Project title: A Feasibility study for an Essential Tremor Brain Bank at the Arizona Study of Aging and Neurodegenerative Disorders
Sponsoring institution: Banner Sun Health Research Institute
Principal Investigator: Shill Holly A.
Degrees: MD
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The purpose of this request is to ask for additional funding to continue into year 3 for our feasibility study. This year, we will continue to follow subjects as per our prior aims as well as add one additional analysis. Our plan is re-screen our much larger sample of autopsied ET individuals to ensure we have not overlooked a potential site of pathology and compare this group to controls.

Specific aim for 2014-2015 year of funding

**Compare neuropathological findings in ET and controls using expanded autopsy cohort**

Using our growing population of autopsied individuals with ET (currently at 79 individuals) in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), we wish to again examine all brain areas using our standardized semi-quantitative assessments with the goal to explore whether there are any brain regions that may have been overlooked in smaller surveys in the past.

For reference, our previous aims from 2012-14:

1) **Clinically categorize action tremor in the elderly and serially assess the tremor and non-motor signs.** Using our population of subjects in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) who are all registered in the Banner Sun Health Research Institute (BSHRI) Brain and Body Donation program (BBDP), we plan to continue to provide annual movement disorder and cognitive assessments. We will identify subjects with action tremor, follow the tremor on an annual basis, and determine whether subjects with tremor have a higher incidence of other motor findings as well as many non-motor signs such as hyposmia, sleep or autonomic disorders, and cognitive impairment. We hypothesize that subjects that meet criteria for essential tremor (ET), in the absence of pre-existing parkinsonism and dementia, will have similar findings as neurological controls in these tests.

2) **Compare clinical features of those with ET onset before age 65 to those with elderly onset.** As there is a predominance of tremor subjects with relatively recent onset tremor (beginning after age 65) in our cohort, this aim is to add 20 age matched subjects (>75 yrs of age) with “classical ET” (age of onset of ET <65 yrs of age) to our brain bank over the next year. The goal will be to compare clinical features (including neuropsychological assessment) between these two subgroups of ET. These subject would be identified though mailings from the IETF and through our local outreach efforts to the community.

3) **Follow a tremor cohort longitudinally for diagnostic changes.** The existing cohort of elderly onset tremor combined with “classical ET” subjects will be followed over the funding period to assess for changes in their neurological condition and diagnostic changes with specific attention to the development of parkinsonism and cognitive decline.

4) **Continue to accrue and evaluate pathological cases of essential tremor.** For ET subjects that come to autopsy during the funding period, combined with those already autopsied, analysis of neuropathological findings will be performed. These will be compared with normal age matched control subjects as well as subjects with Parkinson’s disease and
other neurodegenerative disorders.

5) Do a cross sectional analysis of cognitive functioning in ET, separating the group into those with elderly onset vs. onset before age 65. Using our population of subjects in the Arizona Study of Aging and Neurodegenerative Disorders who are all registered in the Banner Sun Health Research Institute (BSHRI) Brain and Body Donation program (BBDP), we plan to continue to provide annual movement disorder and cognitive assessments. We will identify subjects with action tremor consistent with ET and will study them across a battery of neuropsychological testing, comparing them to a similarly aged control population in the same tissue donation program. We hypothesize that ET will be similar to controls and that elderly onset will be no different from those with onset before age 65.

6) Quantify cerebellar Purkinje cells in autopsied ET subjects and compare to an age similar control population. Using our subjects in the Arizona Study of Aging and Neurodegenerative Disorders who are all registered in the Banner Sun Health Research Institute (BSHRI) Brain and Body Donation program (BBDP) and have come to autopsy, we plan to use linear cell density to quantify cerebellar Purkinje cells.

This initial investment of IETF funds will then result in significant future advances in our understanding of ET, especially the neuropathological basis of ET, and that will allow our group to leverage the IETF funds to obtain larger funds from the NIH or other funding agencies.

**Background/Rationale:**
Tremor in the elderly is relatively common, with published studies supporting prevalence frequencies of essential tremor (ET, the most common cause) ranging from 0.41% in a population over age 40 to 12.6% for those aged 70-79. (1-3) Our unpublished data from the Arizona Study of Aging and Neurodegenerative Disorders cohort reveals a frequency of unspecified tremor of 35% with the average age of the living cohort being 79 years.

The importance of studying tremor in the elderly is multifactorial. First, ET contributes significantly to morbidity with studies suggesting nearly 100% of diagnosed ET subjects having significant disability due to the physical and psychosocial impact of tremor.(4, 5) Second, ET patients may have concomitant neurological problems which might contribute to disability and increased mortality. In particular, ET can be associated with cerebellar gait dysfunction(6, 7) and one recent study speculates that the increased risk of falls might contribute to the increased mortality rate these authors found.(8) Third, ET may be a risk factor for the development of Parkinson’s disease(9-11) which most certainly leads to increased disability and perhaps mortality. Finally, longstanding ET may be associated with mild cognitive dysfunction(12, 13) and onset in the elderly may be a risk factor for the development of dementia.(14, 15)

It has long been debated whether ET is associated with Parkinson’s disease (PD). Most clinical studies focus on subjects being seen in tertiary, subspecialty movement disorder clinics where there may be a bias toward those with more clinically problematic tremor and other movement abnormalities who may indeed already have PD at presentation.(16, 17) Co-existence of PD and ET-like postural and kinetic tremor is certainly recognized and it is not uncommon for tremor-dominant Parkinson’s disease to begin with an ET presentation.(18-20) Adding additional testing such as olfactory testing and dopamine imaging studies might help differentiate ET from
PD where the clinician, despite careful examination, is still unclear. As per our 2012-13 Aim #1, our group has shown that REM sleep disorder and autonomic function are normal in essential tremor. In additional, we have shown that those with incidental Lewy body disorder at autopsy do not have a higher rate of action tremor. Together, all this data suggests that the risk of Parkinson’s disease in ET is low.

The association between ET and dementia has also been debated. The original term for this condition was “Benign Essential Tremor” underscoring the lack of significant impact on morbidity and mortality. A detailed review of the condition in 2000 did not even mention cognitive decline or impact on longevity (see Neurology, 2000, Supplement 4). Neuropsychological profiling of those subjects undergoing surgical treatment of tremor has supported some mild cognitive abnormalities in longstanding ET. More recently, a population based study in Spain suggested that elderly patients with ET have poorer cognitive funding than age matched controls. Follow-up to this study suggests that those subjects with later onset tremor have higher baseline dementia and, at 3 year mean follow-up, develop dementia at a higher rate. Based on 2012-13 year funding, we presented the following abstract entitled “Risk of Developing Dementia in Essential Tremor” at the American Academy of Neurology. We have since gone on to expand this analysis to examine older onset tremor and found that older onset tremor may have a higher risk of dementia. This study has been submitted as a full length manuscript.

While pathological confirmation of PD is the “gold standard” for diagnosis there are only a few pathological studies of ET and they have generated controversy. Most studies have emphasized the lack of consistent brain pathology in ET. One study was of 20 ET patients followed in a movement disorder clinic in Saskatchewan, Canada. Brain histopathology techniques were not detailed, however, the cerebellum and the substantia nigra were included in analysis. No consistent abnormalities were found, unless the patient had additional features of Parkinson’s disease. A second study of 11 patients was part of the Honolulu-Asia Aging Study. Again, researchers found no consistent pathology. A study of 10 patients with ET proposed that non-specific cerebellar degeneration and brainstem Lewy bodies were seen more frequently compared with controls. This was confirmed by these authors in a larger series. In this study, 8/33 (24%) ET cases had Lewy bodies, primarily restricted to the brainstem, compared with 2/21 controls and the remainder had “cerebellar ET” with finding of Purkinje cell loss. Our group reported our initial series emphasizing the lack of standard degenerative pathologies at autopsy. This has been examined very recently again and we have found no evidence for increased risk of incidental Lewy bodies or PSP in the ET population (data in press).

Two groups have reported on quantification of cerebellar Purkinje cells using linear cell density. There were conflicting findings, with one group identifying a reduced number of cells in ET and the other group finding no differences. We have recently completed a study of Purkinje cell linear density on cases and controls and found no differences. This data is now in press for publication.

Recently, genome wide association studies (GWAS) for single nucleotide polymorphisms (SNPs) identified significant associations with SNPs present in the LINGO-1 genes in certain populations and in the LINGO-2 gene in other populations. These results have not been
consistently replicated, but a recently published meta-analysis confirmed that across 11 separate studies LINGO-1 polymorphism rs9652490 was associated with increased risk of familial ET, while LINGO-1 polymorphism rs11856808 was associated with increased risk of sporadic and familial ET across 7 separate studies. Based on this information, we undertook quantitative study of LINGO-1, LINGO-2 and calbindin in frozen samples of ET versus controls and found that LINGO-1 was unchanged, LINGO-2 was increased and calbindin was decreased. This paper is being prepared for submission however, it is worth mentioning that Columbia University group completed a similar study in a smaller population on ET using only LINGO-1 and found differing results.

While we realize that the IETF already supports the centralized brain bank at Columbia University, we believe that any study results published from one institution should have outside validation. Our site has a proven record of longitudinal clinical characterization of ET with eventual autopsy and both neuropathological and neurochemical analysis. Funding our study would provide the independent validation for the Columbia studies. The advantages of our program are the very short post-mortem intervals (<3 hours) which is critical for neurochemistry studies, as well as the extensive age-matched control population with similar assessments that are needed for clinical and neuropathological comparisons. Finally, the infrastructure for performing the annual clinical assessments and the eventual autopsy are already in place such that the amount of funding necessary to complete this protocol has been minimized.

As can be seen from much of our work to date, there has been significant advancement in the understanding of ET and its pathology. We have shown that ET is not associated with an increased risk of Parkinson’s disease. We have shown that ET is not associated with an increased risk dementia but that a subset of older onset, shorter duration tremor may be. We have also shown that ET is not associated with Purkinje cell loss. Lastly, we have shown that ET may be associated with LINGO-2 activity but not LINGO-1 in the cerebellum and that calbindin levels are decreased where the LINGO-1 findings differs from another group. Taken all together, it appears that we still don’t have a definite source of ET pathology. This could be because there is not specific pathology with ET or it could be that pathology has been overlooked in the past because of low numbers of ET subjects in historical surveys. Therefore, we propose to repeat a survey or our now much larger sample of ET brains to ascertain whether there is specific pathology for ET.

**Preliminary work:**
The studies that are the focus of this proposal will dovetail into the existing framework of the BBDP. The BBDP is collaboration between BSHRI and Mayo Clinic Arizona. All infrastructure is already in place and funding is specifically requested to expand the number of ET cases followed, analyze their clinical features and eventually autopsy findings.

The Clinical Core of the BBDP began as collaboration between Mayo Clinic Arizona (Drs. Charles Adler and John Caviness) and Sun Health Research Institute (Drs. Thomas Beach and Jeff Joyce and then Drs. Marwan Sabbagh and Holly Shill) in 1997. Their work reflected the need to prospectively characterize individuals donating their brains for research purposes to determine if signs of PD, cognitive impairment and other degenerative diseases were present. This made the tissue more valuable for investigators at BSHRI, and world-wide for clinical
correlation. The Clinical Core, in an unprecedented way, has also fostered collaboration amongst multiple investigators and institutions in Arizona.

Since inception >1,300 subjects have had one or more movement examinations and >1,100 subjects have had at least one cognitive evaluation. Over 627 subjects have had at least one electrophysiological test and >700 olfactory tests have been performed. The mean age of the cohort is 79 yrs and ~60% of the subjects are female. We currently have 279 individuals with ET, 148 with non-specific tremor and 477 controls without PD or AD. As of the beginning of our funding, we have enrolled 24 new ET subjects. We currently have 79 deceased individuals with ET with tissue available for pathological assessment.

Prior to funding of this feasibility grant, we had reported results on 24 subjects with ET who have come to autopsy and compared them with 21 controls.(32) Brains were examined post-mortem according to standardized protocols for assessment of age-related changes and specific pathological conditions (e.g. Parkinson’s disease, Alzheimer’s disease). Subjects had a mean age of 86.2 years and a mean duration of tremor of 11.1 years. Three had Lewy bodies, one subject had brainstem predominant disease and two had limbic stage. Three subjects had a non-specific cerebral tauopathy and another met pathological criteria for progressive supranuclear palsy. When compared with controls, we did not find an increased incidence of Lewy bodies, other parkinsonism or Alzheimer’s changes in subjects with ET.

In the same population of ET subjects, we examined biochemical changes suggestive of pre-clinical PD.(37, 38) Twenty-three ET cases were compared with 37 controls. Ages at death were 86.2 and 85.6 years respectively. Mean ± SD TH value was 91.7 ± 113.2 (ET) versus 96.4± 102.7 (controls) ng/mg. Removing 3 cases of incidental Lewy bodies from each group resulted in TH values of 99.4±119.3ng/mg (ET) and 104.4±103.7 ng/mg (controls). All differences between groups were not significant by t-test. This study provides neurochemical support that ET does not appear to be pre-clinical PD.

As the number of autopsies increased, and with specific funding for ET research, we examined Purkinje cell linear density. There were 56 ET cases and 62 age matched controls free of dementia and other neurodegenerative disorders included in the study. Mean Purkinje cell linear density was 3.80 ± 0.81 cells per mm for tremor cases and 3.82 ± 0.91 cells per mm for controls (Δ 0.02, 95% CI -0.30 to 0.34). Purkinje cell counts were not associated with tremor duration (r=0.06, 95% CI -0.21 to 0.32). These data demonstrate that essential tremor is not associated with cerebellar Purkinje cell loss. This manuscript has been accepted for publication in Movement Disorders.

Additionally, the LINGO data is in preparation and will be submitted shortly. The abstract is included: Expression of LINGO-1, LINGO-2 and Calbindin in Postmortem Human Cerebellum in Essential Tremor. Essential tremor is one of the most common neurological diseases, though understanding of its cause is still limited. Certain polymorphisms of the genes for “Leucine-rich repeat (LRR) and immunoglobulin (Ig) domain containing, Nogo receptor-interacting protein” (LINGO)-1 and LINGO-2 have been associated with increased risk of ET. LINGO-1 and LINGO-2 have identified roles as negative regulators of neuronal differentiation and remyelination. Gene expression studies with RNA isolated from purified brain derived cells
showed that LINGO-1 mRNA was expressed in neurons, microglia, astrocytes and endothelial cells, while LINGO-2 expression was principally neuronal. Some studies have suggested that this disease has a common pathological basis with Parkinson’s disease; other studies suggest that ET has a separate pathological entity focused on the cerebellum. Abnormal levels of either of these proteins might affect neuronal development and survival, so these known functions along with the genetic studies make them ideal candidates for further investigation in pathological tissue. We used postmortem cerebellum brain tissue selected from 26 elderly control cases (mean age 87.5 yrs) and 42 elderly ET cases (mean age 86.7) and measured the levels of LINGO-1, LINGO-2 proteins and calbindin using western blot methods. Results showed that levels of LINGO-1 protein levels were unaltered between control and ET cases, while there was a significant upregulation of LINGO-2 protein in ET cases. Results for calbindin showed a significant decreased expression providing additional evidence for cerebellar pathology as a feature of ET.

The following abstract was presented at the American Academy of Neurology in 2013: Risk of developing dementia in essential tremor. Objective: To determine if essential tremor is associated with an increased risk of dementia. Background: Previous population studies in the elderly have suggested that patients with tremor might be at higher risk for incident dementia when followed longitudinally. Design/Methods: Subjects without dementia or a neurodegenerative movement disorder at study entry, and who had at least one follow-up visit, were selected from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) database. The incidence of dementia in subjects with ET was compared to that of Controls using Cox regression. Results: There were 90 subjects with ET and 432 subjects without ET. The proportion of women was lower in the ET group (44% versus 70%). Age at study entry ranged from 45 to 100 years. Mean age was not substantially higher in the ET group (79.9 years vs. 77.1 for controls). ApoE genotype was known for 58 subjects in the ET group and 250 subjects in the Control group. The proportion of ApoE ε4 carriers was not substantially different in the ET group (19% vs. 25%). Age at ET onset ranged from 0 to 90 years (mean 67, SD 19), and the duration of ET at study entry ranged from 0 to 72 years (mean 12, SD 18). The incidence of dementia was not higher in the ET group than in the Control group. The incidence of dementia within 5 years of study entry was 11% for both ET and Control groups (95% CI 4% to 17% for ET, and 8% to 14% for Control). The hazard ratio for the association between ET and dementia was 0.97 (95% CI 0.50 to 1.9). Adjustment for age, sex, and e4 status did not increase the hazard ratio for the association between ET and dementia. Conclusion: ET is not associated with increased risk of dementia in this longitudinal aging study.

At the time of this submission, we are evaluating a cross sectional analysis of cognition in ET versus controls, these data are not yet available.

The following other papers have been published in keeping with aims for the 2012-14 years of funding.


Adler CH, Hentz JG, Sabbagh MN, Shill HA, Evidente VGH, Driver-Dunckley E, Vedders L,
Jacobson S, Beach TG, Boeve B, Caviness JN. Increased frequency of probable RBD in Parkinson’s Disease but not in essential tremor or RLS. Park Related Disorders 17:456-8, 2011


Methods:

Annual evaluations are performed at B SHRI, MCA, or the donor’s residence/care facility. This allows us to detect the earliest changes associated with disease, determine disease onset, disease duration, disease progression, and determine final disease status prior to autopsy. Olfactory testing is performed every third year. A subgroup of subjects has every other year electrophysiological testing, including all cases with PD or suspect PD and a control population, of which some of these have tremor.

Annual history evaluation: Obtaining annual medical evaluations (performed by nurses and physicians) is the primary role of the Clinical Core. Given the mean age is 79 yrs subjects are at great risk for developing new medical problems so annual evaluations include by personal interviews, medical record review, and examinations. Establishing a family history of a movement disorder or dementia is critical given the hereditary factors in these disorders.(39-41) Smoking and alcohol information is collected given correlations with neurodegenerative disorders.(42) A sleep questionnaire is utilized given the association between REM sleep behavior disorder and both PD and DLB.(43-45) Autonomic dysfunction is also frequent in neurodegenerative disorders so a questionnaire is utilized.(46)

Annual movement examination

A movement disorder trained neurologist performs annual assessments that include the full UPDRS including cognitive functioning (part I), activities of daily living (part II), motor examination (part III), and assessment of treatment complications and other complications (part IV).(47) As PD is a progressive neurodegenerative disorder longitudinal examinations are critical. Many individuals with signs of PD are often completely unaware of these findings and unless a trained diagnostician specifically looks for these signs, early PD often goes undiagnosed.

The movement examination also assesses other movement disorders. Many subjects with involuntary movements, especially tremor, are unaware of them and they are often missed by physicians not specifically looking for them. Although the significance of action tremor in the elderly is unclear, we categorize these subjects as having a tremor and expect to eventually determine if there is significance to this finding. Tremor scales (0-4 points) for hand, voice, and
head tremor are used. Subjects are diagnosed with ET if they had previously been diagnosed by an outside physician and the examination was consistent with it. Additional subjects were diagnosed with ET if they had the presence of a grade 2 postural and/or kinetic tremor of the hands or forearms without identifiable secondary cause or other exclusion criteria (e.g. prominent unilateral tremor, rigidity or bradykinesia). (48, 49) Subjects with a tremor score between 0.5 and 2 were also considered ET if the research evaluations found the tremor was present for at least 3 years with similar exclusion criteria. Additionally, the presence of isolated head tremor without dystonia was also included as ET. Because we capture both clinical and research definitions of ET, this allows for comparing these groups to each other as well as to controls which should help to further understand tremor in the elderly. All subjects are assessed for restless legs syndrome (RLS) and if present the RLS rating scale is completed.(50-52)

**Neuropsychological tests**

Neuropsychological testing allows for detection and quantification of cognitive changes in PD, as well as the diagnosis of other cognitive disorders (ie. AD, DLB, etc). Distinguishing the overlapping syndromes of PD-D and other dementias antemortem must be established so future scientific use of the tissue compares correctly categorized subjects. Cortical and subcortical function is tested with a core battery that measures memory, attention, language, visuo-spatial ability, frontal/executive function, and screens for depression. We use a cutoff of 1.5 SD from the mean, based on appropriate normative data, to classify an individual as provisionally impaired on a specific test (MCI). However, clinical interpretation of the neuropsychological test results factor in extraneous variables (e.g. motor impairment), psychological variables (anxiety, depression, etc.), and the overall cognitive profile (comparison between tests). This is especially important in a multifactorial disease such as PD. Most tests were chosen to be relatively free of motor impairment (e.g. JLO) or having a component that allows for the motor component to be taken into consideration (e.g. Trails A/B; STROOP). Further, one of the strengths of the longitudinal approach (as opposed to just inclusion/exclusion criteria) is it allows each subject to be their own control, which vastly increases sensitivity to decline in cognitive function, and decreases false positive findings in a progressive disorder. These tests have been grouped into domains for convenience of discussion only as intact performance on most of these tests requires integration of several cognitive systems. Therefore, interpretation of deficits on one or more of the tasks must take into account the pattern of performance on the other tasks. The neuropsychologic battery will include:

**Global measures/staging:** Folstein MMSE(53) is the most commonly used objective clinical measure of cognitive status.

**Memory:** Rey Auditory Verbal Learning Test (AVLT)(54) is a well validated and sensitive measure of verbal learning and memory. This instrument allows assessment of verbal learning, free recall (immediate and delayed), susceptibility to proactive or retroactive interference, tendency to confabulation, and free recall vs recognition performance. It is a sensitive test for detection of early dementia, and may distinguish cortical from subcortical dementias.

**Frontal/Executive:** STROOP(55) reflects the participant's ability to inhibit a habitual response in favor of a novel one. This test is sensitive to frontal/subcortical dysfunction. A second test, Trails A & B(56) has a visuo-motor scanning and tracing task (Trails A) that requires the participant to connect a series of numbers scattered across the page, and a second task (Trails B) of connecting numbers and letters on the page, but alternating number – letter – number – letter, etc. By comparing Trails B to performance on Trails A, a measure of the unique frontal/executive
requirements of the task (beyond the motor and scanning components) can be obtained.

**Language:** Controlled Oral Word Association (COWA)\(^\text{(57)}\) is a measure of word generation under restricted search conditions and is sensitive to many different neurological impairments. Participants are asked to generate in one minute as many words as they can that begin with a designated letter. This is repeated for a total of 3 letters. Category Fluency is a measure of word generation under restricted search conditions. Together these tests measure generative fluency, left-hemisphere integrity and frontal/executive function and can assist in discriminating cortical vs. subcortical profiles.

**Visuospatial:** Clock drawing\(^\text{(58)}\) is a common clinical screening test for visuospatial and constructional impairment. Judgment of Line Orientation\(^\text{(57)}\) provides a measure of visuospatial integration without requiring a significant motor component.

**Attention:** Digits Forward measures simple attention and immediate memory span and Digits Backward assesses attention with greater demands placed on working memory and mental control.\(^\text{(59)}\)

**Depression:** Geriatric Depression Scale\(^\text{(60)}\) measures depression using a 30 item yes/no questionnaire (>11 is considered depression) that can be read by the examiner or self-administered by the participant. Hamilton Depression Scale\(^\text{(61)}\) is administered by the physician and provides evaluation of psychoactive and somatic symptoms.

**Level of Independent Function:** Global Deterioration Scale\(^\text{(62, 63)}\) has seven ordinal stages (stages 1-7) from no cognitive decline to very severe cognitive decline and incorporates both cognitive and functional aspects of aging and dementia. Functional Assessment Staging\(^\text{(63, 64)}\) is a functional assessment scale.

**Olfactory Testing**

Olfactory testing is performed using the University of Pennsylvania Smell Identification Test (UPSIT).\(^\text{(65)}\) This 40 question scratch and sniff booklet forces answers to multiple choice questions. Olfactory dysfunction has been well documented in PD and AD and correlates with disease severity.\(^\text{(65-67)}\) Idiopathic hyposmia may well be a preclinical sign of PD.\(^\text{(33, 68-70)}\) Odor detection and identification was normal in vascular parkinsonism,\(^\text{(71)}\) and RLS \(^\text{(72)}\) while there is conflicting data in essential tremor.\(^\text{(4, 17, 22, 73)}\)

Unique aspects to our approaches are multifactorial. To our knowledge, there is no similar group studying ET in such a comprehensive manner, combing clinical, physiological and pathological assessments. Given our previous successes studying AD and PD, we expect to make meaningful conclusions regarding the relevance of action tremor to these other conditions as well as provide a better understanding of the types of tremor in the elderly. These data will serve as strong and convincing pilot data to better analyze the underlying pathogenesis of ET. Given our strong basic science department, further translational research is expected.

**Pathology**

Subjects who come to autopsy in the Arizona Study of Aging and Neurodegenerative Disorders are examined with standardized protocols to quantify pathologies associated with Alzheimer’s, Parkinson’s disease and other neuropathologic entities, see review for more details.\(^\text{(74)}\) The standardized assessments will be examined between ET and controls to examine potential sites of further exploration.
**Timeline:**

All specific aims will be completed by June 2015.

**Evaluation:**

In addition to the requested progress reports, the collaborative team will meet in person or by teleconference on a quarterly basis to ensure adequate progress of the grant and review findings. The principal investigator will keep minutes of these meetings which may be reviewed for auditing purposes.

**Anticipated Results:**

It is expected that the new screen of the pathology data will yield some new avenues for exploration. If it does not, we will potentially begin expanding previous areas of research such as following up on LINGO findings and further exploration of the gabanergic system.

**Literature Cited**

Budget:

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$29,838 $5,162 $35,000

Budget justification:

Dr. Shill will oversee the project, assist with recruitment, do motor evaluations of subjects and be responsible for presentation and publication of the project. Dr. Dugger and Dr. Shill will do the pathology assessment. Partial support is also requested for two members of the clinical team who work on the brain and body donation program. Currently their work is partially funded through other granting mechanisms but they are contributing substantially to the tremor research currently given the numbers of tremor subjects identified and enrolled in the study. Dr. Jacobson is a neuropsychiatrist who does the cognitive/behavioral assessments and Ms. Davis does the coordination of the staff and visits.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. DO NOT EXCEED FOUR PAGES.

NAME
Shill, Holly A.
eRA COMMONS USER NAME
HShill
POSITION TITLE
Director, Thomas H. Christopher Center for Parkinson’s Research, Sun Health Research Institute
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

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<td>University of Arizona, Tucson, AZ</td>
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A. Personal Statement
I am an academic neurologist specializing in patients with movement disorders. I spend approximately 50% of my time in the clinic managing patients with movement disorders and 50% of my time doing clinical research. This proposal is an extension of work already being done here. We have shown that we have been productive over the last 2 years of funding and we expect that this will not change. We have a tight link to the ET community through our patient population and outreach efforts. This past year, we have done a day long symposium on ET and I have spoken to our local support group on ET research. In addition, as a result of our efforts, we have been approached recently by 2 other research groups interested in using our pathology specimens to further the understanding of ET.

B. Positions and Honors

CURRENT POSITIONS
Director, Thomas H. Christopher Center for Parkinson’s Research, Banner Sun Health Research Institute, Sun City Arizona, October, 2006-present
Staff physician, Cleo Roberts Center for Clinical Research, October 2006-present.
Neurology staff privileges, Banner Boswell Hospital, October 2006-present
Clinical Faculty/Adjunct, School of Biological and Health Systems Engineering (formerly called the Center for Adaptive Neural Systems), Arizona State University, January 2008-present.
Adjunct Associate Professor, Podiatric medicine, Midwestern University, October 2008- present.
Research Associate Professor in the Department of Neurology, University of Arizona College of Medicine- Phoenix. December 2013-present.

PREVIOUS POSITIONS
Clinical Associate (fellowship position), Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, January 2000-May 2002. Mentor: Dr. Mark Hallett
Fellow, Movement Disorders, Barrow Neurological Institute Phoenix, Arizona, July 1999-December 1999
Residency, Neurology, Barrow Neurological Institute, Phoenix, Arizona, July 1996- June 1999
Internship, Internal Medicine, St. Joseph’s Hospital and Medical Center, Phoenix, Arizona, June 1995-June 1996

HONORS AND AWARDS
Baird Scholarship 1987-1989
Eta Kappa Nu, National Electrical and Computer Engineering Honors Society
Honors Academic Scholarship- full tuition 1987-1991
National Merit Scholar 1987
Magna Cum Laude with Honors 1991
Dean’s Scholarship from University of Arizona College of Medicine- full tuition/room/board 1991-1995
Alpha Omega Alpha 1995-present
American Medical Women’s Association, Inc., Janet M. Glasgow Memorial Achievement Citation 1995
Chief resident neurology, July 1998- June 1999
American Academy of Neurology Resident Scholarship, 1999
Fellows Award for Research Excellence (FARE)- 2002
OTHER EXPERIENCE AND PROFESSIONAL MEMBERSHIPS

Parkinson Study Group Member, member since 1999
Certified by American Board of Psychiatry and Neurology- 2001; recertified 2011.
Arizona Neurological Society, Member
American Academy of Neurology, Member since 1996
State of Arizona Medical License 1995-present
Movement Disorder Society since 1999
Alpha Omega Alpha Medical Honors Society since 1995
Active Member, International Neurotoxin Association, 2011-present

C. Peer-Reviewed Publications


D. Research Support

CURRENT RESEARCH
Teva Neuroscience. A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Add-on, Parallel Group Study to Assess the Effect of Rasagiline on Cognitive Abilities in Patients with Parkinson’s Disease. 12/2013-present. Role: Local PI.

Sun Health Foundation, Feasibility study of an early wellness program in Parkinson’s disease and impact on quality of life. 7/2013-present. Role: PI

UCB Biosciences. A multicenter, multinational, double-blind, placebo controlled, 3-arm, phase 4 study to evaluate the efficacy of rotigotine on Parkinson’s disease-associated apathy, motor symptoms and mood (BRIGHT). 6/2013-present. Role: Local PI.

Department of Defense. Validating Diagnostic and Screening Procedures for Pre-Motor Parkinson’s Disease. William Langston PI. Role: Co-investigator. 8/12-present.

Avid Radiopharmaceuticals, 18F-AV-133-B04: An open label, multicenter study, evaluating the safety and efficacy of 18F-AV-133 PET imaging to identify subjects with dopaminergic degeneration among subjects presenting to a movement disorders specialty clinic with an uncertain diagnosis. 6/12-present. Role: Local-PI


The Michael J. Fox Foundation for Parkinson’s Research (MJFF). The Parkinson’s Progression Markers Initiative. 7/10-present. Role: Local PI.

COMPLETED RESEARCH
Schering-Plough/Merck. A Phase 3, Double-Blind, Placebo –and-Active –Controlled Dose-Range –Finding Efficacy and Safety Study of Preladenant in Subjects with Early Parkinsons’s Disease (PO5664). Role: Local PI.

Schering-Plough/Merck, A phase 3, 40-week, active controlled, double blind, double dummy, extension study of Preladenant in Subjects with Moderate to severe Parkinson’s disease (PO6153). 9/11-7/2/2013. Local PI.
Schering-Plough/Merck. A Phase III, 12 Week, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Preladenant in Subjects with Moderate to Severe Parkinson’s Disease (PO7037). 5/11-7/2/2013. Role: Local PI.


Allergan Inc., CD PROBE: Cervical dystonia patient registry for the observation of Botox efficacy. 3/10-10/2012. Role: Local PI.


Teva Neuroscience. A Double-blind, Placebo Controlled, Randomized, Multicenter Study to Assess the Safety and Clinical Benefit of Rasagiline as an Add on Therapy to Stable Dose of Dopamine Agonists in the Treatment of Early Parkinson’s Disease. Role: Local PI.

Chelsea Therapeutics. A multi-center, open-label study to assess the long-term safety of droxidopa in subjects with primary autonomic failure, dopa beta hydroxylase deficiency or non-diabetic neuropathy and symptomatic neurogenic orthostatic hypotension (NOH 304). 4/10-10/2012. Role: Local PI.


Arizona Biomedical Research Commission. Arizona Parkinson Disease Center Prevention of Progression to Parkinson’s Disease and Parkinson’s Disease with Dementia: Development of Biomarkers and Novel Treatment Strategies. 10/31/05-9/30/12. Role: Clinical Core Investigator.

International Essential Tremor Foundation. Neuropathological and biochemical substrates for essential tremor. 7/1/11-6/30/12. The goal of this study is to investigate change in the brainstem and cerebellar neurochemical system in autopsied subjects with ET. Role: Principal Investigator.

Avid Radiopharmaceuticals, Inc. Detection of Striatal Dopaminergic Degeneration and Neocortical Amyloid Pathology in Patients with Dementia with Lewy Bodies, Alzheimer's disease, Parkinson's disease, and Healthy Elderly Volunteers. 3/10-6/12. Role: Local PI.


NIH-NCMRR/NICHD 1R21HD060315-01A2 (Krishnamurthi): Exercise training in Parkinson’s disease: Neural and functional benefits. The goal of this study is to investigate the effects of 12-week regular polestriding exercise training on alleviating the severity of Parkinson’s symptoms. This study will also explore any changes in brain metabolic activity due to regular physical activity. 09/23/08 – 08/31/10. Role: Co-investigator
Parkinson’s Study Group and NIH: RO1NS050324-01A1. Effects of Coenzyme Q10 in Parkinson Disease – Phase 3. 12/08-06/11. Role: Local Principal Investigator.

Parkinson Study Group and National Institutes of Health, Cephalon and H. Lundbeck A/S. A longitudinal Observational Follow-up of the PRECEPT Study Cohort (PostCEPT). 8/06-1/11. Role: Local Principal Investigator

Chelsea Therapeutics, Inc. A multi-center, open-label study, with a two week withdrawal period, to assess the long-term safety and clinical benefit of droxidopa in subjects with primary autonomic failure, dopamine beta hydroxylase deficiency or non-diabetic neuropathy and symptomatic neurogenic orthostatic hypotension (NOH 303). Role: local PI.

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**BIOGRAPHICAL SKETCH**

**NAME**
Dugger, Brittany Nicole

eRA COMMONS USER NAME
BDUGGER

**POSITION TITLE**
Associate Scientist, Banner Sun Health Research Institute

**EDUCATION/TRAINING** *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan State University, E. Lansing, MI</td>
<td>B.S.</td>
<td>2001-2005</td>
<td>Microbiology/Health and Humanities</td>
</tr>
<tr>
<td>Mayo Clinic College of Medicine, Jacksonville, FL</td>
<td>Ph.D.</td>
<td>2006-Aug 2011</td>
<td>Neurobiology of Disease</td>
</tr>
<tr>
<td>Banner Sun Health Research Institute, Sun City, AZ</td>
<td>Postdoctoral Fellow</td>
<td>July 2011-Oct 2013</td>
<td>Neuropathology/Neuroanatomy</td>
</tr>
<tr>
<td>Banner Sun Health Research Institute, Sun City, AZ</td>
<td>Associate Scientist</td>
<td>Oct 2013- present</td>
<td>Neuroanatomy</td>
</tr>
</tbody>
</table>

**Personal Statement**

I am a neuropathology/neuroanatomist with 100% of my time devoted to research. As an undergraduate I received training in microbiology (Michigan State) and hormones and behavior (laboratory of Drs. Breedlove and Jordan). I received a PhD from the Mayo Clinic Graduate School with a focus on neuropathology. My postdoctoral fellowship was at the Banner Sun Health Research Institute, under the direction of Dr. Thomas Beach, where I aided in a research based human autopsy program for the past 2 years. I am currently an associate scientist here, a research collaborator at Mayo Clinic in Scottsdale, Arizona and a research associate at the University Of Arizona College Of Medicine in Phoenix, Arizona. Throughout the majority of my career I have been the interface of neurology and neuropathology and this has resulted in over 20 peer-reviewed manuscripts. Dr. Shill’s proposal is critical in assessing the neuroanatomical/pathological underpinnings of ET, and takes full advantage of the excellent resources at the Banner Sun Health Research Institute. I am enthusiastic to aid in the neuropathological assessment and evaluation to understand the neuropathology underlying ET.
Positions and Honors

Positions and Employment

2003-2006    Michigan State University Department of Neuroscience, East Lansing, MI – research technologist
2004        University of Puerto Rico- Rio Piedras, Department of Biology, San Juan, PR -intern
2006-2007    Mayo Clinic Department of Radiology, Rochester, MN- Graduate research assistant
2007-2011    Mayo Clinic Department of Neuropathology, Jacksonville, FL- Graduate student
2011-2013    Banner Sun Health Research Institute, Sun City, AZ- Post doctoral fellow
2013-        Banner Sun Health Research Institute, Sun City, AZ- Associate Scientist
2013-        Mayo Clinic Department of Neurology, Scottsdale, AZ- Research Collaborator
2013-        Department of Child Health Arizona College of Medicine, Phoenix, AZ- Research Associate

Other experiences and professional memberships

2004-2006  Participant, Brain Awareness Week Michigan State University; East Lansing, MI
2005-      Member, Society for Neuroscience
2006-2011  Coordinator, Brain Awareness Month Mayo Clinic; Jacksonville, FL
2007-2010  Technical coordinator, Mayo Graduate School teaching assistant
2008-2010  Lecturer, Mayo Clinic Graduate School NSCI 8850: Basic Neuroscience
2009      Instructor, Mayo Clinic Graduate School NSCI 8401: Neuroanatomy
2009-      Member, American Academy of Neurology
2009-2010  Member, Mayo Clinic Graduate School education committee
2010      Neurology on the Hill
2010      NIH National Graduate Student Research Festival
2010      Invited speaker, Institute of Neurology at University College London –London, England
2011      External grant reviewer, P.S.I. foundation
2011-     Coordinator, Brain Awareness Month, Banner Sun Health Research Institute
2011-     Coordinator, Seminar Series, Banner Sun Health Research Institute
2012      Instructor, Neuroanatomy- Banner Sun Health Research Institute Internship Program
2013      Invited speaker, 26th International Congress of the Alzheimer’s Disease Research Group- Marseille, France
2013      Research!America Inaugural Advocacy Academy
2013      Arizona Parkinson’s Disease Association, silent auction committee member
2013-     Assistant State Director, Parkinson’s Action Network

Honors

2001      Coca Cola Scholarship
2005      Cum Laude and Honors College graduate, Michigan State University
2007      AAAS/Science Program for Excellence in Science
2013      Parkinson’s Action Forum Fellowship
2013      Asao Hirano Award- Best Paper in Neurodegenerative Diseases, American Association of Neuropathologists
2013      Parkinson’s Action Network Postdoctoral Advocacy Award- $10,000

Selected peer-reviewed publications


**Current Support**

**Arizona Alzheimer’s Research Consortium**
Brittany Dugger (PI)
Dr. Dugger is the principal investigator for an Arizona Alzheimer’s Research Consortium Award. This project aims at understanding the presence of tau species (one of the main pathological hallmarks of Alzheimer’s disease) in peripherally tissues.

**National Alzheimer’s Coordinating Center**
Brittany Dugger (PI)
Dr. Dugger is the principal investigator for the National Alzheimer's Coordinating Center Junior Investigator Award. This project aims as understanding the prevalence of cardiovascular risk factors and conditions amongst the major, clinically-defined dementia subtypes – Alzheimer’s disease, vascular dementia, dementia with Lewy bodies, and other frontotemporal dementias.

**Michael J. Fox Foundation for Parkinson’s Research**
Charles Adler (PI)
This project involves conducting transcutaneous submandibular gland biopsies for a diagnostic test for early Parkinson’s disease. Dr. Dugger serves as a support role by conducting the histochemical and neuropathological analysis.
National Brain and Tissue Resource for Parkinson's Disease and Related Disorders, Thomas Beach (PI) 09/01/2011 – 08/30/16
The funds support the ongoing activities of the Brain and Body Donation Program, a longitudinal study of aging and neurodegenerative disease, and subsidize the costs of tissue and data sharing with investigators across the United States. Dr. Dugger serves as an assistant to the program, aiding in autopsies, tissue requests, consultations as well as generating data for publications.

Arizona Alzheimer’s Disease Core Center 7/30/11-6/30/16
Eric Reiman (PI)
Dr. Dugger aids in the Neuropathology Core for the Arizona ADCC through neuropathological evaluations, inputting items into the neuropathological data set provided by the National Alzheimer’s Coordinating Center, presenting at biannual clinicopathological conferences, and aiding in collaborative work across all 6 of our center sites.
CONFLICT OF INTEREST QUESTIONNAIRE
Grant Proposal Submissions

Pursuant to the purposes and interests of the policy adopted by the IETF Board of Directors requiring disclosure of certain interests, a copy of which has been furnished to me, I hereby state that I or relatives have the following affiliations or interests and have taken part in the following transactions which, when considered in conjunction with my relationship to the International Essential Tremor Foundation (IETF) might create or be a conflict of interest. (Write “none” where applicable).

1. Advisory Board or Panel Affiliation
   Dr. Smith participates on the IETF medical advisory board. I will abstain from review of this proposal and contact any other board members/potential reviewers regarding this proposal.

2. Consulting, Speakers Bureau or Contractual Services
   None

3. Research/Grant Support
   None

4. Financial or Material Support not otherwise listed.
   None

I hereby acknowledge the information given is complete and accurate to the best of my knowledge and belief. I understand that failure to accurately disclose a potential interest may cause revocation of my grant award if approved. I also understand that if any of the above circumstances change, that I am to complete a new questionnaire.

[Signature] HollySmith  2/28/14

Date

GrantConflict5222013

PO Box 14005 | Lenexa, Kansas 66285-4005 | USA | 888.387.3667 (toll free) | 913.341.3880 (local) | essentialtremor.org