Neurology Department
Research Blitz
October 4, 2016
Melissa J. Armstrong, MD, MSc

Movement disorders research: parkinsonism, dementia
- Hospitalization in dementia with Lewy bodies (currently with A.B., C.S.)
- Qualitative interviews of patients with DLB and caregivers about clinic, research priorities
- Designing survey regarding end-of-life experiences for families of patients who died from DLB

Research on guidelines, quality measures, shared decision making
- Studying impact of patient, caregiver, advocate involvement on AAN guidelines (AHRQ K08)
- Reviewing whether North American guideline developers are engaging patients as per IOM standards (with student)
- Designing study about barriers, facilitators to PD quality measure implementation (with K.N-F.)
Christopher Hess, M.D

- Tremor and myoclonus physiologic analyses
- Fine motor dexterity in PD
- High Density EEG
- Functional Near-Infrared Spectroscopy
- Transcranial direct and alternating current stimulation
- Case reports
McFarland: Atypical Parkinsonism research

PSP/Atypical Parkinsonism Clinical-Research Initiative
- Collaboration with Dr. David Vaillancourt (fMRI/DTI)
- Collaboration with Dr. Chris Hass on gait/balance

Mood disorders in Atypical PD
- Depressive sx prevalent
- Apathy
- Anxiety
- Brain circuitry, Tx?
McFarland: Synuclein pathology

- **α-synuclein monomer**, random coil
- Misfolding, dimer, oligomer
- protofibrils
- Insoluble fibrils, aggregates
- Inclusions/LBs
- Oxidative stress
- Mitochondrial dysfxn
- Axonal transport dysfxn
- Protein sequestration
- Mitochondrial dysfxn
- Synaptic dysfxn
- UPS inhibition

**Pathological Pathways**

1. **Phosphorylation**
   - Epi/Genetic, Environmental
   - Oxidative stress
   - Mitochondrial dysfxn

2. **SIRT2 inhibitors**
   - Hsp70, 27, CHIP
   - Molecular Chaperones

3. **Hsp90 inhibitors**
   - Rabs, RER1

4. **Rabs, RER1**
   - Proteasomal degradation
   - UPS

**Molecular Chaperones**

- CHIP
- Hsp70, 27

**Autophagy**

- Lysosomes

**Inclusions/LBs**

- Oxidative stress
- Axonal transport dysfxn
- Protein sequestration
- Mitochondrial dysfxn
- Synaptic dysfxn
- UPS inhibition
Increased vesicles/Impaired ER-Golgi transport

Rab8A/3A
Rab7/9
Rab11
Rab1
Rab8A

Autophagy
- chaperone-mediated
- macroautophagy

ER Stress

Autophagy

- Chaperone-mediated
- Macroautophagy

RER1

Rab1

MG132

RER1

MG

Chlor

Vector

APP

APP-CTFα

β-actin

αSyn wt

RER1

A

B

% αSyn levels

0

20

40

60

80

100

120

αSyn Vector

αSyn RER1

αSyn RER1 + Ø

αSyn RER1 + MG132

V

Δ25

Ø

MG

Chlor

14

28

98

14

6

38
Aparna Wagle Shukla MD
Assistant Professor, Department Of Neurology
Human Motor Functions & Brain Stimulation Lab

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1. K23 NINDS
2. KL2 NIH/CTSI University of Florida
3. Blepharospasm Research Foundation
4. National Organization for Rare Disorders
5. American Brain Foundation
6. Dystonia Medical Research Foundation
7. Dystonia Coalition
8. MBI Brain and Spinal Cord Injury Research Fund
Combined effects of rTMS and botulinum toxin in benign essential blepharospasm: A novel approach

Funding:
Benign Essential Blepharospasm Research Foundation

IRB: Yes

Experimental setup: Yes

Data collection: Yes

Data analysis: In progress

Plan: Abstract submission to AAN 2017 and MDS 2017 followed by publication
rTMS therapy for primary orthostatic tremor

Clinical Tests include TRS score, leg tremor score, TUG test speed, 10m walk test time.

Physiological Tests include amplitude and frequency of tremors, cerebello-cortical inhibition

Funding: National Organization for Rare Disorders

IRB: Yes

Experimental setup: Yes

Data collection: No

Data analysis:

Plan: Abstract submission to AAN 2018 and MDS 2017 followed by publication
Diagram representing the typical injection cycle for subjects with CD receiving BoNT. Approximately, 4-8 weeks after a BoNT injection, subjects reach the peak benefit, BoNT ON. At the time of the next injection, they reach the trough of benefit, BoNT OFF. Times of analysis and data collection are also indicated.

**Funding:** Dystonia Medical Research Foundation

**IRB:** Yes

**Experimental setup:** Yes

**Data collection:** No

**Plan:** Abstract submission to AAN 2019 and MDS 2018 followed by publication
**Combined therapy with rTMS and botulinum toxin in primary cervical dystonia**

Funding:
American Brain Foundation

IRB: Yes

Experimental setup: Yes

Data collection: No

Data analysis:

Plan: Abstract submission to AAN 2018 and MDS 2018 followed by publication
Michael S. Okun, M.D

- **Closed Loop DBS for Tourette (NIH R01)**

- **Closed Loop DBS for Freezing of Gait (MJF)**

- **Closed Loop DBS for Essential Tremor (UH3, Gunduz)**

- **Mobile Computing Platforms for DBS Therapy (NIH R01)**
Movement Disorders- Irene Malaty

- Apathy in Youth with Tourette syndrome- comparing apathy in 12-16yo with Tourette to same age Diabetic youth (Is it age, or illness related?); also assessing depression and SSRI use as potential contributors to risk

- Young onset Parkinson disease- Characteristics vs Typical Age of Onset

- Sensory Integration difficulties in kids with Tourette

- Implementing a Palliative Care Program for patients with Parkinsonism

- Potential: Dynamometer grip strength in Corticobasal syndrome vs Parkinson disease

- Potential: Describe treatment response in sialorrhea patients treated with botulinum toxin

- Case reports

- Number of industry sponsored trials-
  - A new toxin for cervical dystonia (Revance)
  - A new drug for adults and for kids with Tourette (Neurocrine)
  - New drugs for Parkinson disease (Biotie, Pfizer)
  - Characteristics of Huntington disease (Enroll-HD)
Epilepsy/ Cibula

• ACTIVE:
  • SAGE 547-SSE-301 super refractory status epilepticus (ICU study)
  • Upsher Smith: ARTEMIS (for intranasal, midazolam in cluster seizures)
  • Foundation for Anesthesia Education Research: Simulation Model for EEG Education (with Dr Fahy)

• Possibilities:
  • EEG quality studies including skin breakdown, FLEXH validation, alternate electrode development
  • Development of a Baby FLEXH scale
  • Status epilepticus chart reviews (how often, drugs, outcomes, etc)
  • Epilepsy Surgery chart reviews, database development
  • STAT order to EEG time (Hella)
  • Hypothermia chart analyses (how often, outcomes, etc)
  • EEG reading by nonphysicians- survey of programs
Hella Projects

1- EEG & Stroke (w/Dr.Eisenschenk)
   - Subacute EEG as predictive tool for development of seizures following stroke and TIA

2- Management of SE and NCSE at UF Health
   - Quality project on evaluation and treatment of SE and NCSE timing of EEGs, reading, promptness of treatment etc.
1. **EEG & Stroke**  
   • Subacute EEG as predictive tool for development of seizures following stroke and TIA

2. **Epilepsy Surgery Database**  
   • Database includes seizure type, localization, imaging, neuropsychological data, pathology and outcome

3. **Hippocampal Cell Density**  
   • Comparison of cell densities within CA1, CA2, CA3, CA4, and subiculum to seizure type, frequency, duration, imaging, and neuropsychological testing and post-surgical outcome

4. **VA Epilepsy Centers of Excellence Database**
1. Motor Control Deficits Following Transient Ischemic Attack (NIH R21)

2. Effect of Armodafinil on Simulated Driving, Electroencephalogram and Cognitive Performance in Sleep Deprived Healthy Subjects (Haliburton Research Foundation)

3. Driving in Obesity

4. Driving Questionnaire in VA Cooperative

5. Assessment of Driving Following Sleep Deprivation Associated with Consecutive Night Float
1. **Neurocognitive function associated with obesity in bariatric surgery population**
   - Comparison to neuropsychological data
   - Comparison to imaging
   - Comparison to polysomnography
   - Cross correlation of sleep related disorders (sleep deprivation, OSA, RLS, IH, narcolepsy, etc)
Nazario: Migraine Studies

• Calcitonin Gene-Related Peptide (CGRP) receptor antagonist, placebo-controlled randomized studies

**Background**

• CGRP found
  – Trigeminovascular nociceptive system from the trigeminal ganglion to second- and third-order neurons mediating the transmission of pain
  – Brainstem regulatory areas

• CGRP is released during severe migraine attacks
• Effective reversal of the attacks with triptans decrease CGRP levels
• Quality Improvement in the Neuro-ICU and with “Transitions” out of the NICU (e.g. pain medication regimen, urinary retention);

• Outcomes in patients with Subdural Hematoma
Teddy S. Youn, MD

- Improving Multimodal Neuroprognostication of Post-Cardiac Arrest Patients in the Targeted Temperature Management (TTM) Era;

- Health Disparities in Vascular Neurology and Neurocritical Care (i.e. Ethnic/Racial, Geographic Disparities)
1. Hemorrhagic transformation following IV rt-PA
   - Microbleeds
   - Chronic FLAIR hyperintensity/white matter changes

2. Hyperintense vessel sign (HVS) on FLAIR and Outcome
   Distal Vs Proximal HVS

3. Stroke in young adults
   Trends, risk factors, etiology, imaging
Clinically predicting recanalization

- Decline in BP and clinical improvement likely indicates recanalization
- Larger study

FLAIR

- What causes early FLAIR changes in acute stroke?
- Association between CBV and FLAIR

DWI

- Early DWI changes is reversible. Does not necessarily indicate core infarct.
- DKI, Free water imaging, NODDI
Wilson projects

• Stroke projects
  • Predictors of stroke in the young
  • Peripartum stroke
  • Accuracy of inpatient stroke alerts (QI/research)
  • Use of CTP (QI)

• Neurology GME projects
  • Stroke alert OSCE
  • Development of entrustable professional activities for Milestones
• Genome therapy for DM1 (NIH K08)

• Drug screening for DM1 using iPS cells (MBI/Marigold foundation)

• Establishment of iPS cells for neurodegenerative disorders (DM, SCA, ALS, PD) (Department)
POTENTIAL RESIDENT PROJECTS FOR RESIDENTS

S H SUBRAMONY

• Cognition in myotonic dystrophy
  – Study emotional cognition
  – Database mining
• Role of proprioceptive deficits in myotonic dystrophy and FA
• Polyneuropathy in elderly in the community
Research Interests:

Cognitive and neurobiological changes in aging and Alzheimer’s Disease (NIA)

Therapeutics for prevention and treatment of Alzheimer’s disease

Acute and long term effects of Traumatic Brain Injury (TBI)

Neuroimaging in neurodegenerative dementias and TBI
Dr. Heilman – Stroke projects

- **Experiment 1: Verbal Comprehension of Patients with Aphasia.**

- Whereas patients with Wernicke’s aphasia, transcortical sensory aphasia and global aphasia have severe comprehension disorders, almost all aphasic patients have impaired comprehension. Geschwind (1965) noted that often patients appeared to comprehend midline commands better than limb commands. For example, to verbal command they may be better to open and close their eyes than their hand. However, to my (KMH) knowledge and brief search of PubMed I do not think this has been tested. The goal of this study would be to test this hypothesis in stroke patients with aphasia.

- **Experiment 2: Possible Mechanism of Improved Comprehension of Midline Commands.**

- This study could be initiated the Experiment 1 reveal a significant difference between body and limb commands. When patients who develop a hemiparesis with stroke a stroke they are often more impaired making distal limb movements than proximal limb movements. This difference may be related to the location of the stroke or brain organization (i.e., greater ipsilateral –uncrossed corticospinal innervation of proximal movements). Studies of monkeys have revealed that each hemisphere can better control ipsilateral proximal than distal movements. Perhaps patients with left hemispheric stroke can better understand body commands than hand commands because the right hemisphere has a better ability to comprehend these commands. To test this hypothesis healthy volunteers’ brains could undergo functional imaging during the time they are listening to hand versus body commands.

- **Experiment 3: Influence of Reduced Sensory Input on Verbal Comprehension in Patients with Aphasia.**

- “Pressure equals force over area.” Therefore, as the area decreases the pressure gets greater. When a patient with a stroke has impaired comprehension they may allocate their brain processing resources to other domains of sensory input. Thus, a reduction of input may help the redirect these processing resources to verbal comprehension. Our former resident, fellow and faculty member Dr. Hedna thought that his aphasic patients could better comprehend speech when their eyes were closed and the goal of this experiment would be to test this hypothesis.
Dr. Heilman – PD projects

• **Experiment 4: Asymmetries of Limb-Kinetic Apraxia in Patients with Parkinson’s Disease (PD).**

• Patients with PD often reveal limb-kinetic apraxia. In a prior study we found that right handed patients with left hemisphere strokes had a greater impairment of performing coin rotation with their ipsilesional hand than those with a right hemisphere stroke have with their ipsilesional right hand. These results suggest that the left hemisphere is dominant for programing precise independent but coordinated finger movements. Many patients with PD have asymmetrical onset and severity. Therefore, the goal of this study will be to learn if patients with predominantly right sided PD have a greater impairment in coin rotation with both hands than those with predominantly left sided PD.

• **Experiment 5: Treatment of Limb Kinetic Apraxia.**

• Although patients with PD often reveal limb-kinetic apraxia the cause of this disorder is not entirely understood. However, it is known that patients who are unable to use their fingers and hands for several weeks often have a loss of deftness of their fingers and hand. In addition, functional imaging has revealed during this period of inactivity there is a reduction of the contralateral hand area. People with PD may not use their hands as much as normal people and perhaps this inactivity either causes or increases the severity of their limb-kinetic apraxia and disability. The first goal of this study is to learn if practicing coin rotation with their right hand several times of day will improve performance on this task as well as on another unpracticed test, the pegboard. If improvement is found it may also be worthwhile testing the opposite (left) hand to learn if their left hand performance also improves.
Diego Rincon-Limas, PhD. - Neurology Fly Lab

"Identification of therapeutic targets for neurodegenerative diseases"
Examples of targets that suppress TDP-43 toxicity

Components of the TREX (transcription/export) complex

Testing in mammalian systems
Pathophysiology and Experimental Therapeutics of Neurological Disorders

- Mouse/Worm Genetics and Neuroscience Lab
- Focus on Neurobiology of Disease and Pathophysiology, we also work on Preclinical Drug Discovery.
- We study a variety of brain regions: striatum, hippocampus, cerebellum, cerebral cortex, amygdala, and spinal cord.
- Mouse Models of Neurological Disorders: Dystonia, Restless Legs Syndrome, ALS, Epilepsy, Myoclonus, Parkinson’s Disease, and Alzheimer’s Disease
- Depending on student’s interests and experience, project will be in one of the following using the above mouse models: mouse genetic studies, electrophysiological recording, anatomical studies, biochemical studies, or behavioral studies.

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