Published in final edited form as:

Parkinsonism Relat Disord. 2016 December ; 33: 27–35. doi:10.1016/j.parkreldis.2016.10.002.

Knowledge gaps and research recommendations for essential tremor

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Abstract

Essential tremor (ET) is a common cause of significant disability, but its etiologies and pathogenesis are poorly understood. Research has been hampered by the variable definition of ET and by non-standardized research approaches. The National Institute of Neurological Disorders and Stroke (USA) invited experts in ET and related fields to discuss current knowledge, controversies, and gaps in our understanding of ET and to develop recommendations for future research. Discussion focused on phenomenology and phenotypes, therapies and clinical trials, pathophysiology, pathology, and genetics. Across all areas, the need for collaborative and coordinated research on a multinational level was expressed. Standardized data collection using common data elements for genetic, clinical, neurophysiological, and pathological studies was recommended. Large cohorts of patients should be studied prospectively to collect bio-samples, characterize the natural history of the clinical syndrome including patient-oriented outcomes, investigate potential etiologies of various phenotypes, and identify pathophysiological mechanisms. In particular, cellular and system-level mechanisms of tremor oscillations should be elucidated because they may yield effective therapeutic targets and biomarkers. A neuropathology consortium was recommended to standardize postmortem analysis and further characterize neuropathological observations in the cerebellum and elsewhere. Furthermore, genome-wide association studies on large patient cohorts (~10,000 patients) may allow the identification of common genes contributing to risk, and whole exome or genome sequencing may enable the identification of genetic risk and causal mutations in cohorts and well-characterized families.

Keywords

essential tremor; common data elements; genetic association studies; neuropathology

INTRODUCTION

Essential tremor (ET) affects approximately 1% of the general population and 5% of the population over 65 years of age [1]. Despite this high prevalence, there is no satisfactory pharmacologic treatment, the pathological findings are debated, the underlying genes have been elusive, the mechanisms of neural network oscillation are unknown, and the clinical definition of ET has been inconsistent. There are several tangible reasons that may account for the lack of a breakthrough in ET research. ET remains poorly defined and can be diagnosed only on clinical grounds. The main challenges are the lack of stringent diagnostic criteria and the lack of biomarkers. Efforts in ET genetics have been impeded by "phenocopies" that share the phenotype but not the genetic cause, and by genetically heterogeneous changes that present as a syndrome similar to ET. The importance of an accurate diagnosis to study the underlying disease mechanism also applies to the investigation of the pathophysiology and pathology in ET.

In May 2015, the National Institute of Neurological Disorders and Stroke, National Institutes of Health, USA held a workshop to discuss current knowledge gaps in ET and to identify research opportunities regarding ET phenomenology and phenotypes, clinical trials, mechanisms of tremorogenic oscillation, pathology, and genetics. The goal was to develop consensus recommendations for future research, which are presented herein along with a summary discussion for the following topic areas: phenomenology and phenotypes, therapies and clinical trials, physiology, pathology, genetics (table 1).

Phenomenology and phenotypes

The 1998 MDS consensus criteria define “classic ET” as a monosymptomatic disorder with bilateral, largely symmetric postural or kinetic tremor involving the hands and forearms that is visible and persistent, or as isolated head tremor in the absence of dystonic posturing [2]. However, many have challenged this narrow definition and have expanded the phenotype of ET to include subtle cerebellar abnormalities [3], cognitive dysfunction [4], hearing abnormalities [5, 6], and dystonia [7]. Furthermore, it is common for investigators to deviate from the MDS criteria, and patients fulfilling the MDS criteria subsequently may develop signs of Parkinson disease (PD), dystonia and other disorders [8]. As published prevalence estimates of ET vary and genetic risks likely are multiple [9], it is probable that the term ET encompasses multiple disorders [10]. Although the MDS criteria exclude abnormal neurological signs other than tremor, delineating the core phenotypic features of ET is challenging and somewhat arbitrary because there is no diagnostic marker for ET. Furthermore, the common occurrence of subtle or questionable dystonia, parkinsonism, or ataxia creates additional diagnostic uncertainty, regardless of how ET is defined. Moreover, the clinical significance of incident tremor in the upper limbs depends on age of onset; the development of monosymptomatic upper extremity tremor after age 65 is associated with higher risk of incident PD, incident dementia, and mortality [11–14].

While tremor is a common feature of dystonia, the relationship of tremor in one area (e.g., head, voice, upper limb) to dystonia elsewhere is uncertain and frequently debated. It is unclear to what extent task-specific and focal tremors are forms of ET, dystonia, or separate disorders. Dystonic disorders with known genetic causes, such as DYT24, may present with isolated postural and action tremor suggesting that the phenotypic heterogeneity of dystonia may include presentations with isolated tremor[15].

There was general agreement that ET is a common clinical syndrome, not a specific disease, and that this syndrome should be defined and used consistently among clinicians and researchers. Other isolated tremors and isolated tremor syndromes (e.g., isolated head tremor, isolated task-specific writing tremor, and isolated voice tremor) should not be referred to as ET or variants of ET. Over time, some patients may convert to an alternate phenotype, resulting in a change in diagnosis years after the initial syndromic diagnosis of ET. By defining ET as a clinical syndrome, no inference can be made regarding etiologies. To establish a link between clinical presentation and potential etiologies, phenotypic data should be documented to the fullest extent possible, including signs of uncertain significance.

Recommendations

- Regard ET as a specific, common isolated tremor syndrome, not a specific disease. Other monosymptomatic tremors should be referred to as isolated tremor syndromes, not essential tremors.
- Define ET as an isolated tremor syndrome of unknown etiology in which there is bi-brachial action tremor (i.e., postural and/or kinetic tremor) with a duration of at least three years, with or without head tremor or tremor in other regions. A duration of three years is usually sufficient time to rule out alternate diagnoses. There should be no other diagnostic neurologic signs, such as overt dystonia or parkinsonism, or evidence of endogenous (e.g., autoimmune disease) or exogenous (e.g., toxins) disturbances that could cause tremor. Difficulty with tandem walking is permissible, but there should be no abnormality of gait.
- Apply the definition of ET consistently in clinical and research settings.
- Prospectively study large multi-national cohorts of individuals with ET and other isolated tremor syndromes (e.g., isolated head tremor, isolated voice tremor, and other focal and task-specific tremors), using validated assessment tools and standardized terminology (i.e., common data elements) [16] . Such studies will improve our understanding of the phenotype and natural history of ET and its relationship to other isolated tremor syndromes.
- Collect biospecimens using standardized protocols to aid in elucidating underlying etiologies, pathophysiology, therapeutic targets, and biomarkers. Broad subject consent is important to all allow for data and sample sharing.
- Capture neurologic signs and symptoms to the fullest extent possible to ensure unbiased and careful phenotyping. Tremulous people in ET pedigrees and population studies will frequently have neurologic signs and symptoms of uncertain significance.

Therapies and clinical trials

Studying the tremor-modulating properties of pharmacological agents in ET allows inferences on potential tremor mechanisms and may facilitate the development of novel therapeutic agents. Ethanol significantly reduces tremor amplitude in many patients with ET, but data on the sensitivity and specificity of a symptomatic benefit are sparse[16–20]. Ethanol's CNS actions are mediated through many receptor types, including GABA-A, NMDA, glycine, and G-protein-activated inwardly rectifying potassium channels. Other potential mechanisms of ethanol's impact on ET include decreased rhythmic neuronal firing via modulation of T-type calcium channels and blockade of gap junctions [21]. The clinical effect of ethanol has stimulated research into related molecules such as sodium oxybate, 1-octanol and the 1-octanol metabolite octanoic acid as potential therapies in ET [22–24].

Many antiepileptic drugs have been explored in ET, including agents acting on the GABAergic system (e.g., benzodiazepines, barbiturates) and various ion channels that mediate neuronal membrane stability and oscillation. Of the drugs having some efficacy in

ET, primidone and topiramate inhibit sodium channels, and topiramate and gabapentin inhibit calcium channels and glutamatergic transmission.

The beneficial effect of beta-blockers on ET is often quite pronounced but poorly understood. Potential mechanisms include peripheral beta-2 adrenergic antagonism on skeletal muscle and muscle spindles and central blockade of adrenergic and serotoninergic receptors [25, 26].

Reduced tremor amplitude is the principal measure of clinical efficacy in ET and is often viewed as a surrogate for functional improvement. Several clinical rating scales with validated clinimetric properties are available, including the Essential Tremor Rating Assessment Scale (TETRAS) [27] Fahn-Tolosa-Marin scale (FTM) [28], Bain and Findley Tremor Rating and Spirography [29], and the Washington Heights-Inwood Genetic Study of Essential Tremor scale (WHIGET) [30]. These scales, the Quality of Life in Essential Tremor Questionnaire [31], and the Bain and Findley Tremor ADL Scale were recommended by the MDS Task Force on Tremor for use in clinical practice and trials[32].

Interest has grown in the use of portable motion transducers (e.g., accelerometers, gyroscopes, digitizing tablets) to objectively measure tremor amplitude. Unfortunately, the advantages of high linear precision and sensitivity of transducers are mitigated by the large random variability in tremor amplitude. Consequently, the minimum detectable change in tremor amplitude exceeding random variability is comparable for transducers and the clinical rating scales mentioned above [32, 33]. Nevertheless, transducers are capable of capturing tremor severity continuously throughout the day and do not require a clinician to be present at the time of recording. Yet, clinically meaningful changes have not been determined for existing scales or transducers.

There are several surgical treatments for ET, including thalamic deep brain stimulation, or thalamotomy via surgical or magnetic resonance guided focused lesioning. The investigation of the neurophysiological properties of tremorogenic oscillations may lead to the identification of novel targets and treatment strategies.

Recommendations

- Utilize outcome measures (e.g., rating scales, motion transducers, patient reported outcomes) that capture functionally relevant changes in clinical trials in ET.
- Determine clinically meaningful changes for individuals with ET and other isolated tremor syndromes. The relationship between patient reported outcomes, clinical assessment scales, and motion transducers should be evaluated.
- Characterize the influence of tremor subtype and comorbid conditions (e.g., depression, anxiety, cognitive impairment) on treatment response.
- Collect data via standardized approaches in order to allow comparisons between studies. Such efforts may be facilitated by the development of common data elements.

- Develop and validate novel technologies (e.g., long-term tremor monitors) for use in natural history cohorts and clinical trials. The validity, reliability, minimum detectable change, and clinically meaningful change should be determined for these devices and compared with those for rating scales.
- Develop novel, cost-effective, efficient trial designs to rapidly evaluate new therapies for efficacy or futility.

Physiology

It has long been known that ET arises from an abnormal CNS oscillator since ET frequency is not affected by limb inertia or reflex loop time [34]. There is growing evidence that the corticobulbocerebellothalamocortical circuit is the main source of central tremorogenic oscillation [35–38]. However, oscillations involving this circuit occur in many forms of tremor, and the principal abnormalities specific to ET are still unknown [39–41].

Thalamic neurons in the cerebellar relay nucleus ventralis intermedius (VIM) exhibit rhythmic bursts of activity that are correlated with tremor in electromyography (EMG) [37]. A lesion or deep brain stimulation (DBS) targeting VIM reduces the tremor amplitude, as does injection of the GABA-A agonist muscimol [42]. Results from studies using magnetoencephalography, electroencephalography, positron emission tomography and functional magnetic resonance imaging suggest that the motor cortex also plays an important role in ET [43–45].

Positron emission tomography has revealed increased GABA-A receptor binding of 11C-flumazenil in the ventrolateral thalamus, the dentate nucleus of the cerebellum, and the premotor cortex in ET [46]. Alpha-1 GABA-A receptor subunit knock-out mice exhibit tremor with many characteristics of ET [47, 48]. The tremorogenic olivocerebellar oscillation produced by harmaline in laboratory animals has long been viewed as animal model of ET [49, 50], but conclusive evidence of olivary dysfunction in patients with ET is lacking.

Recommendations

- Determine the mechanisms of oscillation in the corticobulbocerebellothalamocortical circuit and the roles played by each node of this oscillating circuit. In particular, the cellular mechanisms of oscillations in this circuit, their relative contribution to postural and kinetic components of tremor, and the effect of lesions and DBS should be thoroughly characterized.
- Use imaging and neurophysiological techniques to identify CNS patterns of activation and interactions that are specific to ET.
- Develop suitable animal models for further study of tremorogenic oscillation.

Pathology

The goals of defining the neuropathologic changes associated with ET are (1) to complement and support physiology studies, (2) to understand the cellular processes associated with cellular injury and progression in order to develop treatments, (3) to identify

pathologic endophenotypes that may allow for recognition of distinct genetic or clinical variants, and (4) to define relationships with other forms of neurodegeneration.

The relationship between neuropathologic findings and clinical symptomatology can be complex and has yet to be elucidated in ET. Such complexity is observed in other disorders such as Alzheimer disease (AD), where there is progressive accumulation of plaques and tangles with synapse and neuron loss along with inflammatory responses, yet the threshold of lesions that results in a given individual developing dementia varies and the lesion distribution and potential downstream effects can greatly shape clinical presentation. While many neurologic disorders have neuropathologically identifiable substrates, assuming that the appropriate brain region is examined with the relevant method, there remain others, such as many cases of epilepsy, where the tools of neuropathology are too crude and too static to detect the functional alterations which lead to dysfunction.

Neuropathologic information about many neurologic diseases comes only from autopsy cases and is therefore cross-sectional data with effectively arbitrary endpoints. The ability to study the neuropathology of diseases only at the endpoint complicates interpretation of initiating events, progression, and heterogeneity. When insights into progression have been gained directly from such studies, large numbers of cases representing a wide range of clinical states have been required(as done by Braak for both neurofibrillary tangles and Lewy bodies [51]). Additionally, because ET does not spread throughout the body, it is not possible to define anatomic regions as “at risk” or as “pre-symptomatic” at the time of autopsy, as can be done with other disorders such as ALS where all motor neurons will eventually be involved if lifespan allows.

When considering the neuropathologic underpinnings of ET, it will be necessary to (1) examine the appropriate brain regions with consideration of somatotopic mapping in order to understand symptoms, (2) apply a wide range of histologic methods with functional markers to detect relevant changes, (3) recognize the potential impact of intercurrent or contributing disease processes such as Lewy bodies and cerebrovascular disease, and (4) sample a wide range of subjects with varying degrees of deficits to gain insight into disease progression at the structural level.

Currently, autopsy studies of ET are limited to relatively small numbers of elderly patients with advanced disease. With only a few groups examining the brains from subjects with ET, there have been conflicting reports of findings that are complicated by varied approaches to examination (including differences in sampling protocols, staining and assessment methods, and subject/control definitions).

The neuropathologic studies in ET have focused primarily on cerebellum and brainstem (including the inferior olives and locus coeruleus) with disagreement over whether there is neurodegeneration in ET [52, 53]. One group has focused on quantitative studies using a standardized section of parasagittal neocerebellum (anterior and posterior quadrangulate lobules in the anterior lobe of the cerebellar cortex: lobules IV–VI), which is involved in motor control [54, 55]. This group has observed structural changes in Purkinje cells and neighboring neurons as well as a reduction in Purkinje cell linear density with “empty

baskets" and Purkinje cell heterotopias. In contrast, two other groups have not detected a reduction in Purkinje cells in ET [56–59]. In addition to the changes in Purkinje cell number, one group has defined a number of changes in the dendritic, axonal and synaptic architecture of the cerebellum [53, 54, 60–67], which have not been examined by other investigators. The differing results regarding Purkinje cell loss in ET may stem from differences in study design, including definitions of cases/controls, sampling of the cerebellum, sample size, and/or the methods of quantification and more detailed study [56, 67, 68]. Similar issues may explainthe conflicting observations regarding Lewy bodies in ET, with some groups reporting higher frequency [52] and other reporting no difference from controls [57].

A critical deficit in the reported autopsy studies is a mapping of lesion burden onto neuroanatomic somatotopy. Does pathology lie in the brain regions that are associated with the body segment affected by ET while being absent or less frequent in comparable anatomic sites for which a body segment is not affected? The observation that comes 14 closest to addressing this critical issue of whether morphologic changes align with disease phenotype comes from the study of a small number of cases with asymmetric tremor in which there was reasonable correlation between the side of tremor and the greater burden of structural changes [69]

Recommendations

- Develop standardized methods for gross and microscopic examination.
- Utilize standardized, unbiased selection criteria and clinical documentation for the collection, sharing, and analysis of postmortem tissues from patients and controls.
- Prospectively collect phenotypic and pathology data to allow for clinicopathologic correlations.

Genetics

It is highly unlikely that there is a single causal genetic abnormality in ET[9]. Work on gene discovery in ET probably has been hampered by a high phenocopy rate, non-Mendelian inheritance, locus heterogeneity in monogenic ET, and a lack of diagnostic biomarkers. Estimates of the proportion of ET patients with a positive family history vary between 20% and 90% [70–72]. Twin studies in the United States and in Denmark/Germany found pairwise concordance rates between 0.60 and 0.93 for monozygotic twins versus 0.27 and 0.29 for dizygotic twins, indicating a high heritability between 45% and 90% [73, 74]. Nevertheless, ET genetics still awaits a breakthrough discovery that improves the understanding of this disorder.

Early linkage analyses of ET families using polymorphic DNA markers revealed linkage to three chromosomal regions: chromosome 13q13 (*ETM1*) [75], chromosome 2p24 (*ETM2)* [76], and chromosome 6p23 (*ETM3*) [77]. However, the causative genes and mutations have not been found. More recently, whole exome sequencing has been used in multiple ET families to identify rare or novel variants, and several potential candidate genes have been reported: *FUS* (fused in sarcoma; OMIM *137070), *HTRA2* (serine peptidase; OMIM

*606441), *TENM4* (teneurin transmembrane protein 4, OMIM *610084), *SORT1* (sortilin, 15 OMIM *602458), and *SCN4A* (voltage-gated sodium channel, type 4, alpha subunit, OMIM *603967)[78–81]. These findings have not been confirmed in other cohorts [82–85].

Genome-wide genotyping of single nucleotide polymorphisms (SNPs) has been used to test for the association of common DNA variants with ET susceptibility. The Icelandic DeCode consortium performed the first ET genome-wide association study (GWAS), finding an association between ET and SNPs in the region of *LINGO1*. The most significant SNP, rs9652490, met genome-wide significance in the combined analysis of both stages of the study [86]. Although replication studies have not consistently found an association with *LINGO1*, most studies of *LINGO1* and protein functions and interactions have continued to support this gene as promising candidate [87–89]. A German GWAS showed association between SNPs in the *SLC1A2* gene region and ET, but the best SNP did not attain genome-wide significance in the replication stage [90]. Recently, a large GWAS of ET cases from Europe and North America detected association with SNPs in 3 chromosomal regions near *STK32B*, *PPARGC1A* and *CTNNA3* [91]. Further replication in independent data sets is essential.

Recommendations

- Develop and use common data elements for phenotyping ET.
- Collect a large sample of approximately 10,000 ET cases to allow for well-powered genotype-phenotype association studies. The ideal would be prospective collection, yet existing samples could be considered if appropriate phenotyping is ensured. The involvement of lay ET associations and advocacy groups would greatly contribute to the accomplishment of this goal. Outreach should be global.
- Store DNA and other bio-samples in a centrally located bank or in multiple locally-maintained biobanks, consented for broad sharing among researchers.
- Phenotype, collect, bank, and genotype pedigree-based (family) and sporadic ET cases through multi-national collaborations.
- Elucidate the full allelic spectrum and the estimated heritability by analyzing large ET samples (using e.g., GWAS, and new sequencing techniques such as exome or genome sequencing)

DISCUSSION

Several important themes emerged from the discussions and recommendations of this workshop. First, ET should be recognized as a common clinical syndrome, not a specific disease. ET should be defined and the term used consistently. The definition of ET should not impede or deter researchers from defining and studying other isolated tremor syndromes, but these syndromes should be clearly distinguished from ET. This novel syndromic definition recognizes that ET is a common phenotypic presentation of multiple different etiologies.

A second recurring theme was the need for common data elements to standardize the characterization and study of ET and other isolated tremor syndromes. Common data elements can be expected to facilitate international collaborations and data sharing. Furthermore, outcome measures utilized in clinical trials should capture functionally relevant changes across the phenotypic spectrum of ET.

Third, ET is a very common clinical syndrome, but it appears to be genetically heterogeneous. Therefore, large numbers of patients are needed for genetic research. Studies characterizing the phenotype-genotype relations in ET will require standardized data collection, multinational collaboration, and strong support from lay ET associations and advocacy groups.

Finally, the success of functional neurosurgery illustrates that a single treatment can be very effective for tremors of diverse etiology and pathophysiology. The etiologic heterogeneity and syndromic definition of ET are not incompatible with the design of valid clinical trials and the discovery of effective pharmacotherapy. Further elucidation of tremorogenesis in the corticobulbocerebellothalamocortical loop should provide important new directions toward more effective treatment.

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Full financial disclosures:

Franziska Hopfner: none

Dietrich Haubenberger: none

Kailash P Bhatia received funding for travel from GlaxoSmithKline, Orion Corporation, Ipsen, and Merz Pharmaceuticals, LLC; serves on the editorial boards of Movement Disorders and Therapeutic Advances in Neurological Disorders; receives royalties from the publication of Oxford Specialist Handbook of Parkinson’s Disease and Other Movement Disorders (Oxford University Press, 2008); received speaker honoraria from GlaxoSmithKline, Ipsen, Merz Pharmaceuticals, LLC, and Sun Pharmaceutical Industries Ltd.; personal compensation for scientific advisory board for GSK and Boehringer Ingelheim; received research support from Ipsen and from the Halley Stewart Trust through Dystonia Society UK , and the Wellcome Trust MRC strategic neurodegenerative disease initiative award (Ref. number WT089698), a grant from the Dystonia Coalition and a grant from Parkinson’s UK (Ref. number G-1009).; co-applicant PD UK grant K-1303, "Single-centre open label exploratory phase two pilot study of exogenous oral Melatonin for the treatment of Nocturia in Parkinson’s disease"

Wendy Galpern none

Katrina Gwinn none

Ashlee Van't Veer none

Samantha White none

Charles Adler has received consulting fees from Allergan, AbbVie, Acadia, Ipsen, Lilly, Lundbeck, Merz, and Teva, and received research funding from Avid Radiopharmaceuticals, the Michael J Fox Foundation for Parkinson's Research, and the NIH/NINDS.

Dr. Eidelberg serves on the scientific advisory board and has received honoraria from the Michael J. Fox Foundation for Parkinson's Research; is listed as coinventor of patents re: Markers for use in screening patients for nervous system dysfunction and a method and apparatus for using same, without financial gain; and has received research support from the NIH (NINDS, NIDCD, NIAID) and the Dana Foundation.

William Ondo has received speaker fees from Lundbeck, TEVA, Merz, Xenoport, Avanir, Otsuka; advisory fees from Lundbeck, ACADIA, Xenoport, InSightec, TEVA and Sage; and grant support from Lundbeck, Tremor Research Group, CIVITAS, and the Dystonia Coalition.

Glenn Stebbins has received honoraria from Acadia Pharmaceuticals, Adamas Pharmaceuticals, Ceregene Inc., CHDI Management, Ingenix Pharmaceutical Services (i3 Research), Neurocrine Biosciences, Pfizer, International Parkinson and Movement Disorder Society, American Academy of Neurology, Michael J. Fox Foundation for Parkinson's Research. He has received research grants from the National Institutes of Health, Michael J. Fox Foundation for Parkinson's Research, the Dystonia Coalition, CHDI, International Parkinson and Movement Disorder Society, and CBD Solutions.

Caroline Tanner has received advisory fees from Neurocrine Biosciences, Ultragenyx Pharmaceuticals, Voyager Therapeutics, and Intec Pharma.

Rick Helmich has received grant support from the Dutch Brain Foundation.

FA Lenz: none

Roy Sillitoe received grant support from Baylor College of Medicine, IDDRC Grant U54HD083092, NINDS R01 NS089664.

David Vaillancourt has received grant support from NIH (R01 NS058487, R01 NS075012), Bachmann-Strauss Foundation, Tyler's Hope Foundation, and consults for projects at UT Southwestern Medical Center, University of Illinois at Chicago, Scott & White, and Great Lakes NeuroTechnologies. He is co-founder and manager of Neuroimaging Solutions, LLC.

Jerrold Vitek has received consulting fees and honoraria from Medtronic, Boston Scientific, Great Lakes Neuro Technologies and St. Jude Medical, and he has stock ownership in Surgical Information Systems. He receives research support from the National Institutes of

Health NINDS R01 NS058945 (principal investigator), NINDS R01 NS037019 (principal investigator) and NINDS R01 NS077657 (principal investigator).

Elan Louis has received research support from the National Institutes of Health: NINDS R01 NS042859 (principal investigator), NINDS R01 NS39422 (principal investigator), NINDS R01 NS086736 (principal investigator), NINDS R01 NS073872 (principal investigator), NINDS R01 NS085136 (principal investigator) and NINDS R01 NS088257 (principal investigator).

Holly Shill received research support from NIH, US World Meds, Sun Health Foundation, Michael J Fox Foundation for Parkinson Research, Adamas, Kyowa, Cynapsus, International Essential Tremor Foundation, and Avid Radiopharmaceuticals

Matthew Frosch: National Institute on Aging/National Institutes of Health: Grant funding (P50 AG005134)

Tatiana Foroud has received grant support from the National Institutes of Health: U24AG021886 and U24NS095871.

Gregor Kuhlenbäumer received project grants from the Deutsche Forschungsgemeinschaft (DFG), the University of Kiel, the University of Münster, the Heinrich-Hertz Foundation and the Rolfs-Dierich Foundation.

Andrew Singleton receives funding from the Intramural Research Program of the National Institute on Aging, National Institutes of Health, Department of Health and Human Services. Project ZO1 AG000957 (ABS).

Claudia Testa is employed by Virginia Commonwealth University (VCU). She has received honoraria from MedLink Neurology, the Society for Neuroscience, and Lundbeck Pharmaceuticals. She is the Co-principal investigator (PI) on two clinical trials with the Huntington Study Group and Auspex Pharmaceuticals. Dr. Testa is the VCU site PI for the Enroll-HD study sponsored by the non-profit CHDI Foundation, the PRIDE-HD and Open PRIDE-HD studies sponsored by Teva Pharmaceuticals, and the Dystonia Coalition study, funded under NIH/NORD grant 5 U54 NS065701.

Mark Hallett serves as Chair of the Medical Advisory Board for and may receive honoraria and funding for travel from the Neurotoxin Institute. He may accrue revenue on US Patent: Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US Patent: Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. Dr. Hallett's research at the NIH is largely supported by the NIH Intramural Program. Supplemental research funds have been granted by BCN Peptides, S.A. for treatment studies of blepharospasm, Medtronic, Inc., for studies of deep brain stimulation, UniQure for a clinical trial of AAV2-GDNF for Parkinson Disease, Merz for treatment studies of focal hand dystonia, and Allergan for studies of methods to inject botulinum toxins. Dr. Hallett is involved in the development of Neuroglyphics for tremor assessment, and has a collaboration with Portland State University to develop sensors to measure tremor.

Rodger Elble receives research grant support from the Spastic Paralysis Research Foundation of Kiwanis International, Illinois-Eastern Iowa District, and he received consulting fees from Sage Therapeutics. He was also paid by InSightec to rate videotaped exams of patients undergoing thalamotomy with high-intensity focussed ultrasound.

Günther Deuschl has received lecture fees from Medtronic and Desitin and has been serving as a consultant for Medtronic, Sapiens and Boston Scientific. He received royalties from Thieme publishers. He is a government employee and he receives through his institution funding for his research from the German Research Council, the German Ministry of Education and Health and Medtronic.

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Rodger Elble: Research project: A, B, C; Manuscript Preparation: B

Günther Deuschl: Research project: A, B, C; Manuscript Preparation: B

Financial Disclosures /Conflict of Interest concerning the research related to the manuscript

Funding sources: National Institute of Neurological Disorders and Stroke

Franziska Hopfner	none
Dietrich Haubenberger	none
Kailash Bhatia	none
Charles H. Adler	none
David Eidelberg	none
Mark Hallett	none
William Ondo	none
Glen Stebbins	none
Caroline Tanner	none
Rick Helmich	none
Fred A. Lenz	none
Roy Sillitoe	none
David Vaillancourt	none
Jerrold L. Vitek	none
Elan D. Louis	none
Holly A. Shill	none
Matthew Frosch	none
Tatiana Foroud	none
Gregor Kuhlenbäumer	none
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Highlights

- More collaborative and coordinated research across all disciplines is needed for future research in ET.
- Standardized data collection using common data elements are required.
- Very large cohorts of patients should be studied prospectively on a multinational level.
- Characterization of the natural history of the ET syndromes is needed.
- A neuropathology consortium should be formed and bio-samples should be collected.

Table 1

Recommendations for future research in essential tremor.

Phenomenology and phenotypes	Therapies and clinical trials	Physiology	Pathology	Genetics
Consider ET as a specific, common isolated tremor syndrome, not a specific disease	Utilize outcome measures that capture functionally relevant changes in clinical trials in ET	Determine the mechanisms of oscillations in the corticobulbocerebello-thalamocortical circuit, their relative contribution to postural and kinetic components of tremor, and the effect of lesions and deep brain stimulation	Develop standardized methods for gross and microscopic examination	Develop and use of common data elements for phenotyping ET
Define ET as an isolated tremor syndrome consisting of: • Bi-brachial action tremor (i.e., postural or kinetic tremor) • Duration of 3 years or more • With or without head tremor or tremor in other locations • No other diagnostic neurologic signs (e.g, overt dystonia or parkinsonism) • No identifiable endogenous or exogenous disturbances that could cause tremor • Difficulty with tandem walking is permissible, but no abnormality of gait.	Determine clinically meaningful changes for outcome measures, including the development and implementation of patient-oriented outcomes.	Identify ET-specific CNS activation and interaction-patterns using imaging and neurophysiological techniques	Use standardized, unbiased selection criteria and clinical documentation for the collection, sharing, and analysis of postmortem tissues from patients and controls.	Collect a large cohort (> 10,000) of ET cases to allow for well-powered genotype-phenotype association studies
Consistently applyET definition in clinical and research setting	Characterize the influence of tremor subtype and comorbid conditions on treatment response	Develop suitable animal models	Include clinicopathological correlation based on prospectively collected phenotype and pathology data	Store DNA and other bio-samples in a centrally located bank or in multiple locally-maintained biobanks, consented for broad sharing among researchers
Prospectively collect large multi-national cohorts of individuals with ET and other isolated tremors using validated assessment tools, standardized terminology, and protocols for collection of bio-samples	Standardize data collection to allow comparisons between studies			Phenotype, collect, bank, and genotypepedigree-based and sporadic ET cases through multi-national collaborations
Capture neurologic signs and symptoms of unknown significance to fullest extent possible to ensure unbiased phenotyping	Develop and validate novel technologies, including determination of reliability, minimum detectable change, clinically meaningful change, and comparison with those for rating scales			Analyze large ET samples (using e.g., GWAS, and new sequencing techniques such as exome or genome sequencing) to elucidate full allelic spectrum and estimated heritability
	Develop and apply efficient trial designs for early determination			

Parkinsonism Relat Disord. Author manuscript; available in PMC 2017 December 01.

Phenomenology and phenotypes	Therapies and clinical trials	Physiology	Pathology	Genetics
	of efficacy or futility of novel therapies			