Update on the DLB Module

ADC Directors Meeting

Baltimore, MD

October 14-15, 2016

Committee Members

- James Galvin, Florida Atlantic University (Chair)
- James Leverenz – Cleveland Clinic
- Brad Boeve – Mayo Clinic, Rochester
- Tanis Ferman – Mayo Clinic, Jacksonville
- Jennifer Goldman – Rush Medical Center
- Debbie Tsuang – University of Washington
- Carol Lippa –Thomas Jefferson University
- Daniel Weintraub – University of Pennsylvania
- Douglas Galasko – University of California San Diego
- John Growdon – Harvard Medical School

Goals

- Develop a companion module to the Uniform Data Set (UDS) to improve characterization of DLB and PDD
- Harmonize efforts with those of the Movement Disorder Society efforts to characterize the non-motor features of Parkinson's disease
- Capitalize on previous efforts to create a FTD module
- Standardize battery of clinical and cognitive tools for DLB and PDD that can be databased at NACC and shared amongst investigators.

Requirements

- Choose instruments and measurements from each workgroup
- Harmonize new data with variables captured as part of UDS 3.0
- Instruments or measurements selected should be free of licensing fees or that an agreement is in place to make their use free to the ADC program
- Not burden ADC sites

Motor and Non-Motor Features of PD

- Committee: Goldman, Weintraub
- Additional consultants: Ray Chaudhuri, David Burn
- Identified deficiencies in quantifying motor symptoms
- Capture age of onset of motor and non-motor symptoms
- Capture evolution of symptoms, particularly prodromal
- Capture common disturbing symptoms such as drooling, dysphagia
- Capture autonomic features
- Harmonize with data collected by UDALL Centers, PPMI, PPPMI, etc.

Sleep, Arousal, Attention, and Fluctuations

- Committee: Boeve

- Additional Consultants: Don Bliwise, Ron Postuma

- Capture REM sleep behavior disorder, excessive daytime sleepiness, cognitive fluctuations, and obstructive sleep apnea

- Both patient and informant questions

- UDS 3.0 has several Yes/No questions that may capture the symptoms but no clear determination of how the decision was made that the symptoms were present.

Behavior and Mood

- Committee: Tsuang, Lippa

- Additional questions regarding the age of onset for 4 symptoms:
  - Hallucinations
  - Delusions
  - Anxiety
  - Apathy

- Temporal relationship with DOPA-related medications

- Capture presence since disease onset rather than the past 4 weeks

Global Clinical Tools

- Committee: Leverenz, Galvin
- Incorporating global functioning in activities of daily living
- Patient-reported (UDS has only caregiver reported)

Neuropsychological Tests

- Committee: Ferman

- Additional Consultants: David Salmon, Alex Troster, Brenna Cholerton

- Try not to interfere with legacy tests at other centers, while keeping a focus to discriminate between DLB and AD

- Domains lacking or under-represented in UDS 3.0:
  - Attention, Executive function, and Visual-Spatial Perceptual tasks

- Add approximately 20 minutes to the UDS 3.0 battery
  - Test administration plus instructions

Biomarkers

- Committee: Growdon, Galasko

- No additional funding so no mandate requiring the Centers to prospectively collect any new biomarkers

- Record what biomarkers obtained and whether they are available for sharing – similar to what is done for AD biomarkers

Draft DLB Module: Motor and Non-Motor

- MDS-UPDRS
  - Part II: Motor Aspects of Experiences of Daily Living (patient reported)
  - Part III: Motor Examination (clinician reported)
- Estimate age of onset for motor symptoms and evolution of prodromal symptoms
  - RBD, olfaction, constipation
- Add sitting and standing BP and Pulse to physical exam
- Autonomic Checklist
  - NMSS
    - Drooling, dysphagia, sexual dysfunction, weight loss, olfaction, vision
  - SCOPA-AUT
    - Bowel, bladder, thermoregulatory

Non-Motor Features Checklist

In the past six months….	Yes	No	Not Applicable	Age of Onset
Does the patient dribble saliva during the day				
Does the patient have difficulty swallowing				
Does the patient have altered interest in sex				
Does the patient have problems having sex				
Does the patient have a recent change in weight (not related to dieting)				
Does the patient report a change in the ability to taste or smell				
Does the patient experience excessive sweating (not related to hot weather)				
Does the patient report having difficulty tolerating cold weather				
Does the patient report having difficulty tolerating hot weather				
Does the patient experience double vision (2 separate real objects and not blurred vision)				
Does the patient have problems with constipation				
Does the patient have to strain hard to pass stools				
Has the patient had involuntary loss of stools				
Has the patient had the feeling that after passing urine their bladder was not completely empty				
Has the patient had to pass urine within 2 hours of previous urination				
Has the patient had vivid dreams/nightmares or act out their dreams				
Has the patient complained of feeling lightheaded or dizzy when standing up				
Has the patient become lightheaded after standing for some time				
Has the patient fainted				

Draft DLB Module: Sleep

- Mayo Fluctuations Questionnaire

- Mayo Sleep Questionnaire
  - Subject
  - Informant

- Epworth Sleepiness Scale
  - Subject
  - Informant

- STOP-BANG Questionnaire

1. Snoring
   Do you *snore* loudly (louder than talking or loud enough to be heard through closed doors)?
   Yes   No

2. Tired
   Do you often feel *tired*, fatigued, or sleepy during daytime?
   Yes   No

3. Observed
   Has anyone *observed* you stop breathing during your sleep?
   Yes   No

4. Blood *pressure*
   Do you have or are you being treated for high blood *pressure*?
   Yes   No

5. BMI
   BMI more than 35 kg/m^2?
   Yes   No

6. Age
   Age over 50 yr old?
   Yes   No

7. Neck circumference
   Neck circumference greater than 40 cm?
   Yes   No

8. Gender
   Gender male?
   Yes   No

High risk of OSA: answering yes to three or more items
Low risk of OSA: answering yes to less than three items

Draft DLB Module: Behavior and Mood

- Expanded NPI screening questionnaire (NPI-C)
  - Delusions
  - Hallucinations/Illusions
  - Anxiety
  - Apathy
- Additional components
  - Age of onset of symptoms
  - Medications to treat symptoms

Draft DLB Module: Global Clinical Tools

- Focus on Patient-reported activities
- MDS-UPDRS Part II

Draft DLB Module: Neuropsychology

- _Modified Stroop Color-Word-Interference Task_

- Test of attention, processing speed, and executive function.

- May distinguish between DLB/PDD and AD

- Different from the copyrighted version

- Similar to the one normed by the Mayo group

- Developing norms

- Each component takes 45 seconds(maximal allowed time)

Draft DLB Module: Neuropsychology

Word Condition

BLUE   GREEN

RED   BLUE

GREEN   RED

Color Condition

####

####

####

Interference Condition

BLUE   RED

GREEN   BLUE

RED   GREEN

Word Scoring Key: Put "/w" to mark last response at 45 seconds

1	Blue	Green	Blue	Green	Blue
2	Red	Blue	Green	Red	Red
3	Green	Red	Red	Blue	Green
4	Red	Blue	Green	Red	Red
5	Green	Green	Red	Green	Blue
6	Blue	Red	Blue	Blue	Green
7	Green	Blue	Red	Green	Red
8	Red	Red	Blue	Blue	Green
9	Blue	Green	Green	Red	Blue
10	Red	Red	Red	Blue	Green
11	Blue	Blue	Green	Green	Blue
12	Green	Green	Blue	Red	Red
13	Blue	Red	Green	Blue	Blue
14	Green	Green	Blue	Red	Green
15	Red	Blue	Red	Green	Red
16	Green	Green	Blue	Red	Green
17	Blue	Red	Red	Blue	Red
18	Red	Blue	Green	Green	Blue
19	Blue	Red	Red	Blue	Green
20	Red	Green	Blue	Red	Blue

Color Scoring Key: Put "/c" to mark last response at 45 seconds
Color-Word Key: Put "/cw" to mark last response at 45 seconds

1	Red	Blue	Red	Green	Blue
2	Blue	Green	Blue	Blue	Red
3	Green	Red	Green	Red	Green
4	Red	Blue	Blue	Green	Blue
5	Blue	Red	Green	Red	Green
6	Red	Green	Red	Blue	Red
7	Blue	Blue	Green	Red	Green
8	Green	Green	Red	Blue	Red
9	Blue	Red	Blue	Green	Blue
10	Green	Blue	Red	Red	Red
11	Red	Green	Blue	Green	Blue
12	Green	Red	Green	Blue	Green
13	Blue	Green	Blue	Red	Blue
14	Green	Blue	Red	Green	Red
15	Red	Green	Green	Blue	Blue
16	Blue	Red	Blue	Red	Green
17	Green	Blue	Red	Green	Red
18	Blue	Red	Green	Red	Green
19	Red	Green	Red	Blue	Blue
20	Green	Blue	Blue	Green	Red

Word Score _____

Color Score _____

Color-Word Score _____

Draft DLB Module: Neuropsychology

- *Noise-Pareidolia*
  - Yokoi et al, 2014; Mamiya et al 2016

- There are two types of images:
  - An array of ink blots with a facial image (Scen
  - An array of ink blots with no facial image (No

- Responses are recorded
  - Is there a face: Yes or No
  - Point to where the face is

- The scores are based on the number of:
  - Correct answers: "Yes" when there is a face o
    "No" when there is no face
  - Pareidolia: "Yes" when there is no face or "Yes"
    when there is a face but points to wrong spot
  - Missed responses: "No" when there is a face

- Short Form: 20 Items (13 Foils, 7 Faces)

- Each panel 30 seconds (10 minutes max)
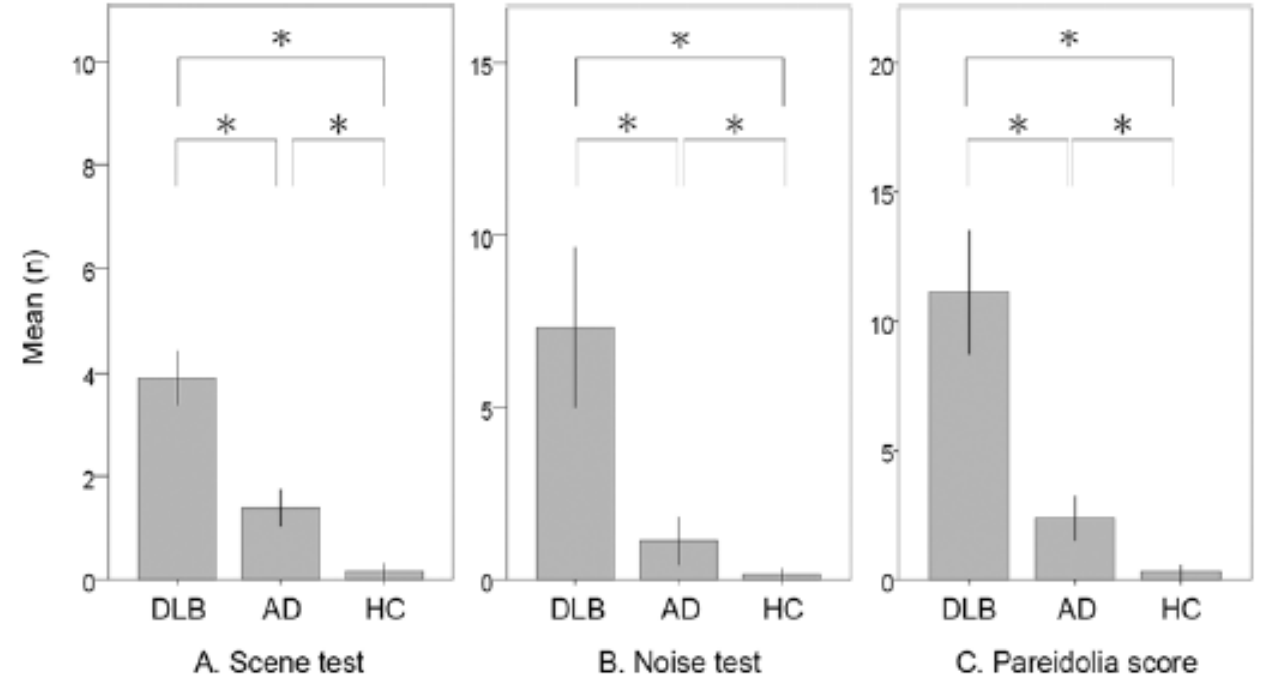
Differentiation between DLB and AD

	Scene Test	Noise Test	Pareidolia Score
Sensitivity	**0.92**	0.60	**0.81**
Specificity	0.58	**0.92**	**0.92**
ROC AUC	0.86	0.82	**0.92**
Cut-Off Score	1/2	2/3	4/5

#	Stimulus	Select Response	
1	Face	**Yes**	No or wrong place
2	Noise	Yes	**No**
3	Noise	Yes	**No**
4	Face	**Yes**	No or wrong place
5	Noise	Yes	**No**
6	Noise	Yes	**No**
7	Noise	Yes	**No**
8	Face	**Yes**	No or wrong place
9	Noise	Yes	**No**
10	Face	**Yes**	No or wrong place

#	Stimulus	Select Response	
11	Noise	Yes	**No**
12	Noise	Yes	**No**
13	Face	**Yes**	No or wrong place
14	Noise	Yes	**No**
15	Noise	Yes	**No**
16	Face	**Yes**	No or wrong place
17	Noise	Yes	**No**
18	Face	**Yes**	No or wrong place
19	Noise	Yes	**No**
20	Noise	Yes	**No**

Correct Face responses   _____/7   Number of **Yes** responses to face stimuli that point to the correct location

Correct Noise responses _____/13   Number of **No** responses to noise stimuli without face images

Total Correct   _____/20   Correct **Yes** face responses + Correct **No** noise responses

Noise (Pareidolia) responses _____/13   Number of Yes responses to noise stimuli (points to a face where there is no face)

Draft DLB Module: Biomarkers

- Genetics

- Biofluids
  - DNA
  - Plasma
  - Serum
  - CSF

- Neuroimaging
  - Structural MRI
  - Functional MRI
  - PET (FDG, amyloid, tau, future synuclein)
  - DAT scan
  - MIBG

Harmonization with EU –JPND Effort

	Level 1	Level 2
Cognition		
Staging	**CDR**	CGI-S, CGI-C
Global	MMSE, **MOCA**	
Memory	CERAD word list	**Benton visual retention test**
Visuospatial	Degraded letter test (VSOP)	Benton line orientation
Executive	Similarities (WAIS)	**Stroop test**
Attention	Adaptive digit ordering	**Trail making test**
Language	**Fluency, animals**	**Boston Naming, 15-item**
Psychiatric Symptoms		
Profile	**NPI Questionnaire**	**NPI**
Depression	**NPI item 4, GDS-15**	Cornell scale
Apathy	**NPI item 7**	Apathy evaluation scale
Psychosis	**NPI items 1+2**	CUSPAD misidentification, NEVI

	Level 1	Level 2
Other		
Quality of life	QoL-AD	
Caregiver burden	Zarit burden inventory	
Autonomic	**Orthostatics, NMSS**	ECG
Sleep	**Sleep items, NMSS**	**Mayo sleep questionnaire**
Motor	**UPDRS III**, timed up-and-go	Finger tapping, **H & Y**
Fluctuations	**Mayo fluctuation scale**	Fluctuation assessment scale
Falls	**Semi-quantitative question**	Tinetti scale
ADLs	**FAQ**	
Milestones	CDR=3, admission, death	

New U01 (NINDS/NIA) Consortium

- Develop a longitudinal cohort of well-characterized subjects with dementia with Lewy bodies (DLB) or DLB/mild cognitive impairment (DLB-MCI)
- Nine sites: Cleveland Clinic (coordinating center), Florida Atlantic University, University of Pennsylvania, University of Pittsburgh, Thomas Jefferson University, University of North Carolina, Rush Presbyterian, University of Washington/Puget Sound VA, University of California San Diego
- 216 subjects with strict recruitment targets and timelines
- Detailed clinical, cognitive, behavioral and functional evaluation at enrollment (with dopamine imaging), six months, and then annually for the five year duration of the study.
- At each annual visit blood and cerebrospinal fluid and this will be collected and stored, in collaboration with the Parkinson's Disease Biomarker Program (PDBP), at the NINDS. UDS data will shared with NACC
- Neuropsychological Data from DLB module will be used

Next Steps

- Working on permission agreements for last few hold-outs
  - In particular the MDS-UPDRS
  - May require change to original UPDRS
- Finalize forms in UDS/NACC formats
- Propose to pilot at a few centers
- Plan to have completed module for late winter/early spring 2017