum, R. and Mayberg, H. (2000) The role of the cerebellum in cognition and behavior: a selective review. *J Neuropsychiatry Clin Neurosci* 12: 193–198.

Remy, F., Mirrashed, F., Campbell, B. and Richter, W. (2005) Verbal episodic memory impairment in Alzheimer's disease: a combined structural and functional MRI study. *Neuroimage* 25: 253–266.

Reyes, M., Perez-Lloret, S., Roldan Gerschcovich, E., Martin, M., Leiguarda, R. and Merello, M. (2009)

Addenbrooke's Cognitive Examination validation in Parkinson's disease. *Eur J Neurol* 16: 142–147.

Rittman, T., Ghosh, B. C., McColgan, P., Breen, D. P., Evans, J., Williams-Gray, C. H. *et al.* (2013) The Addenbrooke's Cognitive Examination for the differential diagnosis and longitudinal assessment of patients with parkinsonian disorders. *J Neurol Neurosurg Psychiatry* 84: 544–551.

Roselli, F., Pisciotta, N., Pennelli, M., Aniello, M., Gigante, A., De Caro, M. *et al.* (2010) Midbrain SERT in degenerative parkinsonisms: a 123I-FP-CIT SPECT study. *Mov Disord* 25: 1853–1859.

Sahin, H., Terzi, M., Ucak, S., Yapici, O., Basoglu, T. and Onar, M. (2006) Frontal functions in young patients with essential tremor: a case comparison study. *J Neuropsychiatry Clin Neurosci* 18: 64–72.

Salemi, G., Savettieri, G., Rocca, W., Meneghini, F., Saporito, V., Morgante, L. *et al.* (1994) Prevalence of essential tremor: a door-to-door survey in Terrasini, Sicily. Sicilian Neuro-Epidemiologic Study Group. *Neurology* 44: 61–64.

Schmahmann, J. (1996) From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. *Hum Brain Mapp* 4: 174–198.

Schmahmann, J. and Sherman, J. (1998) The cerebellar cognitive affective syndrome. *Brain* 121: 561–579.

Schmidtke, K. and Hull, M. (2002) Neuropsychological differentiation of small vessel disease, Alzheimer's disease and mixed dementia. *J Neurol Sci* 203–204: 17–22.

Schwartz, M., Badarny, S., Gofman, S. and Hocherman, S. (1999) Visuomotor performance in patients with essential tremor. *Mov Disord* 14: 988–993.

Shill, H., Adler, C., Sabbagh, M., Connor, D., Caviness, J., Hentz, J. *et al.* (2008) Pathologic findings in prospectively ascertained essential tremor subjects. *Neurology* 70: 1452–1455.

Shill, H., De LaVega, F., Samanta, J. and Stacy, M. (2009) Motor learning in essential tremor. *Mov Disord* 24: 926–928.

Shin, D., Han, B., Kim, H. and Lee, P. (2008) Diffusion tensor imaging in patients with essential tremor. *AJNR Am J Neuroradiol* 29: 151–153.

Siddiqui, M., Fernandez, H., Garvan, C., Kirsch-Darrow, L., Bowers, D., Rodriguez, R. *et al.* (2009) Inappropriate crying and laughing in Parkinson disease and movement disorders. *World J Biol Psychiatry* 10: 234–240.

Silveri, M., Leggio, M. and Molinari, M. (1994) The cerebellum contributes to linguistic production: a case of agrammatic speech following a right cerebellar lesion. *Neurology* 44: 2047–2050.

Singer, C., Sanchez-Ramos, J. and Weiner, W. J. (1994) Gait abnormality in essential tremor. *Mov Disord* 9: 193–196.

Stolze, H., Petersen, G., Raethjen, J., Wenzelburger, R. and Deuschl, G. (2001) The gait disorder of advanced essential tremor. *Brain* 124: 2278–2286.

Thawani, S., Schupf, N. and Louis, E. D. (2009) Essential tremor is associated with dementia: prospective population-based study in New York. *Neurology* 73: 621–625.

Tierney, M. C., Black, S. E., Szalai, J. P., Snow, W. G., Fisher, R. H., Nadon, G. *et al.* (2001) Recognition memory and verbal fluency differentiate probable Alzheimer disease from subcortical ischemic vascular dementia. *Arch Neurol* 58: 1654–1659.

Tolosa, E. and Molinuevo, J. (2010) Cognition in essential tremor: should we worry about progressive cognitive decline? *Eur J Neurol* 17: 1227–1228.

Traykov, L., Baudic, S., Thibaudet, M., Rigaud, A., Smagghe, A. and Boller, F. (2002) Neuropsychological deficit in early subcortical vascular dementia: comparison to Alzheimer's disease. *Dement Geriatr Cogn Disord* 14: 26–32.

Trillenberg, P., Fuhrer, J., Sprenger, A., Hagenow, A., Kompf, D., Wenzelburger, R. *et al.* (2006) Eye-hand coordination in essential tremor. *Mov Disord* 21: 373–379.

Troster, A., Fields, J., Pahwa, R., Wilkinson, S., Strait-Troster, K., Lyons, K. *et al.* (1999) Neuropsychological and quality of life outcome after thalamic stimulation for essential tremor. *Neurology* 53: 1774–1780.

Troster, A., Woods, S., Fields, J., Lyons, K., Pahwa, R., Higginson, C. *et al.* (2002) Neuropsychological deficits in essential tremor: an expression of cerebello-thalamo-cortical pathophysiology? *Eur J Neurol* 9: 143–151.

Wallesch, C. and Horn, A. (1990) Long-term effects of cerebellar pathology on cognitive functions. *Brain Cogn* 14: 19–25.

Watson, P. (1978) Nonmotor functions of the cerebellum. *Psychol Bull* 85: 944–967.

Williams, D. and Lees, A. (2009) Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol* 8: 270–279.

Wills, A., Jenkins, I., Thompson, P., Findley, L. and Brooks, D. (1994) Red nuclear and cerebellar but no olivary activation associated with essential tremor: a positron emission tomographic study. *Ann Neurol* 36: 636–642.

Woods, S., Scott, J., Fields, J., Poquette, A. and Troster, A. (2008) Executive dysfunction and neuropsychiatric symptoms predict lower health status in essential tremor. *Cogn Behav Neurol* 21: 28–33.