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 – UC- San Diego
- John Growdon – Harvard University

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

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's stream of urine been weak or reduced				
Has the patient had to pass urine within 2 hours of previous urination				
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				

Adapted from Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord 2004; 19:1306-1312, and Chaudhuri R and Forbes A. Non-motor symptom assessment scale for Parkinson's disease. International Parkinson's disease non-motor group.

Draft DLB Module: Sleep, Attention….

- Mayo Fluctuations Questionnaire
- Mayo Sleep Questionnaire
  - Subject
  - Informant
- Epworth Sleepiness Scale
  - Subject
  - Informant
- STOP-BANG Questionnaire

1. *S*noring
   Do you *s*nore loudly (louder than talking or loud enough to be heard through closed doors)?
   Yes No
2. *T*ired
   Do you often feel *t*ired, fatigued, or sleepy during daytime?
   Yes No
3. *O*bserved
   Has anyone *o*bserved you stop breathing during your sleep?
   Yes No
4. Blood *p*ressure
   Do you have or are you being treated for high blood *p*ressure?
   Yes No
5. *B*MI
   *B*MI more than 35 kg/m^2?
   Yes No
6. *A*ge
   *A*ge over 50 yr old?
   Yes No
7. *N*eck circumference
   *N*eck circumference greater than 40 cm?
   Yes No
8. *G*ender
   *G*ender 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

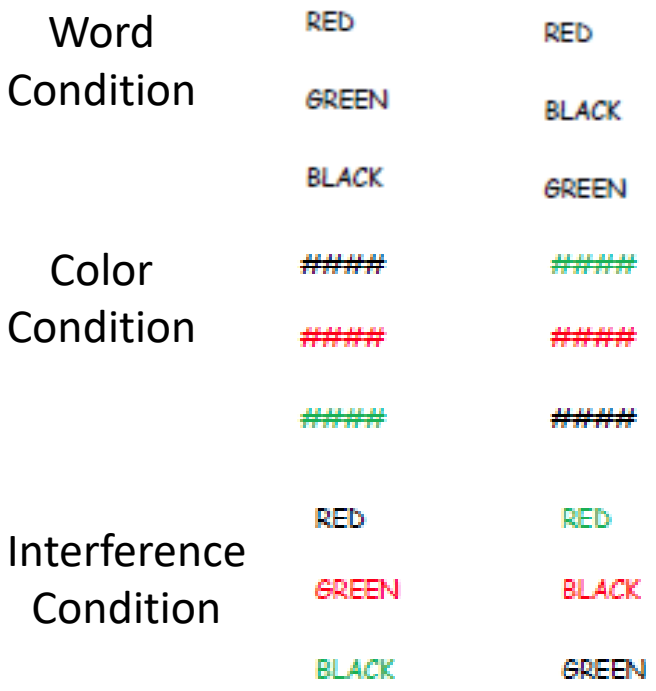
- Expanded NPI screening questionnaire (NPI-C)
  - Delusions
  - Hallucinations/Illusions
  - Anxiety
  - Apathy
- Additional components
  - Age of onset of symptoms
  - Medications to treat symptoms

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.
- There is evidence that it distinguishes between DLB/PDD and AD

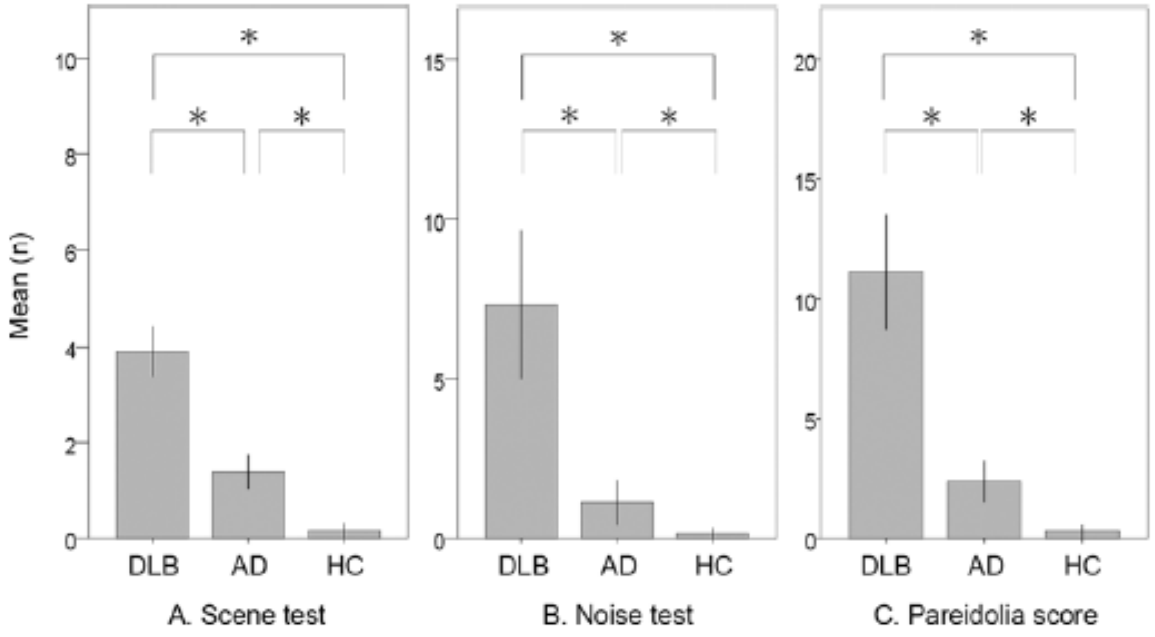


	Raw
Word Score	
Color Score	
Color-Word Score	

- Different from the copyrighted version
- Similar to the one normed by the Mayo group
- Developing norms

Draft DLB Module: Neuropsychology

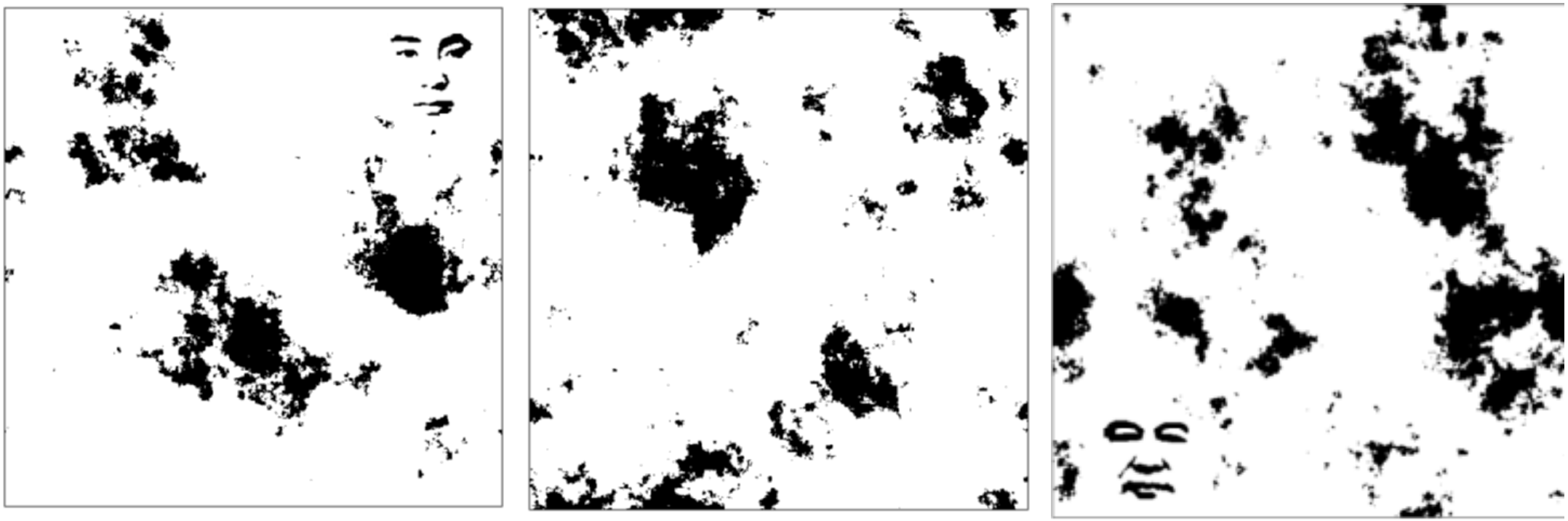
- Noise-Pareidolia (Yokoi et al, 2014)
- There are two types of images:
  - An array of ink blots with a facial image (Scene)
  - An array of ink blots with no facial image (Noise)
- Responses are recorded
  - Is there a face: Yes or No
  - Point to where the face is
- The scores are based on the number of:
  - Correct answers: “Yes” when there is a face or “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)
- Takes 5-10 minutes



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

Draft DLB Module: Neuropsychology



Draft DLB Module: Biomarkers

- Genetics
- Biofluids
  - DNA
  - Plasma
  - Serum
  - CSF
- Neuroimaging
  - Structural MRI
  - Functional MRI
  - PET
  - 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

- Newly funded (NIH/NINDS/NIA) collaborative group with the aim to develop a longitudinal cohort of well-characterized subjects with dementia with Lewy bodies (DLB) or "high likelihood" 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 DLB or DLB-MCI will be recruited
- Subjects will either fulfill consensus diagnostic criteria for DLB or have mild cognitive impairment and at least one of the follow three features (RBD, significant parkinsonism, abnormal dopamine transporter scan).
- Each subject will undergo 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. In addition to demographics and family history, scales for activities of daily living, behavior, cognition, sleep, parkinsonism, and smell will be utilized.
- 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 and pilot at a few centers
- Plan to have completed module for late winter/early spring 2017