**Program**

DEMENTIA: A Comprehensive Update  
May 27 – 30, 2020  
Livestream

**Thursday, May 28, 2020**

8:30 - 8:35  Morning PreTest.................................................................B. Dickerson, MD, MMSc
8:35 - 9:10  Neuropathology of AD/ADRD: A Guide for Practicing Clinicians.............................................M. Frosch, MD, PhD
9:10 - 9:50  Attentional and Executive Systems - Don’t Leave Home Without Them.........................................K.R. Daffner, MD, FAAN
9:50 - 10:30 Frontotemporal Dementias: Focus on Behavioral/Executive Variants.................................................B. Miller, MD
10:30 - 10:45  Morning Coffee Break
10:45 - 11:25  Language Systems & Aphasia-predominant Dementia Syndromes...................................................M.-M. Mesulam, MD
11:25 - 12:05pm  Vascular Cognitive Impairment & Dementia.................................................................C. DeCarli, MD
12:05 - 12:35  Morning Post-Test and Panel Discussion and Q & A.................................................................Morning Faculty
12:35 - 1:35  Lunch Break
1:35 – 1:40  Afternoon PreTest..........................................................................................................................A. Atri, MD, PhD
1:40 - 2:30  Lewy Body Disease and Parkinsonian Dementias..................................................................................J.E. Galvin, MD, MPH
2:30 - 2:50  Assessment of Cognition in Clinical Practice......................................................................................A. Atri, MD, PhD
2:50 - 3:10  Providing Practical Compensatory Strategies for Cognitive Decline..............................................L. Shaughnessy, PsyD, ABPP
3:10 - 3:35  Assessment of Daily Function and Neuropsychiatric Symptoms/Behavior and Staging of Dementia in Practice..............................................................................................................B. Dickerson, MD, MMSc
3:35 - 3:50  Afternoon Coffee Break
3:50 - 5:00  Cased-based Assessment and Application of Biomarkers in Dementia Clinical Practice.................A. Atri, MD, PhD
B. Dickerson, MD, MMSc
J.C. Sherman, PhD
D. Wolk, MD
5:00 - 5:30  Afternoon Post-Test, Panel Discussion and Q & A .................................................................All Faculty

**Clinical Pearls with Faculty: **Now Included with Tuition
Clinical Pearls Dine & Learn with Faculty Optional Program: Ask the Professors and "Practical strategies for facilitating cognitive impairment & dementia detection, care and research opportunities in the community by Paul Solomon, PhD"
Neuropathology of AD/ADRD: A Guide for Practicing Clinicians

Matthew P. Frosch, MD, PhD
Neuropathology of dementias

Matthew P. Frosch, MD, PhD

Lawrence J. Henderson Associate Professor of Pathology, Harvard Medical School

Director, C.S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital
DISCLOSURES

• Sponsored research agreements with Biogen & Voyager to perform autopsies on subject from clinical trials

No data from this work will be presented here
Learning objectives

• Understand how neuropathologists render diagnoses

• Know how to read an autopsy report and interpret it for a family

• Appreciate clinico-neuropathological correlations associated with dementia
Diseases to be discussed

- Alzheimer disease
- Lewy body diseases
- Frontotemporal lobar degenerations
- Chronic traumatic encephalopathy

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- Cerebrovascular diseases
Critical concept

• Neurodegenerative diseases are progressive disorders (from normal cognition to dementia)
• Pathologic lesions can be seen in advance of clinical end-point
• Therefore, can find lesions in subjects who are normal/mildly impaired

\textit{disease} \neq \textit{dementia}
Alzheimer disease

• Plaques
  – Extracellular deposits of Aβ (40-42 amino acid peptide cleaved from a larger protein)
  – Genetic evidence links Aβ to AD
Assessment of amyloid

• Where is it?
  – Distribution across anatomic structures
  – Thal scoring of amyloid
Thal scoring of amyloid

• **Distribution** of parenchymal deposits

• **Stages:**
  1 – Neocortical
  2 – Allocortex (hippocampus)
  3 – Thalamus, striatum, NbM
  4 – Brainstem
  5 – Cerebellum

[Thal et al. Neurology. 2002; 58(12):1791-800]
Assessment of amyloid

• Where is it?
  – Distribution across anatomic structures
  – Thal scoring of amyloid

• What does it do to the surrounding brain?
  – Presence of neuritic plaques (abnormal neuronal processes around the amyloid deposit)
  – CERAD scoring of neuritic plaques
Silver stain
AD: CERAD

- Neuritic plaques
- Frontal, temporal and parietal cortex
- Assess on WORST area
- Reporting:
  - Absent
  - Sparse
  - Moderate
  - Frequent
Alzheimer disease

• Plaques
  – Extracellular deposits of Aβ (40-42 amino acid peptide cleaved from a larger protein)
  – Genetic evidence links Aβ to AD

• Tangles
  – Deposits of hyperphosphorylated tau (microtubule binding protein)
  – Genetic evidence links tau to FTLD
AD: Braak & Braak

- Developed as a staging scheme
- Assumption: lesion develop in a stereotyped order across anatomic sites

AD: Braak & Braak

• Stages I-II: “transentorhinal” disease
  – No cases had clinical diagnosis of dementia

• Stages III-IV: “limbic” disease
  – 5 of 10 Stage III cases and 5 of 10 Stage IV cases had clinical diagnosis of dementia

• Stages V-VI: “isocortical” disease
  – All cases had clinical diagnosis of dementia
National Institute on Aging–Alzheimer’s Association guidelines for the neuropathologic assessment of Alzheimer’s disease: a practical approach

Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman

Featured Articles

National Institute on Aging–Alzheimer’s Association guidelines for the neuropathologic assessment of Alzheimer’s disease

Bradley T. Hyman\textsuperscript{a}, Creighton H. Phelps\textsuperscript{b}, Thomas G. Beach\textsuperscript{c}, Eileen H. Bigio\textsuperscript{d}, Nigel J. Cairns\textsuperscript{e,f}, Maria C. Carrillo\textsuperscript{g}, Dennis W. Dickson\textsuperscript{h}, Charles Duyckaerts\textsuperscript{i}, Matthew P. Frosch\textsuperscript{j}, Eliezer Masliah\textsuperscript{k,l}, Suzanne S. Mirra\textsuperscript{m}, Peter T. Nelson\textsuperscript{n}, Julie A. Schneider\textsuperscript{o,p,q}, Dietmar Rudolf Thal\textsuperscript{r}, Bill Thies\textsuperscript{g}, John Q. Trojanowski\textsuperscript{s}, Harry V. Vinters\textsuperscript{t,u}, Thomas J. Montine\textsuperscript{v-x}.
2012 NIA-Alzheimer Association

- Any plaques (± tangles) implies “Alzheimer disease neuropathologic changes” [ADNC]
- Report an “ABC” score
  - **A** is for Amyloid (Thal)
  - **B** is for Braak
  - **C** is for CERAD
- Use population-based observations to suggest likelihood of cognitive impairment
## 2012 NIA-Alzheimer Association

### A
Based on Thal staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - - - - - 0</td>
<td>None</td>
</tr>
<tr>
<td>1 - - - - 1 or 2</td>
<td>Sparse</td>
</tr>
<tr>
<td>2 - - - - - 3</td>
<td>Moderate</td>
</tr>
<tr>
<td>3 - - - - - 4 or 5</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

### B
Based on Braak staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - - - - - 0</td>
<td>None</td>
</tr>
<tr>
<td>1 - - - - I or II</td>
<td>Sparse</td>
</tr>
<tr>
<td>2 - - - III or IV</td>
<td>Moderate</td>
</tr>
<tr>
<td>3 - - - V or VI</td>
<td>Frequent</td>
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</tbody>
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### C
Based on CERAD score

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>0 - - - - None</td>
<td>None</td>
</tr>
<tr>
<td>1 - - - - Sparse</td>
<td>Sparse</td>
</tr>
<tr>
<td>2 - - - Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>3 - - - Frequent</td>
<td>Frequent</td>
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<tr>
<td>AD Neuropathologic Change</td>
<td>B</td>
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<td>---------------------------</td>
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<tr>
<td>A</td>
<td>0 or 1</td>
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<td>0</td>
<td>Low</td>
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<td>1</td>
<td>Low</td>
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<tr>
<td>2 or 3</td>
<td>Low</td>
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<td>2</td>
<td>Low</td>
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<tr>
<td>0 or 1</td>
<td>Intermediate</td>
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<tr>
<td>2 or 3</td>
<td>Intermediate</td>
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<tr>
<td>3</td>
<td>Intermediate</td>
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Not

Low
Alzheimer disease reporting

- Alzheimer disease neuropathologic changes [ADNC]
  - Thal score for amyloid
  - Braak & Braak stage of tangles
  - CERAD score for neuritic plaques
  - ABC score, with interpretation of likelihood of cognitive impairment
Dementia with Lewy Bodies (DLB)

• Pathologic features:
  – Lewy bodies *(absolute requirement)*
  – Lewy neurites
  – Appropriate neuronal loss in brain stem (SN, LC)
  – Spongiform changes, especially in upper layers of entorhinal cortex *[common not required]*
Braak staging of LB pathology

<table>
<thead>
<tr>
<th>Medulla</th>
<th>Pons</th>
<th>Midbrain</th>
<th>Limbic ctx</th>
<th>Assn. ctx</th>
<th>Primary ctx</th>
</tr>
</thead>
<tbody>
<tr>
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<td>6</td>
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</tbody>
</table>

- presymptomatic phase
- symptomatic phase

Parkinson’s disease-related alterations
- neocortex, primary, secondary
- neocortex, high order association
- mesocortex, thalamus
- substantia nigra, amygdala
- gain setting nuclei
- dorsal motor X nucleus
- stages of the PD-related path. process
2012 NIA-Alzheimer Association Reporting LB changes

<table>
<thead>
<tr>
<th>None</th>
<th>No LBs or related changes in IHC for $\alpha$-synuclein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem-predominant</td>
<td>LBs in medulla, pons, or midbrain</td>
</tr>
<tr>
<td>Limbic (Transitional)</td>
<td>LBs in cingulate or entorhinal cortices, usually with brainstem involvement</td>
</tr>
<tr>
<td>Neocortical (Diffuse)</td>
<td>LBs in frontal, temporal, or parietal cortices usually with involvement of brainstem and limbic sites, which may include amygdala</td>
</tr>
<tr>
<td>Amygdala-predominant</td>
<td>LBs in amygdala with paucity of LBs in the above regions</td>
</tr>
</tbody>
</table>
Frontotemporal lobar degenerations (FTLD)

- Degenerations not dementias
- Basis for classification:
  - Distribution of lobar atrophy
  - Type of inclusions
  - Pattern of clinical symptoms
    - bvFTD vs PPA (including subtypes)
FTLD

- Severe cortical neuronal loss and gliosis (basis for gross atrophy)

- Microscopic changes mirror the grossly evident atrophy

  But…

- Microscopic changes commonly exceed the gross changes
FTLD -- inclusions

- Basis for neuropathologic classification
- Range of proteins can aggregate in these disorders
- No one-to-one mapping of neuropathologic classification onto clinical syndromes
FTLD-tau

• Tau: microtubule binding protein
• Mutations in MAPT (chromosome 17) are causative – BUT many cases are sporadic
• Mutations can be coding region or change in splicing
• Hallmark: Tau without Aβ (sometimes distinct types of inclusions)
FTLD-tau

- Normal tau has multiple isoforms with either 3 or 4 copies of the microtubule binding region (3R & 4R)
- PSP & CBD: 4R tau inclusions
- Pick disease: 3R tau inclusions
FTLD-tau/Pick Disease  [3R tauopathy]
FTLD-tau

FTLD-tau/PSP [4R tauopathy]

Tufted astrocyte

C

Coiled body

E

FTLD-tau/CBD [4R tauopathy]

Astrocytic plaque

Feany and Dickson, Am J Pathol, 1995
Dickson et al, Brain Pathol, 2007
FTLD-TDP (TDP-43)

- Nuclear RNA-binding protein (many targets)
- Disease:
  - Aggregates and relocates to cytoplasm (neuronal cytoplasmic inclusions)
  - Intra-nuclear aggregates (neuronal intra-nuclear inclusions)
  - In neurites (dystrophic neurites)
TDP-43 associated diseases

- Sporadic and genetic FTLD-TDP exist
  - TDP-43 gene
  - C9orf72 hexanucleotide repeat expansion
  - Progranulin (haploinsufficiency)
  - Valosin-Containing Protein (VCP)

- Relationship with ALS:
  - Clinical and familial (C9orf72>>TDP-43)
  - Shared patterns of inclusions (distinct from ALS with SOD1 mutations)
FTLD -- inclusions

Tau & TDP-43: 
~90-95% of cases of FTLD
FTLD Reporting

FTLD

- FTLD-Tau
  - 3R Tau
    - PICK
    - FTLD-Tau MAPT mutation
  - 4R Tau
    - CBD
  - 3R/4R Tau
    - Tangle dominant disease
    - PSP
    - CTE
    - Globular Gial Tauopathy
    - ALS/PDC Guam
    - AGD
    - FTLD-Tau MAPT mutation
- FTLD-TDP
  - FTLD-TDP Sporadic
  - FTLD-MND Sporadic
  - FTLD-TDP GRN mutation
  - FTLD-TDP TARDBP mutation
  - FTLD-TDP VCP mutation
  - FTLD-TDP C9orf72 Expansion
- FTLD-FUS
  - NIFID
  - aFTLD-U
  - FTLD-FUS FUS mutation
- FTLD-UPS
  - FTLD-UPS CHMP2B mutation
  - BIBD
- FTLD-NOS
  - DLDH/FTLD-NI
Related entities

- Primary Age-Related Taupathy (PART)
  - Tangle only dementia
  - Predominantly in temporal lobe
  - Late life onset dementia with prominent amnestic component

- Hippocampal sclerosis (HS)
  - TDP43-related process
  - CA1 neuronal loss without ischemic event
  - Primarily amnestic disorder
Chronic traumatic encephalopathy (CTE)

McKee et al, J Neuropathol Exp Neurol 2009
Chronic traumatic encephalopathy (CTE)
CTE Consensus Criteria (NINDS, 2015)

• Required:
  – Abnormal accumulation of tau in neurons, astrocytes, and cell processes, in an irregular pattern in the depths of cortical sulci

• Supportive:
  – Cavum or fenestrated septum, 3rd ventricular dilatation, old injury
  – Tau in layer 2-3 neurons, CA2 and 4 neurons, and deep gray
  – Tau in subpial and subependymal thorn-shaped astrocytes

• Exclusionary:
  – Amyloid plaques, CA1 hippocampal sclerosis (AD)
  – Severe basal ganglia involvement (CBD)
  – Cerebellar dentate involvement (PSP)
Cerebrovascular disease

• Large vessel diseases
  – Atherosclerosis
  – “Strategic” infarction

• Small vessel diseases
  – Arteriolar sclerosis (hypertension)
  – Leukoariosis (white matter changes)
  – Microinfarcts
  – Cerebral amyloid angiopathy
Clinicopathologic correlation

- Presence of one neuropathologic disease is not ‘protective’ for other diseases

- Dementia is commonly associated with evidence of multiple neuropathologic processes

- Impossible to assign “blame”
Interaction of infarct and AD

Table 2.—Prevalence of Dementia for Participants Without and Participants With Brain Infarcts Who Met Neuropathologic Criteria for Alzheimer Disease*

<table>
<thead>
<tr>
<th>Type and Location of Infarct</th>
<th>Proportion Demented (No. Demented/No. at Risk)</th>
<th>Multivariate-Adjusted Odds Ratio for Dementia (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 Lacunar infarcts in basal ganglia, thalamus, or deep white matter</td>
<td>0.93 (14/15)</td>
<td>20.7 (1.5-288.0)</td>
</tr>
<tr>
<td>≥1 Large infarcts in lobes of neocortex</td>
<td>0.75 (9/12)</td>
<td>6.7 (0.9-48.3)</td>
</tr>
<tr>
<td>No brain infarcts</td>
<td>0.57 (21/37)</td>
<td>...</td>
</tr>
</tbody>
</table>

Snowdon, et al. (1997) JAMA 277:813-817
Impact of microinfarcts

<table>
<thead>
<tr>
<th>Cognitive Outcome</th>
<th>Estimate (SE), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognition</td>
<td>−0.287 (0.113), 0.012</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>−0.279 (0.138), 0.044</td>
</tr>
<tr>
<td>Semantic memory</td>
<td>−0.391 (0.130), 0.003</td>
</tr>
<tr>
<td>Working memory</td>
<td>−0.146 (0.099), 0.139</td>
</tr>
<tr>
<td>Perceptual speed</td>
<td>−0.400 (0.117), &lt;0.001</td>
</tr>
<tr>
<td>Visuospatial abilities</td>
<td>−0.153 (0.098), 0.119</td>
</tr>
</tbody>
</table>

Adjusted for age-at-death, sex, education, large infarcts, AD and LB

1242 cases with neuropathologically diagnosed AD
Diseases discussed

• Alzheimer disease
• Lewy body diseases
• Frontotemporal lobar degenerations
• Chronic traumatic encephalopathy

• Cerebrovascular diseases
Attentional and Executive Systems - Don’t Leave Home Without Them

Kirk R. Daffner, MD, FAAN
The Frontal Lobes: Don’t leave home without them

Kirk R. Daffner, M.D.
J. David and Virginia Wimberly Professor of Neurology
Harvard Medical School
Director, Center for Brain/Mind Medicine
Brigham and Women’s Hospital
May 28, 2020

I have nothing to disclose

Conditions Impacting Different Components of Frontal Networks

<table>
<thead>
<tr>
<th>Lateral PFC</th>
<th>Paralimbic PFC</th>
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</thead>
<tbody>
<tr>
<td>Alzheimer Disease</td>
<td>bvFTD</td>
</tr>
<tr>
<td>(Normal aging)</td>
<td>Traumatic Brain Injury</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subcortical White Matter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Dementia</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>(Normal aging)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD Dementia</td>
</tr>
<tr>
<td>PSP</td>
</tr>
</tbody>
</table>
Case

- 39-year-old formerly hard-working woman with progressive changes in personality and behavior
- Jobless; sleeping on the street or in her ex-husband’s van
- Numerous examples of very poor judgment
- No impairments in memory, basic attention, language, or composing a detailed narrative
- 30/30 on MMSE
- Digit span 7F, 5B; 14 S words/minute; well-constructed clock
- Behaviorally, very inappropriate, labile affect
- No insight into her predicament
- Sensory-motor exam WNL
- Mother h/o progressive neuropsychiatric disorder; died in early 50s

Ferenczi et al., 2020; Chemali et al., 2010

PET Imaging
- Marked bilateral hypometabolic activity within the orbitofrontal cortex, extending to the cingulate gyrus and caudate bilaterally

Genetic Testing
- Mutation of the MAPT gene on Chromosome 17

Brain Pathology
- FTLD due to tauopathy

Diagnosis: Behavioral Variant Frontotemporal Dementia (bv-FTD)
Case

- A 64 yo highly educated woman presented with concerns about memory loss
  - Forgetting dates of planned events; but rapidly recalls information if cued
  - Difficulties with multi-tasking and problem solving
  - Handling family finances and meals, but unable to set up on-line banking and avoids new recipes
  - Social graces well maintained, empathic and caring
  - Acquaintances and most friends seem unaware of her difficulties

- Estimated IQ 122
- MMSE 25/30 (3 points memory; 1 point “world” backwards; 1 point exact date)
- Poor memory retrieval (e.g., CERAD delayed recall 4/10; Recognition 10/10)
- Impaired Executive Functions (very slow Trails B and Digit Symbol; poor phonemic fluency)
- Relatively intact visuospatial skills, language, motor speed
- Sensory-motor exam WNL
Insidiously progressive cognitive and functional decline

- Increasing word finding pauses; slowed processing speed
- Increasing apathy/disengagement
- Age 66: Unable to manage family $ 
- Age 68: began day program
- Age 71: died in a nursing home

- Pathology: NFTs and plaques in frontal, temporal, and parietal lobes, hippocampus, and amygdala (Alzheimer’s disease)

Case

- 72 yo R-handed home maker
- Brought to an ER in Boston by her family. They told the ER docs that she was acting like she had had a “frontal lobotomy”
- Physicians noted the patient was hyperglycemia and hypertensive
- Discharged from the ER on oral hypoglycemic agent and an antihypertensive medication
- Brought back to the ER by her family a few hours later for ongoing concerns about her inappropriate behavior and change in personality

Sandson et al., 1991

Sandson et al., 1991
Case

- 76 yo man with 14 years education
- H/o hypertension, DM, and high cholesterol, 50 pack years of smoking
- Progressive slowing of motor and cognitive responses. Forgetful, unable to multitask
- Onset 2-3 years ago. More rapid decline recently
- Needs assistance with iADLs
- Relatively poor judgment and decision-making skills
- Became delirious after recent surgical procedure

Subtle L facial palsy and pronator drift
- Slow finger-nose-finger testing
- Gait slow and mildly unsteady
- Cognitive testing revealed problems with speed of processing, executive control, activation/retrieval
- CERAD Word List Learning 4/10, 7/10, 8/10 over 3 trials. After delay, spontaneously recalled 2/10 words. 10/10 recognized with MC
- Word finding pauses. 14/15 on short form of Boston Naming Test. No other language deficits
- 16 animals/min; 8 F words/min
**Conditions Associated with Frontal Network Dysfunction**

- bvFTD
- Alzheimer’s Disease
- Vascular Dementia
- Lewy Body Disease (e.g., PDD)
- Tauopathies (e.g., PSP)
- Traumatic Brain Injury
- White matter disease (e.g., MS)
- Tumor/NPH
- CNS infections (e.g., HIV, Syphilis)
- Developmental disorders (e.g., ADHD)
- Normal cognitive aging
Theories of Normal Cognitive Aging

- Inhibitory Deficit Hypothesis (Hasher & Zacks 1988)
- Executive Deficit (Frontal Aging) Hypothesis (West 1996)
- Slowed Processing Speed Hypothesis (Salthouse 1996)
- Common Cause (Li and Lindenberger, 1999)

Frontal-Executive Systems – So What?

- Injury to frontal networks is observed in many different kinds of illnesses and disorders
- The underlying disorders are often common
- Disruption of frontal-executive functioning can lead to profound impairments in attention, cognition, personality and behavior
- We need to understand what operations and functions are carried out by different components of the frontal networks

Functions Attributed to the Frontal Lobes

- Judgment
- Foresight
- Insight
- Abstract Reasoning
- Self-Governance
- Perspective Taking
- Mental Flexibility
- Perseverance
- Curiosity
- Initiative and Drive
- Planning and Sequencing of Complex Behavior
- Delay of Gratification
- Inhibition of Inappropriate or Overlearned Behavior
- Context Appropriate Behavior
Frontal-subcortical Networks
Direct pathway (net excitatory)

- Frontal Lobe
- Striatum
- GPi/SNr
- Thalamus

Hyperdirect Pathway

- Frontal Lobe
- Striatum
- GPe
- STN
- GPe/SNr
- Thalamus

Indirect Pathways

Reactive and proactive inhibitory systems
Executive Control Functions

Complex set of cerebral processes that operate to exert top-down, volitional control over sensory input, cognition, emotion, and motor output, allowing individuals to carry out goal-directed behaviors.

The Frontal Lobe Team

- Dorsolateral PFC
- Ventrolateral PFC
- Anterior Cingulate Cortex
- Orbitofrontal Cortex
- Rostromedial PFC
- Frontoinsular Cortex
**The Executive Control Team**

- Keeping Task-Relevant Goals On-Line (Task-setting)
- Initiating (Starting) and Sustaining Activity (Energization)
- Anticipating and Monitoring Outcomes/Rewards
- Inhibiting (Stopping) Activity
- Predicting the mental states/responses of others
- Evaluating and responding to changes in salience

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**Frontal Anatomy**

- **Dorsolateral PFC**
- **Ventrolateral PFC**
- **Anterior Cingulate Cortex**
- **Orbitofrontal Cortex**
- **Rostromedial PFC**
- **Frontoinsular Cortex**

**Control Function**

- WM/ Goals-on-Line
- Initiating/ Sustaining
- Anticipation/ Monitoring
- Inhibition
- Social/Interpersonal
- Salience Integration

---

**Keeping Task-Relevant Goals On-Line (Task-setting/Processing Priorities)**

- Critical function of Working Memory
  - Holding on-line and manipulating internalized representations to guide future behavior
- Executive Control Network
  - Dorsolateral PFC
  - Posterior Parietal Cortex

---

Footnotes:

Baddeley, 1992; Goldman-Rakic, 1987; Miller et al., 2000; Owen et al., 2005; D'Esposito et al., 1998; Smith et al., 1996; Courtney et al., 1996; Wilson et al., 1993; D'Esposito et al., 1999; Petrides, 2000; Wagner et al., 2003; Rypma et al., 1999; Miller & Cohen, 2001; Mesulam, 2000.
Keeping Task-Relevant Goals On-Line
(Task-setting/Processing Priorities)

- Posterior – Anterior gradient in the lateral PFC
  - Posterior (closer to motor cortex) – immediate/less abstract tasks or actions
  - Anterior (towards the frontal pole) – more abstract, less temporally immediate tasks or action rules

Initiating and Sustaining Activity
(Energization)

- Purposeful, self-generated commencement and maintenance of an overt act or mental activity
- Anticipating the potential reward value of actions serves as the basis of motivating/energizing behavior
- Medial Prefrontal Cortex

Anticipating and Monitoring Outcomes/Rewards

- Decoding/anticipating the reward value of sensory signals, objects, and choices
- Orbital Frontal Cortex
Keeping track of a designated set of external or internal stimuli. Discrepancies from expectation are registered and can trigger additional processing and response.

- Dorsal Anterior Cingulate

Stroop Effect: Color/Word Tests

Instructions: print on card stock and cut each page into horizontal strips. See the Science Buddies project What Conflicting Mental Tasks Reveal About Thinking: The Stroop Effect for complete information.

Inhibiting (Stopping) Activity

- Suppression of a specific behavioral output, mental activity, or emotional response (usually an automatic, prepotent, or overlearned)
  - Lateral Prefrontal Cortex—cognitive
  - Orbitofrontal Cortex—emotional
  - Subcortical structures — critical modulatory role

Liddle et al., 2001; Kouider et al., 1998; Brown et al., 2000; Anderson et al., 2004; Wager et al., 2006; Knight et al., 1981; Davidson & Marrocco, J Neurophysiol., 2000; Ochsner, Bunge, Gross, & Gabrieli, J.Cogn Neurosci., 2002)
Understanding and predicting the mental states and responses of others

- Representations of the self
- Monitoring of one’s emotional states
- TOM (representations of the mental states and intentions of others)
  - TPJ, STS, TP, PCC
- Prosocial emotions (e.g., empathy, compassion, gratitude, reputation)
  - Reward system/ventral striatum, STS
- “Affect sharing”
  - TF, amygdala

Dissociation between preserved TOM/ Absent Affect Sharing

- Sociopaths
Dissociation between preserved TOM/ Absent Affect Sharing

- Sociopaths
- Some politicians
- Some politicians
- Most demagogues

Preserved Affect Sharing/ Impaired TOM

- Some patients with AD
- Some patients with ASD
Gateway to Social-Emotional Semantics

- Representations of social-emotional experience
- Stored knowledge underlying social rules and expectation

- R Temporal Lobe

Evaluating and responding to changes in salience

- Identifying the most homeostatically relevant stimuli through the rapid integration of sensory, visceral, autonomic, and hedonic signals

- Frontoinsular Cortex

Ventral attention network

Carbetta and Shuman, 2002
Sensory Input | Thought/Cognition | Emotion | Motor Output | Social/Interpersonal
---|---|---|---|---
Executive Control Functions | | | | |
Enhancement Deficits | | | | |
Inhibition Deficits | | | | |

Based on schema by Gazzaley & D'Esposito, 2007

Selective attention
• Facilitates processing of sensory input that is most relevant to task demands or behavioral goals
• Bases sensory processing on enhancement of neural activity in response to task relevant features and/or suppression of neural activity in response to task irrelevant ones

Reduced Ability to focus attention

Increased distractibility by task-irrelevant sensory input

Working Memory
• Control over the on-line content of internal thought
• Active maintenance of current processing priorities (task setting)
• Management of the execution of multiple cognitive operations and the shifting of mental sets

Inability to hold information or task priorities on-line

Loss of mental set

Poor planning and organization

Increased distractibility by task-irrelevant cognitive input
<table>
<thead>
<tr>
<th>Emotion/Motivation</th>
<th>Functions</th>
<th>Regulation of affective and motivational states</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initiation and sustaining of mental activity and engagement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mapping and integration of visceral, autonomic, and hedonic markers of experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Determination of affective weights/values of objects, actions, and potential outcomes</td>
</tr>
<tr>
<td>Enhancement Deficits</td>
<td>Apathy – motivational inability to carry out goal-directed behavior</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emotional blunting</td>
<td></td>
</tr>
<tr>
<td>Inhibition Deficits</td>
<td>Uninhibited behavior</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emotional lability</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor Output</th>
<th>Functions</th>
<th>Eye movements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reaching behaviors</td>
<td></td>
</tr>
<tr>
<td>Enhancement Deficits</td>
<td>Reduced ability to initiate movements</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impersistence</td>
<td></td>
</tr>
<tr>
<td>Inhibition Deficits</td>
<td>Impulsivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perseveration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Utilization Behavior</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impairments in motor sequencing</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social/Interpersonal</th>
<th>Functions</th>
<th>Representations of the self</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Representations of intentions of others</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitoring of emotional states of oneself and others</td>
</tr>
<tr>
<td>Deficits</td>
<td>Decreased self-monitoring awareness of one’s internal states</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inability to distinguish one’s own mental states from those of others (TOM impairment)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diminished capacity for “affect sharing”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Failures of empathy/compassion</td>
<td></td>
</tr>
</tbody>
</table>
**Frontal Anatomy**

Dorsolateral PFC  | WM/ Goals-on-Line
Ventrolateral PFC  | Initiating/ Sustaining
Anterior Cingulate Cortex  | Anticipation/ Monitoring
Orbitofrontal Cortex  | Inhibition
Rostromedial PFC  | Social/Interpersonal
Frontoinsular Cortex  | Salience Integration

**Conditions Impacting Different Components of Frontal Networks**

**Lateral PFC**
- Alzheimer Disease
- Normal aging

**Paralimbic PFC**
- COVID
- Traumatic Brain Injury

**Subcortical White Matter**
- Vascular Dementia
- Multiple Sclerosis
- HIV
- Normal aging

**Basal Ganglia**
- PD
- Huntington’s
- PSP
- Normal aging
Frontotemporal Dementias: Focus on Behavioral/Executive Variants

Bruce Miller, MD
Overview

- Modern subtyping – molecules, pathology and genes
- Non-medical interventions
  - Lifestyle influence on genetic FTD
  - Speech therapy on primary progressive aphasia
- Burden of caregiving
- bvFTD phenotype – empathy and emotion
- Treatment: Bluefield and Tau Consortiums
Models of Degenerative Dementia

All degenerative dementias have:

- Genetic and sporadic form
- Cell culture and animal model
- Preclinical, early symptomatic and symptomatic phase
- Abnormal protein aggregation
- Proteins spread from cell to cell

Network-based Neurodegeneration

Syndrome-Specific Regional Atrophy Patterns: Patients vs. Controls

Seeley et al Neuron 2009
Neuropathologic Inclusions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Inclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Aβ-42 &amp; tau</td>
</tr>
<tr>
<td>FTD/ALS</td>
<td>tau or TDP-43</td>
</tr>
<tr>
<td>PSP, CBD</td>
<td>tau</td>
</tr>
<tr>
<td>PD, DLB, MSA</td>
<td>α-synuclein</td>
</tr>
<tr>
<td>CJD</td>
<td>PrPsc</td>
</tr>
</tbody>
</table>

Frontotemporal Dementia (FTD)

- **Common** cause pre-senile dementia
  - 1:1 with AD 45–64 years (Ratnavalli, Hodges 2002),
    most common dementia <60 (Knopman 2004)
  - More common if ALS, PSP & CBD, CTE considered
- Also occurs after 70
  - 25% FTD over 65, late onset tau more common (SW Seo 2018)
FTD/ALS Linked: Gordian Knot

- Both are often preceded by psychiatric disorder
- Separating one from the other is “a trap and a snare”
- Trials should take advantage of the Gordian Knot
- Need joint efforts as part of a unified family devoted to curing a disease

3 Types Frontotemporal Dementia

- Behavioral Variant
  - Rarely genetic
  - Tau, TDP, FUS
  - ½ TDP

- Language Variants
  - Semantic Variant
  - Often genetic
  - Tau, TDP, FUS
  - 83% TDP-C
  - Nonfluent Variant
  - Some genetic
  - 85% Tau, TDP-A

Slide courtesy of Bill Seeley
Chronic Traumatic Encephalopathy/Tau

MRI: Frontoinsular Atrophy

Early FTD: Speckled TDP-43 Inclusions
VEN and Fork Cell TDP-43 Pathobiology in Pathologically Pure ALS (n = 4)

% of each cell type w/ TDP-43 abnormality

- VENs
- Fork cells
- L5 NNs
- L2-3 Ns

Three Main Genetic Mutations

- **MAPT**: 52 years, MRI symmetrical, bvFTD with parkinsonian syndromes, 1998 (tau aggregation), therapy: turn off or degrade tau
- **GRN**: 62 years, MRI asymmetric, bvFTD, PPA, PD, AD, 2006 (TDP A) haploinsufficient, therapy: replace PGRN
- **C9orf72**: 56 years, MRI symmetric, cerebellar involvement (subtler frontal involvement), bvFTD and ALS, 2011 (TDP B, dipeptides) (hexanucleotide repeat), therapy: turn off gene

Rohrer 2015
How Many Familial FTD Do You Follow?

ARTFL / LEFFFTDS Longitudinal FTLD (ALLFTD)
Why Go to South America?

- Incidence declining in high- and middle-income countries
- Dementia increase in South America
- South America 6% world’s population (422 million people)
- Big families
- New genes
- Explore socioeconomic status

US-South American Initiative for Genetic-Neural-Behavioral Interactions in Neurodegenerative Disease

Ibanez, Yokoyama, Possin, Nitrini, Custudio, Lopera, ........
Disease Progression in FTLD

GRN Increased Connectivity 4 Networks

Suzee Lee  Neuroimag Clin, 2019
Brain atrophy may be detected over 8 weeks in GRN mutation carriers

Asymptomatic Asymptomatic bvFTD MCI nfvPPA bvFTD

1–2% annualized decline

Sha et al., Alz & Dementia: 2017

Neurofilament Predicts State/Decline

Rojas 2019
Baseline NfL levels predict future decline in functional status and brain structure

NfL in Genetic Subtypes

Rojas 2019
Lifestyle Alter Cognitive Trajectory Genetic FTD?

Gene Carriers (n=54)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>48.4 (13.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, %F</td>
<td>46.3% (25)</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.2 (2.4)</td>
</tr>
<tr>
<td>Genotype (%, n)</td>
<td></td>
</tr>
<tr>
<td>C9orf72</td>
<td>38.9% (21)</td>
</tr>
<tr>
<td>GRN</td>
<td>20.4% (11)</td>
</tr>
<tr>
<td>MAPT</td>
<td>40.7% (22)</td>
</tr>
<tr>
<td>Visits (n, %)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>100% (54)</td>
</tr>
<tr>
<td>2</td>
<td>53.3% (74)</td>
</tr>
<tr>
<td>3</td>
<td>1.9% (1)</td>
</tr>
<tr>
<td>Years Followed (median, IQR)</td>
<td>1.01 (0, 1.08)</td>
</tr>
<tr>
<td>FTLD-CDR global (median, IQR)</td>
<td>0 (0, 0.5)</td>
</tr>
</tbody>
</table>

Self-reported Activities at Baseline
- Cognitive Activities (e.g., reading, concerts, museums)
- Physical Activities

Casaletto, et al Alz Demen 2020

Lifestyle Moderates Genetic FTD

*Adj. baseline frontotemporal volumes, age, sex, education, FTLD-CDR sum of boxes

Casaletto, et al 2020 Alz Demen
Retraining Speech Production Fluency nfvPPA

- **Treatment**: repeated rehearsal of scripts via structured treatment with a clinician and practice at home
- Significant improvement in production correct words for trained topics, reduced grammatical errors trained topics, increase intelligibility trained and untrained topics post-treatment
- Follow-up testing, maintenance of gains for trained scripts up to 1 year post-treatment

Henry et al. 2018

---

**Neurodegeneration Fiction & Fact**

1. Degenerative disorders begin with changes in cognition or movement
2. Psychiatric symptoms lack scientific relevance to dementia
3. Mood, anxiety, withdrawal are a reaction to the illness
4. Psychiatric symptoms in neurodegeneration irrelevant to typical psychiatric disorders

1. Most start with a psychiatric prodrome that is the key to early intervention
2. These symptoms are key to the understanding dementia
3. These changes reflects anatomy/chemistry of disease
4. They are the roadmap for understanding mood, emotion, psychosis, compulsions, etc.
International Research Criteria for bvFTD

1. Early (2–3 yrs) behavioral disinhibition
2. Early (2–3 yrs) apathy or inertia
3. Early (2–3 yrs) loss of emotional reactivity, sympathy & empathy
4. Perseverative, stereotyped or compulsive/ritualistic behavior
5. Hyperorality and dietary changes
6. FTD neuropsychological profile
7. Frontal or anterior temporal atrophy on MRI
8. Presence of known mutation
Medial Versus Lateral Orbital Cortex
+ monitoring reward value
+ punishers leading to change in behavior

Kringelbach & Rolls 2004 meta-analysis

The wife of a man with FTD explains why they no longer attend church.
Crime with Dementia

<table>
<thead>
<tr>
<th>Dx</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>545</td>
<td>7.7%</td>
</tr>
<tr>
<td>bvFTD</td>
<td>171</td>
<td>37.4%</td>
</tr>
<tr>
<td>svPPA</td>
<td>89</td>
<td>27%</td>
</tr>
<tr>
<td>HD</td>
<td>30</td>
<td>20%</td>
</tr>
<tr>
<td>MCI</td>
<td>243</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Liljegren & Naasan, Englund et al JAMA Neurol 2015; Lillegren JAMA 2019

Loss of Empathy

- R temporal pole
- R medial OFC
- R caudate
- R medial frontal
- Only right hemisphere mediates these empathy changes

Rankin et al. Brain 2006
Autonomic Deficits in bvFTD

Embarrassment Reactivity

Disgust Reactivity

Baseline Parasympathetic Activity

Baseline Sympathetic Activity

Sturm et al., 2006, 2008, 2012; Eckart et al., 2012; Woolley et al., 2015; Verstaen et al., 2016; Guo et al., 2016; Joshi et al., 2014

Parasympathetic Activity Drives Behavior

Higher heart rate variability associated with:
- Social engagement
- Empathy
- Emotion regulation
- Positive emotion
- Prosocial behavior
- Optimism and agreeableness

“Be kind whenever possible. It is always possible.”
- Dalai Lama
Relationship Turmoil and Empathy in FTD

- Marital dissolution and infidelity significantly greater in the bvFTD group than nfvPPA, svPPA, CBS, PSP, AD
- Across all patients, empathy loss was associated with marital dissolution
- bvFTD patients who experienced marital dissolution or infidelity had significantly lower empathy scores than those who did not

Brain Atrophy Caregiver Health

Caregiver Psychopathology
Caregiver Global Health

Patient Brain

Covariates:
- caregiver age and sex
- patient diagnosis, disease severity, cognitive functioning, head size
- MRI scanner field strength

Hua Dementia Geriatric Cognitive Disorder, 2019

Takeda et al, ADAD 2019
Neural Correlates Worse Caregiver Health

Hua, Wells, Haase, Chen, Rosen, Miller, Levenson 2019 Dementia and Geriatric Cognitive Disorders

Bluefield Research Consortium: GRN

Progranulin knockout and knock-in mice (Farese, Harvard)

Behavior (Roberson, UAB; Gan, UCSF)

Progranulin & granulin pathways (Gan, Kao UCSF)

High throughput screen (Herz & Gang, UTSW; Gan, Kao UCSF; Haggarty, Harvard)

Clinical/pathology/gene carrier (Sealey, Lee, Rosen, B Miller, UCSF; Van Swieten, Erasmus)

Skin/iPS/neuron (Farese; Ward NIH, Kao UCSF)

PGRN genetics (Rademakers, Mayo; Yokoyama, UCSF)

Lysosome (Ferguson, Yale; Farese & Walther, Harvard; Huang, UCSF)

Treatment trials (Boxer, Z Miller, Ljubenkov, Rojss, UCSF)
Kao et al., Nat Rev Neurosci 2017

Chronic Neuroinflammation Contributes Neurodegeneration
Loss PGRN activates innate immune cells

Ahmed et al., Am J Pathol 2010
Critical Role of Microglia and TNFα Signaling in Progranulin Deficient FTD

Ab Accumulation

PGRN-deficient microglia

Neuronal deficits & OCD-like behaviors

Minami et al., Nat. Med., 2014
Krabbe et al., PNAS, 2017

GRN Deficient FTD Exhibit OCD-like Behavior

Healthy Control

Positive

Negative (25)

GRN mutation Carriers

Negative (15)

Positive (20)

Simple stereotypies

8

8

6

3

Repetitive checking

Repetitive grooming

Collecting

David Perry, Bruce Miller, UCSF
Krabbe et al., PNAS, 2017
C1qa

Remove C1qa (Grn−/−; C1qa−/− Mice) Protects Synaptic Pruning, Restore Thalamic Microcircuit Function, Mitigate OCD-like Behaviors, Improves Survival

E Huang Lab in Cell

Virus-driven expression of progranulin rescues cellular deficits in Grn+/- mice

Arrant et al., 2017
Lysosome and Neurodegeneration

Lysosome cell’s digestive system:
Degrades:
• Proteins
• Lipids
• Nucleic Acids
• Bacteria
• Viruses

Disorders of Lysosome:
• Neuronal Ceroid Lipofuscinosis

Lysosomal Storage Features GRN Deficiency

- Homozygote GRN lysosomal storage disease neuronal ceroid lipofuscinosis (NCL)
  (Smith K 2012, Almeida M 2016)

- Heterozygous GRN mutation show NCL-like storage material in the CNS

M Ward et al., Sci Transl Med 2017
Rare Variant Enrichment $MFSD8$ FTLD Risk

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Gene</th>
<th>Variants Tested</th>
<th>FTLD MAC (% carriers)</th>
<th>Control MAC (% carriers)</th>
<th>SKAT-O $P_{\text{Raw}}$</th>
<th>SKAT-O $P_{\text{Bonf}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>$MFSD8$</td>
<td>9</td>
<td>4 (6.5%)</td>
<td>10 (0.4%)</td>
<td>$4.9 \times 10^{-6}$</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>$TEDC2$</td>
<td>9</td>
<td>6 (9.7%)</td>
<td>17 (0.7%)</td>
<td>$2.0 \times 10^{-5}$</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>$HAUS5$</td>
<td>18</td>
<td>7 (11%)</td>
<td>40 (1.5%)</td>
<td>$2.5 \times 10^{-5}$</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>$HSF5$</td>
<td>13</td>
<td>3 (4.8%)</td>
<td>15 (0.6%)</td>
<td>$3.4 \times 10^{-5}$</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>$TIAF1$</td>
<td>5</td>
<td>4 (6.5%)</td>
<td>12 (0.5%)</td>
<td>$5.5 \times 10^{-5}$</td>
<td>0.79</td>
</tr>
</tbody>
</table>

SNP, single nucleotide polymorphism; MAC, minor allele count.

Yokoyama, Acta Neuropathologica 2018

Lipid Storage, Homo versus Heterozygosity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Enzyme</th>
<th>Peripheral organs</th>
<th>Neuropsychiatric Features</th>
<th>Heterozygote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult neuronal ceroid lipofuscinosis</td>
<td>CLN1-8, PPT1 (progranulin recessive)</td>
<td>Granular osmiophilic deposits WBC, skin, neurons</td>
<td>Manic to dementia, retinopathy, seizures</td>
<td>FTD (progranulin)</td>
</tr>
<tr>
<td>Gaucher’s</td>
<td>Glucocerebrosidase</td>
<td>Liver spleen, bone marrow</td>
<td>Dementia, vertical gaze, parkinsonian</td>
<td>PD</td>
</tr>
<tr>
<td>Niemann-Pick-C</td>
<td>NPC-1, NPC-2 (transport protein)</td>
<td>Liver spleen</td>
<td>Schizophrenia-like, vertical gaze, parkinsonian, cerebellar ataxia</td>
<td>PD</td>
</tr>
<tr>
<td>Adult Tay-Sachs</td>
<td>Hexosaminidase A</td>
<td>—</td>
<td>Childhood disease, retinal. Early death</td>
<td>Low levels = adults have FTD/ALS, psychosis AD</td>
</tr>
<tr>
<td>Nasu-Hakola PLOSL</td>
<td>TREM-2 (recessive)</td>
<td>Bone cysts</td>
<td>FTD-syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DAP-12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Tau Consortium

Synthesis
(Bateman, Disney, Gan, Holtzman, Kao, T Miller)

Clearance
(Cuervo, Gestwicki, Haggarty, Rubinsztein)

Propagation
(Diamond, Duff, Goate, Han, Prusiner)

Models
(Mucke, Rubinsztein)

Stem cells
(Crary, Goate, Haggarty, Ichida, Kampmann, Kao, Karch, Temple)

Genomics
(Coppola, Geschwind, Goate, Lee, Yokoyama)

Biomarkers
(Geschwind, Grinberg, Kramer, Mathis, B Miller, Neylan, Rabinovici, Seeley, Steen, Nasdev, Walsh)

Treatments
(Arkin, Boxer, Cuervo, Diamond, Disney, Gan, Gestwicki, Haggarty, Kosik, Krichevsky, T Miller, Prusiner, Rubinsztein)

Pure Tauopathies vs. Mixed Tauopathy

- Mutations – bvFTD, nfvPPA, PSP, CBD
- Pick – bvFTD, nfvPPA
- CBD – bvFTD, nfvPPA, executive/motor
- PSP – falls, gaze, axial PD, dementia
- AD*
- CTE*
- Guam-PD-Dementia
- Postencephalitic Parkinson’s
- Niemann-Pick disease
Tau Spreads Like a Prion

Image courtesy of Marc Diamond

Functional Connectivity Dorsal Midbrain Tegmental Network & Tau PET in PSP

Coming Next

- Better diagnosis FTD
- New causal and risk genes (UCSF PPG, Ibanez SAC)
- Big grants (Boxer, Boeve & Rosen ALLFTD Genetics, Rohrer GENFI, Ibanez South American Initiative)
- Tau-lowering trials – small molecules, antibodies and CRISPR
- For TDP-43 subtypes
  - Anti-inflammatory compounds for svPPA
  - Progranulin-elevating therapies (AAV-delivery)
  - Genetic therapies silence gene in C9ORF72 (anti-oligonucleotides)

Psychiatric Syndromes

- Bipolar
- Antisocial personality
- Schizophrenia
- Borderline personality
- Schizoaffective disorder
- Depression
- Addictive
- Borderline
- Conversion
- Body dysmorphic disorder
- Schizotypal
- Schizoidal
Language Systems & Aphasia-predominant Dementia Syndromes

M-Marsel Mesulam, MD
NEUROFIBRILLARY TANGLES IN MILD AD

THIS TYPICAL PATTERN IS SEEN IN 95% OF AD PATHOLOGY
THE RESULTANT AMNESTIC DEMENTIA IS ALSO KNOWN AS THE DEMENTIA OF THE ALZHEIMER-TYPE (DAT)
FRONTOTEMPORAL LOBAR DEGENERATIONS (FTLD)

FOCAL NEURONAL LOSS WITH GLIOSIS \(\rightarrow\) (REGIONAL ATROPHY)

FTLD-TAU
- MAP-TAU
- CHR 17

FTLD-TDP
- PGRN
- CHR 17
IN CONTAST TO DEMENTIAS OF THE ALZHEIMER TYPE, MEMORY IS USUALLY PRESERVED.
SYNDROME OF PRIMARY PROGRESSIVE APHASIA (PPA)

a) Impaired usage or comprehension of words (i.e., aphasia)

b) The language disorder represents the principal deficit during the initial stages of the disease (i.e., primary)

c) The cause is a neurodegenerative disease (i.e., progressive)
73 yr Old Man With PPA
Longitudinal Neuropsychological Investigations in a PPA Patient Tested 6 and 9 years After Onset (M.K.)

Weintraub, Rubin & Mesulam, Archives of Neurology 1990.
Density of Abnormal TDP-43 Deposits
(Gliebus, Bigio, Caplan, Weintraub, Mesulam, Geula, Neurology, 2010)
FREQUENCY OF LEARNING DISABILITY IN 699 SUBJECTS

AGRammatic
(PPA-G)
- low fluency of word output
- distorted syntax
- good comprehension

MOSTLY
FTLD-TAU
(≈20% AD)

Semantic
(PPA-S)
- high but aberrant fluency
- poor comprehension
- severe anomia

MOSTLY
FTLD-TDP
(≈20% AD)

logopenic
(PPA-L)
- variable fluency
- word-finding hesitations
- disrupted repetition
- good comprehension

MOSTLY
AD
(≈40% FTLD)

(Mesulam, Wiencke, Rogalski, Cobia, Thompson, Weintraub- Arch Neurol, 2009)
HOW TO TELL IF PPA IS CAUSED BY FTLD OR AD?

• APOLIPOPROTEIN E – not useful
• F18-2DG PET METABOLISM – not useful
• CSF TAU AND AMYLOID - promising
• PET AMYLOID IMAGING – most informative if negative
TREATMENT IN PPA?

- Bromocriptine - no
- Memantine - no
- Anticholinesterases – maybe in PPA-L
- Lithium for PPA-G?
- Intraspinal ethanercept, omental transplant, steroids
- Speech therapy - initially yes
- SSRI for depression
- Psychosocial interventions
- Promote neural plasticity?
Welcome to the International PPA Connection
This site offers resources and support for patients and family members. It also provides a central location to support and disseminate international collaborative research on PPA, helping clinicians and researchers to better help patients.

What is PPA?
PPA (Primary Progressive Aphasia) is a clinical syndrome that is diagnosed when the following features are present:

- A disorder of spoken or written language (i.e., aphasia)
- The aphasia is caused by a degenerative brain disease (i.e., progressive)
- The aphasia is initially the most salient feature and the chief cause of daily living limitations (i.e., primary)

Frequently Asked Questions about PPA
Detailed Diagnostic Criteria for PPA

88 investigators from 21 countries have registered 260 patients
THE ANATOMY OF THREE DEMENTIAS

• THE CLINICAL PICTURE IS DETERMINED BY ANATOMY.
• ACCURATE CLINICAL DIAGNOSIS HELPS TO PREDICT PROBABLE NEUROPATHOLOGY.
• KNOWING THE NEUROPATHOLOGY IS ESSENTIAL FOR RATIONAL TREATMENT.
Vascular Cognitive Impairment

Charles DeCarli, MD
Victor and Genevieve Orsi Chair in Alzheimer’s Research
Director
Alzheimer’s Disease Center
University of California at Davis

Disclosure

● Consultant to Novartis on a safety trial for heart failure
Overview

● Introduction
  • Revised concept of dementia pathophysiology
  • Concept of vascular cognitive impairment

● Clinical Phenotypes
  • Clinical criteria
  • Imaging
  • Clinical pathological correlation
  • Vascular disease and cognition in “normal” older individuals

● Conclusion

Heterogeneous Pathology of Dementia

Kapasi, et al., Acta Neuropathologica, 2017
Combinations of Disease Associated with Dementia

Boyle et al. Annals of Neurology, 2018

Future Risk of Stroke or Dementia at Age 65

Concept of Vascular Disease in Dementia

Vascular dementia: Diagnostic criteria for research studies

Report of the NINDS-AIREN International Workshop*

G.C. Román, MD; T.K. Tatemiuchi, MD; T. Erkinjuntti, MD; J.L. Cummings, MD; J.C. Masefield, MD; J.H. Garcia, MD; L. Amaducci, MD; J.-M. Oggogolo, MD; A. Brun, MD; A. Hofman, MD, PhD; D.M. Mold, MD; M.D. O'Brien, MD; T. Yumaguchi, MD; J. Grifman, PhD; B.P. Drayer, MD; D.A. Bennett, MD; M. Fisher, MD; J. Ogata, MD; E. Kato, MD; F. Bermejo, MD; P.A. Wolf, MD; P.B. Gorelick, MD; K.L. Bick, PhD; A.K. Pajewski, MD; M.A. Bell, DPhil; C. DeCarli, MD; A. Columbus, MD; A.D. Korczyn, MD; J. Bogousslavsky, MD; A. Hartmann, MD; and P. Scheinberg, MD

Vascular cognitive impairment

Defining Vascular Cognitive Impairment

- All deficits from mild cognitive impairment to dementia of vascular origin
Definition of Dementia

- Decline in cognitive function from previously attained level sufficient to affect activities of daily living
- Must be based on cognitive testing of at least 4 cognitive domains
  - 2 or more must be affected
- Deficits in ADLs must be independent of motor/sensory impairments due to vascular event

Probable VaD

- There is cognitive impairment and imaging evidence of CVD and
  - Clear temporal relationship
  - There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical CVD pathology (eg, as in CADASIL)
- No history of gradually progressive cognitive deficits before or after stroke to suggest neurodegenerative disorder
Possible VaD

- No clear temporal relationship between stroke and cognitive decline
- Lacking brain imaging evidence of CVD
- Aphasia
  - If documented normal ability before stroke, and dementia criteria afterwards, then probable VaD diagnosis still can be made
- Absence of neurodegeneration or other diseases that might affect cognition

Clinical Subtypes of Vascular Dementia

- Multi-infarct dementia
  - Large complete infarcts in cortex, subcortical areas
- Strategic Infarct dementia
  - Single infarct in functionally critical areas: angular gyrus, thalamus, PCA territory, ACA territory
- Subcortical Ischemic Vascular dementia
  - Lacunar state
  -Binswanger’s disease
  - Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
  - Cerebral Amyloid Angiopathy

Román, Clinical Forms of Vascular Dementia, 2005
Clinical Features of Vascular Dementia

- **Infarct Dementias**
  - Sudden onset, stepwise course, temporal association with stroke
- **SIVD**
  - Slowly progressive ‘cognitive-motor’ syndrome that may or may not be accompanied by symptoms of stroke, but accompanied by evidence of vascular brain injury by imaging

Neurological Signs of Vascular Dementia

- **Cognitive**
  - Focal Cortical syndromes
  - Executive dysfunction, slowed processing
  - Memory impairment, encoding > retrieval
- **Motor**
  - Focal cortical impairments
    - Hemiplegia, hemianopsia etc
  - Pseudobulbar palsy
  - ‘Frontal’ extrapyramidal signs
“There are no generally accepted for post-mortem assessment in cases of suspected vascular cognitive impairment”

Study Design

- 113 subjects with low-likelihood AD by current criteria
- 64 cognitively normal, 48 cognitively impaired
- A priori definition of CVD measures
- Multiple raters
- Sophisticated statistical analyses
Pathological Criteria for VCI

Relevant pathologic features of VaD

- **Pure VaD**
  - Multiple lacunes >4
  - Large cortical infarcts
  - Multiple small cortical infarcts

- **Mixed**
  - Extensive leukoencephalopathy with lacunes
  - Large cortical infarcts
  - Small cortical infarcts >1
  - Multiple lacunes >2

Knopman et al, Arch Neurol, 2003
Relevant diagnostic features of VaD

- Temporal link between stroke and onset of dementia (within 3 months)
  - 43% Sens, 92% Spec, PPR: 5.7
- Bilateral gray matter infarctions of cortex, thalamus or basal ganglia
  - 35% Sens, 92% Spec, PPR: 4.6
- Either of above
  - 65% Sens, 86% Spec, PPR: 4.8

Summary

- The phenotype of VCI is complex
  - Clinical stroke
  - Specific motor signs
  - Specific cognitive syndromes
- AD phenotype does not exclude VCI
Imaging of Vascular Dementia

- Large Cortical, subcortical complete infarctions
- Small strategic infarctions
- Multiple lacunes
- White matter hyperintensities
- Cerebral Atrophy
  - May include hippocampal atrophy

Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration

A word about WMH and Silent Infarcts

Moderate WMH

Extensive WMH

Silent MRI Infarct

Dementia Risk with MRI Vascular Measures

Debette et al, Stroke, 2010
Identification of pure subcortical vascular dementia using $^{11}$C-Pittsburgh compound B


*Neurology* 2011:77:18; Published online before print May 18, 2011.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic, clinical, and MRI characteristics of PiB + and PiB – patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total SIVD (N = 44)</td>
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<tr>
<td>MF</td>
<td>1.9 ± 1.6</td>
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<tr>
<td>Age, y</td>
<td>74.6 ± 7.0</td>
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<tr>
<td>Disease duration, y</td>
<td>5.4 ± 2.5</td>
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<tr>
<td>Education, y</td>
<td>9.1 ± 5.0</td>
</tr>
<tr>
<td>Risk factors, %</td>
<td></td>
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<tr>
<td>DM</td>
<td>25.3</td>
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<tr>
<td>HTN</td>
<td>67.8</td>
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<tr>
<td>Previous stroke</td>
<td>43.9</td>
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<tr>
<td>Hypotension</td>
<td>43.9</td>
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<tr>
<td>Cardiac disease</td>
<td>19.5</td>
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</table>

PiB in SIVD

A. PiB negative

B. PiB positive
Cognitive Testing

<table>
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<tr>
<th>Neuropsychological tests</th>
<th>Total (n = 45)</th>
<th>PiB+ (n = 14)</th>
<th>PiB− (n = 31)</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVLT immediate recall</td>
<td>12.0 ± 4.9</td>
<td>8.2 ± 4.1</td>
<td>13.7 ± 4.4</td>
<td>&lt;0.001(<em>) 0.006(</em>)</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>1.0 ± 2.1</td>
<td>0.1 ± 0.4</td>
<td>2.2 ± 2.3</td>
<td>&lt;0.001(<em>) 0.019(</em>)</td>
</tr>
<tr>
<td>Recognition</td>
<td>17.3 ± 3.1</td>
<td>15.2 ± 3.4</td>
<td>18.3 ± 2.5</td>
<td>0.001(<em>) 0.006(</em>)</td>
</tr>
<tr>
<td>RCFT immediate recall</td>
<td>41 ± 4.5</td>
<td>10 ± 1.9</td>
<td>50 ± 4.7</td>
<td>&lt;0.001(<em>) 0.028(</em>)</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>3.1 ± 4.0</td>
<td>0.5 ± 0.9</td>
<td>4.3 ± 4.4</td>
<td>&lt;0.001(<em>) 0.034(</em>)</td>
</tr>
<tr>
<td>Recognition</td>
<td>15.9 ± 3.3</td>
<td>14.4 ± 3.8</td>
<td>16.6 ± 2.9</td>
<td>0.044 0.06</td>
</tr>
</tbody>
</table>

Association Between WMH volume and PiB Index
Summary

- Imaging features of vascular brain injury are becoming better described
  - WMH and SBI are intermediate biomarkers of subtle vascular injury
- The presence of amyloid DOES NOT exclude VCI
Example of Clinically probable VaD with stroke

HPI and PMHx

69 year old gentleman with history of TIA in 1990 and 1994. TIA included loss of vision in the left eye and right sided weakness. After the second TIA, the patient had a change in behavior in which he excessively spent savings leading to substantial debt. His wife subsequently took over the finances. He was also significantly more fatigued after the second TIA and is less physically active. Wife believes patient was depressed.

Approximately 6-8 months ago, the wife noted problems with memory, particularly recollection of conversations and confusion regarding the time.

PMH Diabetes with complications of peripheral neuropathy, neurogenic bladder, diabetic nephropathy, and severe peripheral vascular disease. He also has hypertension, hypercholesterolemia, coronary artery disease with angina, an abdominal aortic aneurysm and is status post bilateral iliac bypass and bilateral carotid endarterectomy surgery.

Medications include atenolol, amlodipine, fosinopril, isosorbide, atorvastatin, gemfibrozil, ntirofurantoin, insulin.
Neurological Examination

- Mini Mental Status Examination Score  28/30
- Mild right hemiparesis with reduced sensation on the right
1 year later….

The patient returns. His wife now notes that he’s having trouble with short-term memory. Five months ago he had a new myocardial infarction and underwent coronary artery bypass grafting and repeat left carotid endarterectomy.

On neurological examination: No change except memory 0/3 items at 1 minute.

10 months later……

The patient experienced a new stroke with left hemiparesis, associated with step-wise decline in cognitive ability. He is now repetitive and easily confused. He occasionally has trouble recognizing friends and relatives. There is some emotional lability.

Neurological examination: MMSE=24/30, new left hemiparesis with difficulty walking.

The patient died, and an autopsy was performed.
Temporal lobe, infarct, 20x
Temporal lobe infarct, 100X

Hippocampus, normal aging, rare tangles, 200X
NEUROPATHOLOGIC DIAGNOSIS

- MULTIPLE LARGE OLD CEREBRAL INFARCTS, CHIEFLY IN THE RIGHT MIDDLE CEREBRAL ARTERY DISTRIBUTION WITH SECONDARY DESCENDING MOTOR PATHWAY DEGENERATION
- CEREBRAL ATHEROSCLEROSIS AND ARTERIOSCLEROSIS, MODERATE TO SEVERE
- NORMAL AGING CHANGES (BRAAK AND BRAAK STAGE I), WITHOUT NEURITIC OR DIFFUSE PLAQUES

Example of Clinically Probable VaD with severe subcortical disease
Initial Evaluation

● 78 y.o. Rt. Handed Male
  ◆ Memory decline starting ~2003.
  ◆ 2005- Mild problems with language; including comprehension
  ◆ 2000- CVA- dragging L foot; stroke dx’d.
    Residual L hemiparesis and L arm dysaethesias

● Concerns regarding driving- since 2003- not staying in his lane, drifting towards incoming traffic. Not getting lost.

● Chronic problems with irritability and anger. Hx of depression, personality problems.

Initial Evaluation (cont’d)

● Late 2004-
  ◆ hands ‘shaking’, difficulty with yard work and painting
  ◆ Hx falls and minor incontinence for a couple of yrs. Cane for 5 yrs, occasional walker

● Recent difficulties with organization and taking medications
  ◆ Can handle money and operate home appliances

● MMSE= 26 (06/2005) → 25 (4/2006); started on Aricept (5 mg), ‘MCI vs. mild dementia?’, increased to 10 mg (8/2006).
Initial Evaluation

- **PMH**: CVA 2000, mild hypertension increased cholesterol
- **Meds**: amitriptyline (25 mg), Gabapentin (800 TiD), HCTZ, Simvastatin
- **SH**: retired mechanic, 12 yrs. Educ., Smoked 100 pkyrs then quit in 2002, no current ETOH
- **FH**: Mother had LO-AD

Physical Exam (IE)

- **PE**: Cor- frequent PVCs. Ext- decreased pulses in the LEs.
- **Neuro Exam**:
  - MMSE = 29/30 (-1 season) BIMC = 32/33
  - CNS: decreased sensation lower L face, decreased hearing bilaterally
  - Motor: slightly spastic L arm; decrease in strength L arm and leg; L intention tremor; decreased RAMs on L more than R.
  - DTRS: 3+ L KJ; 2+ R side except absent AJs bilaterally; L plantar responses equivocal.
  - No Frontal Release Signs.
Consensus Diagnosis

● Multi-domain amnestic MCI; vascular etiology likely, AD somewhat likely

1 year later....

● No decline in cognitive function
  ◆ Wears pad for some urinary incontinence, No bowel incont.
  ◆ Wife continues to dispense meds
  ◆ Mood ‘good’, but occasionally ‘crabby’, sleeps 12 hrs/night
  ◆ Uses a cane ‘to support knees’
  ◆ No longer drives, but has license
  ◆ No difficulty with basic ADL’s
  ◆ Goes to church, bowls weekly (scores ~ 135), watches TV, plays dominoes
1 year later...

- **Neuro Exam:**
  - MMSE = 26 (-1 year, day, date, place)
  - STM: 2/5 on name and address → 4/5 with cue
    - 1.5/3 nonsense shapes after delay, intact recognition
  - Motor: slight L arm spasticity, strength 5- R side; L WE, BC, TC 4+; deltoid 4; FE, FF 4-; L leg 4+ except dorsiflexors and plantar flexors 5-; RAMs moderately reduced on L, mildly reduced on R; No limb ataxia, Couldn’t do HTS on L.
  - DTRs: 2 upper extremities and sym., 2+ KJs, trace AJs. L toe equivocal.

Additional F/U visits

- 2 years later...
  - MMSE 24/30 & BDS 23/33
- 5 years later...
  - MMSE 16/30 & BDS 13/33
  - CDR = 2
End-of-life History

- Died 05/22/2010
  - Due to Pulmonary embolism.
  - No Hx of additional strokes.

MRI Results
MRI Results

PiB Imaging
GROSS BRAIN EXAM

- Brain weight (fixed): 1333 grams.
- Moderate to severe atherosclerosis of the circle of Willis.
- Bilateral and multifocal cystic, non-cavitary, and lacunar infarcts in subcortical white matter and basal ganglia.
- Old lacunar infarct – basis pontis.
NEUROPATHOLOGIC DIAGNOSIS

- Cerebrovascular disease:
  - Atherosclerosis, moderately severe in major branches of the circle of Willis, extending focally into many leptomeningeal arteries
  - Arteriolosclerosis/ lipohyalinosis, variably severe throughout the brain, in many parenchymal arteries
  - Vascular calcinosis, severe and extensive, in ganglionic arteries
NEUROPATHOLOGIC DIAGNOSIS

- Alzheimer’s disease changes, Braak stage III:
  - Neurofibrillary tangles confined to the hippocampi/parahippocampal regions
  - Senile plaques, sparse to moderate, in cortex and hippocampi
  - No amyloid angiopathy

FINAL COMMENTS

- The preponderance of neuropathologic change in this brain is related to sequelae of cerebrovascular disease.
- The degree of “Alzheimerization” is relatively modest.
**Strategic Infarct--Thalamus**

Neuropsychology
- Memory
  - Intact to severely impaired
- Executive
  - Generally impaired

**Gerstmann’s Syndrome**

Finger agnosia
Right/left confusion
Dyscalculia
+/- Language impairment
Summary

- Vascular brain injury affects cognition in a variety of ways that include clinical phenotypes which overlap with AD
- Emphasis is on identifying and estimating vascular injury sufficient to impair cognition even in the absence of AD or other brain pathologies

Treatment

- Identification of Risk Factors
  - Common: Hypertension, diabetes, hypercholesterolemia, atrial fibrillation (intermittent)
  - Less Common: OSA, CHF, elevated homocysteine

- Diagnostics
  - Labs
  - 24 hour BP monitoring/ECG
  - Sleep study
  - Echo
  - CT angiogram
Treatment Continued

- Secondary Stroke Treatment is indicated even if vascular disease is asymptomatic
  - Aspirin or other antiplatelet (if indicated)
  - Statin
  - Anticoagulation (if indicated)
- Ideal Control of Vascular risk Factors
The American Heart Association Life's Simple 7 and Incident Cognitive Impairment: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study
Evan L. Thacker, PhD; Sarah R. Gillett, PhD; Virginia G. Wadley, PhD; Frederick W. Unverzagt, PhD; Suzanne E. Judd, PhD; Leslie A. McClure, PhD; Virginia J. Howard, PhD; Mary Cushman, MD, MSc

Study Design

- **17,761 Individuals > 45 years of age**
  - Free of Stroke and Dementia
- **Study Duration: 2003-2012**
- **Biennial Assessment of Cognition**
  - Word list immediate and delayed recall
  - Animal fluency
Definition of Impairment

- Less than 1.5 sd of mean based on age, race, gender and education
- Must have 2 or more of the 3 test components at this level

Impact on Cognition

![Impact on Cognition Chart](chart.png)

- Percentage impaired
- Overall
- Whites
- African Americans
- 0-6 Pts
- 7-8 Pts
- 9-14 Pts
Association of Ideal Cardiovascular Health With Vascular Brain Injury and Incident Dementia

Matthew P. Pase, PhD; Alexa Beiser, PhD; Danielle Enserro, MA; Vanessa Xanthakis, PhD; Hugo Aparicio, MD; Claudia L. Satizabal, PhD; Jayandra J. Himali, PhD; Carlos S. Kase, MD; Ramachandran S. Vasan, MD; Charles DeCarli, MD; Sudha Seshadri, MD

Impact on Cognition and Brain

<table>
<thead>
<tr>
<th>Measures</th>
<th>Recent Ideal CVH</th>
<th>Remote Ideal CVH</th>
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<tr>
<td></td>
<td>(\beta\pm SE)</td>
<td>(P\text{Value})</td>
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<tr>
<td>Cognitive decline</td>
<td></td>
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<tr>
<td>Global decline</td>
<td>0.003\pm0.002</td>
<td>0.07</td>
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<tr>
<td>Visual reproductions delayed</td>
<td>0.02\pm0.01</td>
<td>0.01</td>
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<tr>
<td>Similarities</td>
<td>0.02\pm0.01</td>
<td>0.04</td>
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<tr>
<td>Trail A</td>
<td>0.001\pm0.002</td>
<td>0.46</td>
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<tr>
<td>Trail B</td>
<td>–0.01\pm0.004</td>
<td>0.13</td>
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<tr>
<td>Logical Memory Delayed</td>
<td>–0.01\pm0.01</td>
<td>0.51</td>
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<tr>
<td>Brain atrophy and white-matter injury</td>
<td></td>
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<tr>
<td>Total brain volume</td>
<td>0.09\pm0.08</td>
<td>0.26</td>
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<tr>
<td>Frontal brain volume</td>
<td>0.31\pm0.10</td>
<td>0.003</td>
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<tr>
<td>Lateral ventricular volume</td>
<td>0.02\pm0.01</td>
<td>0.10</td>
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<tr>
<td>WMHV</td>
<td>–0.0002\pm0.01</td>
<td>0.98</td>
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**Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia**

A Randomized Clinical Trial

The SPRINT MIND Investigators for the SPRINT Research Group

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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Treatment Group</th>
<th>Intensive</th>
<th>Standard</th>
<th>Hazard Ratio (95% CI)*</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td>No. With Outcome/Person-Years</td>
<td>Cases per 1000 Person-Years</td>
<td>No. With Outcome/Person-Years</td>
<td>Cases per 1000 Person-Years</td>
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<tr>
<td>Probable dementia</td>
<td>149/20 569</td>
<td>7.2</td>
<td>176/20 378</td>
<td>8.6</td>
<td>0.83 (0.67-1.04)</td>
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<td>Mild cognitive impairment</td>
<td>287/19 690</td>
<td>14.6</td>
<td>353/19 281</td>
<td>18.3</td>
<td>0.81 (0.69-0.95)</td>
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<td>Composite of mild cognitive impairment or probable dementia</td>
<td>402/19 873</td>
<td>20.2</td>
<td>469/19 488</td>
<td>24.1</td>
<td>0.85 (0.74-0.97)</td>
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**Time Course of Effectiveness**

![Cumulative incidence graph showing the time course of effectiveness between Standard and Intensive treatments.](chart.png)

- **Trial phase**
- **Trial and cohort phase**
- **Cohort phase**

<table>
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<tr>
<th>Follow-up, y</th>
<th>No. at risk Standard treatment</th>
<th>No. at risk Intensive treatment</th>
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<td>87</td>
<td>93</td>
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<tr>
<td>8</td>
<td>0</td>
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</table>
Effect of Potential Treatment Risk Factors

- Results not influenced by
  - Age > 75
  - Sex
  - Race (Black v White)
  - Cardiovascular disease History
  - Chronic Kidney Disease
  - Baseline systolic Blood Pressure
  - Presence of Orthostatic Hypotension

Conclusions

- Cerebrovascular brain injury is common to older individuals
- The goal in treatment:
  - Identify the extent and risk factors that may contribute to progressive vascular brain injury
  - Mitigate further injury through
    - Ideal risk factor control
    - Secondary stroke treatment
Lewy Body Disease and Parkinsonian Dementias

James E. Galvin, MD, MPH
The Parkinsonian Dementias

James E. Galvin, MD, MPH
Professor of Neurology
Director, Comprehensive Center for Brain Health
Director, Lewy Body Dementia Research Center of Excellence
University of Miami Miller School of Medicine

Topics

• Lewy Body Dementias/Synucleinopathies
  • Dementia with Lewy Bodies
  • Parkinson's Disease Dementia
  • Mild Cognitive Impairment subtypes

• Tauopathies
  • Progressive Supranuclear Palsy
  • Corticobasal Degeneration
The Most Common Disease You Never Heard Of

- 2\textsuperscript{nd} most common cause of dementia after AD
  - Causes 10-12\% of irreversible dementia
- Includes Dementia with Lewy Bodies (DLB) and Parkinson’s Disease Dementia (PDD)
  - PDD: Movement Disorder begins 1\textsuperscript{st}, at least 2 years before cognitive
  - DLB: Any other pattern
- At least 75\% of PD patients who live 10 years will develop dementia
- More common in men
- May have faster decline than AD
- The combined sum of patients Lewy body dementia is estimated at 1.4 million
- Often significant delay to diagnosis and treatment
  - Commonly misdiagnosed as late-onset psychiatric disorder

Lewy Body Dementia Association (LBDA.org)

Parkinson’s Disease

UK Parkinson’s Disease Society Diagnostic Criteria

- **Step 1** Diagnosis of Parkinsonism
  - Bradykinesia
  - At least one of following:
    - muscular rigidity
    - 4-6 Hz resting tremor
    - postural instability
- **Step 2** Exclusion Criteria for PD
  - Parkinsonism due to other cause
  - Oculogyric crises
  - Sustained remissions
  - Supranuclear gaze palsy
  - Cerebellar signs
  - Early severe autonomic insufficiency
  - *Early dementia*
  - Poor response to L-dopa

- **Step 3** Supportive Criteria for PD
  - Three or more of following:
    - Unilateral onset
    - Resting tremor
    - Progressive signs and symptoms
    - Persistent asymmetry
    - Excellent early response to L-dopa with persistence \(\geq 5\) yrs
    - L-dopa induced dyskinesia
    - Clinical course \(\geq 10\) years

*J Neurol Neurosurg Psychiatry* (1992) 55:181
Historical Perspective

• “the senses and intellect being unaffected”
  • James Parkinson, 1817
• Described changes in cognition and personality
  • Jean-Marie Charcot 1888
• “Parkinsonism is not necessarily accompanied by any mental change, and the sufferer’s intellectually capacity...may continue unimpaired behind the mask in which his disorder fixes his features”
  • Lord Brain, 1933


Parkinson Disease Dementia

• Develops in the context of established PD
  – At least 2 years after a diagnosis of PD
  – Impairment in more than one cognitive domain
    • Attention, executive, visuospatial, memory, language
  – Decline from premorbid level
  – Deficits severe enough to impair daily life
• Exclusion of other dementias
• MMSE below 26 or Impairment in at least two of the following:
  • Months reversed or Seven backward
  • Lexical (category) fluency or Clock drawing
  • MMSE Pentagons
  • 3-Word recall
• Supportive features: apathy, depression, delusions, or daytime sleepiness.

DLB Criteria

Revised criteria for the clinical diagnosis of probable and possible DLB

**Essential** for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

### Core clinical features (the first 3 typically occur early and may persist throughout the course)
- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations that are typically well-formed and detailed
- REM sleep behaviour disorder, which may precede cognitive decline
- One or more spontaneous cardinal features of parkinsonism: bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity

### Supportive clinical features
- Severe sensitivity to antipsychotic agents
- Postural instability
- Repeated falls
- Syncope or other transient episodes of unresponsiveness
- Hypersomnia
- Hyposmia
- Severe autonomic dysfunction, eg, constipation, orthostatic hypotension, urinary incontinence
- Hallucinations in other modalities
- Systematized delusions
- Apathy, anxiety, and depression

---

**DLB Criteria: Biomarkers**

- **Indicative Biomarkers**
  - Reduced dopamine transporter uptake in basal ganglia by PET or SPECT
  - Abnormal (low) uptake MIBG myocardial scintigraphy
  - Polysomnographic confirmation of REM sleep without atonia

- **Supportive Biomarkers**
  - Relative preservation of medial temporal lobe structures on MRI/CT
  - Generalized low uptake on SPECT/PET with reduced occipital activity +/- cingulate island sign on FDG-PET
  - Prominent posterior slow wave activity on EEG

McKeith et al, Neurology (2017)
First pathological description

“A 69 year old white male was hospitalized...in the 12 months before admission, the patient’s daughter noted a gradual mental deterioration...examination described a well-developed white male actively hallucinating and disoriented in all spheres...the patient’s mental status continued to deteriorate. Rigidity in flexion of all extremities developed during hospitalization...

Microscopically, the outstanding finding was the presence of circumscribed, polychromatophillic, argentophillic, intracytoplasmic ganglionic structures surrounded by more or less well-defined halos. The bodies were usually oval or circular, but rarely of irregular contours... The(se) inclusions, when observed in cerebral cortex were identical to those noted in other locations except for the absence of definite cores... no morphological or histochemical distinction could be established between these bodies and those commonly associated with paralysis agitans (i.e. the Lewy body).”

Okasakı et al JNEN 12:217-244 (1961)

First Clinical Description

“A 66 year old man...complaining of shaking of his hands for several months...there was typical parkinsonian tremor, cogwheeling rigidity...he began to have visual hallucinations, telling his wife he saw ‘midgets’... he seemed confused for about an hour...His confusion increased and he confabulated...He remained alert but confused until...he became stuporous...eighteen days following the initial confusion and hallucinations, he began to improve...until his death four months later, remained profoundly demented”

Wolff S. Arch Neurol (1973)
Quickie Review of Things Associated With DLB

Movement Problems
- Bradykinesia
- Rigidity
- Postural instability with repeated falls
- Slow, shuffling gait
- Myoclonus
- Rare rest tremor but may have postural or action tremor

Cognitive Problems
- Visual tracking and attention
- Visual-spatial and perceptual
- Verbal and motor initiation
- Clock drawing and block design (construction)
- Timed attention tasks
- Executive tasks

Psychiatric/Behavioral Problems
- Visual Hallucinations
- Hallucination in other modalities
- Delusions
- Depression
- Anxiety
- Apathy
- REM Sleep behavior disorder
- Cognitive fluctuations

Autonomic/Constitutional Problems
- Loss of Smell
- Constipation
- Urinary incontinence
- Drooling
- Runny nose
- Dizziness and lightheaded
- Abnormal sweating
- Sexual dysfunction
- Oily flaky skin
Simple Hallucinations in LBD

• Sense of presence
  • Sensation that someone is looking over your shoulder
  • Deceased relative, animal

• Passage
  • Seeing something pass sideways in the peripheral of vision
  • People, previously owned pet
  • Shadows

• Illusions
  • Misperception based on actual objects
  • Seeing a person when there is a coat on a hanger
  • Images emerging from wall paper

Complex Hallucinations in LBD

• Predominantly visual in nature
  • Occur early in the course of the disease
  • May not be frightening to patients
  • Typically of little people, children, or furry animals
  • May or may not have an auditory component
  • Complex in nature

• Auditory (hear)
• Olfactory (smell)
• Gustatory (taste)
• Tactile (feel)
Common Delusions in LBD

- Capgras
  - Familiar people are thought to be identical or near-identical imposters
- Fregoli
  - Familiar people are thought to be disguised as strangers
- Othello
  - Jealousy – usually spousal infidelity
- Cotard
  - Belief that one does not actually exist or is dead
- Reduplicative paramnesia
  - A place simultaneously exist in two or more physical locations
- Mirrored self-identification
  - Not recognizing self in mirror
- Ekboim
  - Infestation by insects or parasites
- Diogenes
  - Self-neglect, domestic squalor

Frequency of Core and Supportive Features

<table>
<thead>
<tr>
<th>Characteristic (%)</th>
<th>Likelihood of LBD</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Possible</td>
<td>Probable</td>
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<tr>
<td>Parkinsonism</td>
<td>8.3</td>
<td>53.8</td>
<td>100</td>
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<tr>
<td>Bradykinesia</td>
<td>12.5</td>
<td>61.5</td>
<td>100</td>
</tr>
<tr>
<td>Rigidity</td>
<td>0</td>
<td>7.7</td>
<td>100</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
<td>7.7</td>
<td>33.3</td>
</tr>
<tr>
<td>Postural Instability</td>
<td>4.2</td>
<td>38.5</td>
<td>88.9</td>
</tr>
<tr>
<td>Hallucinations (any)</td>
<td>4.2</td>
<td>7.7</td>
<td>66.7</td>
</tr>
<tr>
<td>Fluctuations</td>
<td>33.3</td>
<td>59.5</td>
<td>93.5</td>
</tr>
<tr>
<td>RBD</td>
<td>4.3</td>
<td>22.2</td>
<td>36.7</td>
</tr>
<tr>
<td>Falls</td>
<td>23.3</td>
<td>47.6</td>
<td>83.3</td>
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<tr>
<td>Depression</td>
<td>23.5</td>
<td>28.6</td>
<td>52.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>22.1</td>
<td>25.7</td>
<td>32.0</td>
</tr>
</tbody>
</table>
Lewy Body Pathology

- **Macroscopic**
  - Mild atrophy, predominantly affecting limbic system
  - Depigmentation of the substantia nigra

- **Microscopic**
  - Essential – Lewy bodies
  - Associated (but not essential)
    - Lewy neurites
    - Regional neuronal loss including brainstem and nucleus basalis
    - Microvacuolation
    - Pale bodies
  - May also be present
    - Senile plaques
    - Neurofibrillary tangles

---

Neurodegeneration in DLB vs AD

Dopaminergic cell loss is observed in the substantia nigra of a DLB patient (black arrows, A) compared with AD (B) and control (C).

In the same patients, atrophy of the medial temporal lobe is evident in AD (black arrows, E), whilst it is relatively spared in DLB (D) and control (F). Both scale bars represent 1 cm.
Propagation of LB Pathology

Schematic representation of α-synuclein pathology spreading routes in Lewy body disorders. **a.** Caudorostral route in PD
**b.** Hypothetical olfactory route in DLB

Light red arrows = weak incursions of α-synuclein pathology; dark red arrows = aggressive incursions of α-synuclein pathology

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Imaging in LBD

---

**Legend:**
- AD: Alzheimer's Disease
- DLB: Dementia with Lewy Bodies
- NC: Normal Controls
- C: Controls
- PD: Parkinson's Disease
- PDD: Parkinson's Disease with Dementia
- DBL: Dementia with Lewy Bodies
- PAF: Parkinson's disease with dementia and FTD
- MSA: Multiple System Atrophy

**Notes:**
- Am = amygdala; DMV = dorsal motor nucleus of the vagus; ENS = enteric nervous system; Ent = entorhinal cortex; LC = locus coeruleus; OB = olfactory bulb; SN = substantia nigra.
Research Criteria for Prodromal LBD

• One or more core clinical features may develop years before dementia
  • Spontaneous parkinsonism
  • REM sleep behavior disorder
  • Autonomic complaints (orthostasis, constipation, olfaction)
• Three defined presentations for prodromal phases
  • Mild Cognitive Impairment
  • Delirium-onset Presentation
  • Psychiatric-onset Presentation

McKeith et al, Neurology 2020

MCI with Lewy Bodies

• Concern by patient, informant, or clinician
• Objective evidence of impairment in 1 or more cognitive domains
• Preserved or minimally affected ADLs
• Core features
  • Fluctuating cognition
  • Visual hallucinations
  • RBD
  • Parkinsonism

McKeith et al, Neurology 2020
Delirium-Onset LBD

- Patients with underlying LBD more susceptible than underlying AD
- Provoked by multiple factors (surgery, infections, fever, medications)
- Prodromal DLB should be suspected
  - Other provoking factors not found
  - Prolonged or recurrent delirium
  - Later develop progressive cognitive decline
- Core features have limited diagnostic weight
  - Can occur with other causes of delirium

McKeith et al, Neurology 2020

Psychiatric-Onset LBD

- Characterized by predominant psychiatric symptoms
  - Visual hallucinations
  - Systematized delusions (Capgras)
- May present with apathy, anxiety, and depression
- May be severe enough to require hospitalization
- Core features may mimic other psychiatric presentations or be due to treatment of symptoms
  - Bradykinesia mimicked by psychomotor retardation
  - Parkinsonism induced by medications
  - RBD induced by antidepressants

McKeith et al, Neurology 2020
Cognitive Profiles

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>LBD</th>
<th>bvFTD</th>
<th>VaD</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Episodic Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free recall</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Recognition</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prompting</td>
<td>x</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Intrusions</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Semantic memory</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Procedural memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Insight</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Attention</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Executive functions</strong></td>
<td>++</td>
<td>typical AD</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>+++  frontal variant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visuospatial skills</td>
<td>++</td>
<td>typical AD</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+++  PCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+++ Early and severe impairment; ++ moderate impairment; + mild impairment; +/- impairment in some studies but not others; - no significant impairment; x not helpful; √ helpful.

Karantzioulis and Galvin, Neurotherapeutics 2014; Galvin JE Practical Neurology 2019

Comparing PDD, DLB and AD

**PDD vs. DLB**
- These groups were nearly identical in all clinical features.
- PDD: Postural instability
- DLB: Spasticity

**PDD vs. AD**
- PDD: male predominance, EPS, cognitive fluctuation, visual and auditory hallucinations, falls, depression and sleep disturbances.

**DLB vs. AD**
- DLB: male predominance, EPS, visual and auditory hallucinations, myoclonus, depression and sleep disturbance

**PDD autopsy**: 38% neocortical LBs only
- 32% neocortical LBs with AD
- 30% subcortical LBs only

## DLB vs PDD

<table>
<thead>
<tr>
<th>Clinical differences</th>
<th>Motor features</th>
<th>Rest tremor more frequent in PDD 58-61</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>More severe parkinsonism in PDD 51-73</td>
</tr>
<tr>
<td>Cognitive features</td>
<td>Cognitive domains related to frontal and temporal regions are more prominently affected in DLB 71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Episodic verbal memory significantly more affected in DLB 60-72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Faster rate of cognitive decline in DLB 73, 74</td>
<td></td>
</tr>
<tr>
<td>Neuroimaging differences</td>
<td>MRI imaging</td>
<td>Bilateral frontal atrophy in PDD vs. periventricular and occipital atrophy in DLB 83</td>
</tr>
<tr>
<td></td>
<td>Amyloid imaging</td>
<td>More severe PIB uptake in DLB 30, 82</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>More common for DLB to have an AD-like CSF profile 85</td>
</tr>
<tr>
<td>Pathological differences</td>
<td>Substantia nigra</td>
<td>More severe neuronal loss in PD, PDD than DLB 112</td>
</tr>
<tr>
<td></td>
<td>Lewy body pathology</td>
<td>More frequent 6-synuclein pathology in the mesocortex and limbic system, especially in the hippocampal CA1/2 areas in DLB 151</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Higher AD load in cortex and stratum in DLB 151</td>
</tr>
<tr>
<td></td>
<td>Tau</td>
<td>Increased tau load in the cortex and stratum of DLB 151</td>
</tr>
<tr>
<td></td>
<td>Cholinergic deficit</td>
<td>More profound cholinergic neuronal loss in PDD 153</td>
</tr>
<tr>
<td></td>
<td>5-HT1A receptor binding</td>
<td>Reduced 5-hydroxytryptamine in cholinergic cell loss in hallucinating PDD but not in DLB 152</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher cortical 5-HT1A receptor binding in DLB 9</td>
</tr>
</tbody>
</table>

Hansen D et al, Neuropath App Neurobio 2019

## Mortality in LBD and AD

### A

**Diagnosis**
- 
- **AD**
- **DLB**

<table>
<thead>
<tr>
<th>Age at Death</th>
<th>Cumulative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBD: 78.0y, AD: 84.6y</td>
<td>(\chi^2 = 19.9, \ p &lt; 0.001)</td>
</tr>
</tbody>
</table>


### B

**Diagnosis**
- 
- **AD men**
- **AD women**
- **DLB men**
- **DLB women**

<table>
<thead>
<tr>
<th>Age at Death</th>
<th>Cumulative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBD men: 76.8y, AD women: 85.9y</td>
<td>(\chi^2 = 33.5, \ p &lt; 0.001)</td>
</tr>
</tbody>
</table>
Survival in LBD and AD


DLB has poorer outcomes compared to AD

Predictors of DLB Mortality and Poor Outcomes

- Cost
  - Nursing home admission
  - Caregiver burden
  - Neuropsychiatric symptoms

Survival
- Comorbid Alzheimer’s disease pathology
- Male sex
- Disease severity
- Age
- Comorbidities
- Functional impairment
- Neuroleptic prescription
- Extrapyramidal signs
- Gait abnormalities
- Orthostatic hypotension
- Hallucinations
- Decreased hippocampal volume
- Increased CSF tau

Based on several, higher score, studies
Based on more than one study
Based on one study
Established predictors in dementia
Predictors studied in dementia with Lewy bodies

Caregiver Experience With Diagnosis

- 78% of patients had been diagnosed with something else first
  - 53% AD or other dementia
  - 39% PD or other movement disorder
  - 24% Primary psychiatric disorder

- 2/3 of patients saw at least 3 physicians before LBD diagnosis

- Median time to diagnosis was 12-18 months

62% of diagnosing physicians were neurologists, and only 6% were PCPs

PD = Parkinson’s disease
Caregiver Perception of Physician Knowledge

- 70% had difficulty finding a physician knowledgeable about diagnosing LBD
- After diagnosis, 53% of patients returned to primary care for management
- 77% had difficulty finding a physician knowledgeable about treating LBD

How useful it is to get a diagnosis?

- DLB causes significantly greater functional disability than AD\textsuperscript{1}
- Care costs of DLB are twice those for AD\textsuperscript{2}
- Quality of life for people with DLB is significantly worse than for those with AD, with 1 in 4 caregivers rating DLB as worse than death\textsuperscript{3}
- A correct DLB diagnosis increases the chances of correct management\textsuperscript{4}

Experiences in LBD Caregiving

Adult child and spouse caregivers experience LBD differently

- Adult children vs Spouse
  - Less likely to live with patient
  - More likely to be caring for their mothers
  - Patients are more impaired
  - Report lower quality of life, more caregiver burden
  - Report greater social support
  - Report less grief

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spouse</th>
<th>Adult Child</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Caregiver Quality of life</td>
<td>39.0 (7.1)</td>
<td>33.5 (7.6)</td>
<td>&lt; .001†</td>
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<tr>
<td>Social Support</td>
<td>57.4 (17.8)</td>
<td>66.8 (20.9)</td>
<td>&lt; .001†</td>
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<tr>
<td>Emotional</td>
<td>25.6 (8.3)</td>
<td>28.1 (9.0)</td>
<td>.006†</td>
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<tr>
<td>Tangible</td>
<td>10.7 (4.7)</td>
<td>13.3 (5.1)</td>
<td>&lt; .001†</td>
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<tr>
<td>Affective</td>
<td>8.9 (3.3)</td>
<td>10.9 (3.6)</td>
<td>&lt; .001†</td>
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<tr>
<td>Positive Social Interaction</td>
<td>11.4 (4.6)</td>
<td>14.3 (4.8)</td>
<td>&lt; .001†</td>
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<td>Social Networks</td>
<td>17.3 (4.5)</td>
<td>18.2 (4.5)</td>
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<td>Depression</td>
<td>1.9 (1.6)</td>
<td>2.2 (1.8)</td>
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<td>Psychological well being</td>
<td>83.5 (12.6)</td>
<td>81.7 (13.0)</td>
<td>.169</td>
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<td>Caregiver grief</td>
<td>62.4 (12.9)</td>
<td>60.8 (12.7)</td>
<td>.229</td>
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<td>Caregiver burden</td>
<td>24.8 (8.3)</td>
<td>26.9 (8.4)</td>
<td>.009</td>
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<td>Role strain</td>
<td>11.7 (3.9)</td>
<td>12.6 (4.5)</td>
<td>.045</td>
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<tr>
<td>Personal strain</td>
<td>4.4 (2.7)</td>
<td>4.9 (2.7)</td>
<td>.072</td>
</tr>
<tr>
<td>Worry about performance</td>
<td>8.6 (3.3)</td>
<td>9.5 (3.2)</td>
<td>.009</td>
</tr>
</tbody>
</table>

Designing Programs to Help Caregivers

Self-Efficacy and Social Support Mediate Psychological Well-Being in LBD Caregivers

- Self-efficacy: $a = -0.3330$ ($p < 0.0005$)
- Social Support: $b = 1.7002$ ($p < 0.0005$)

Direct ($c') = -0.3893$ ($p < 0.0005$); indirect (ab) = -0.722 ($95\% CI = -0.834$ to $-0.610$)

- Social Support: $b = 0.1540$ ($p < 0.0005$)
- Caregiver Grief: $a = -0.0840$ ($p < 0.0005$)

Direct ($c') = -0.3879$ ($p < 0.0005$); indirect (ab) = -0.472 ($95\% CI = -0.541$ to $-0.403$)

Park et al, Social Work in Mental Health, 2018
Noise Pareidolia

- 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)
- Each panel 30 seconds (10 minutes max)

<table>
<thead>
<tr>
<th>Differentiation between DLB and AD</th>
<th>Scene Test</th>
<th>Noise Test</th>
<th>Pareidolia Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.92</td>
<td>0.60</td>
<td>0.81</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.58</td>
<td>0.92</td>
<td>0.92</td>
</tr>
<tr>
<td>ROC AUC</td>
<td>0.86</td>
<td>0.82</td>
<td>0.92</td>
</tr>
<tr>
<td>Cut-Off Score</td>
<td>1/2</td>
<td>2/3</td>
<td>4/5</td>
</tr>
</tbody>
</table>
Noise Pareidolia Test Discriminates LBD

Galvin et al, In Preparation

Proxy Markers of Basal Ganglia Dysfunction

<table>
<thead>
<tr>
<th>Test</th>
<th>Pursuits (2 Hz Gain%)</th>
<th>Saccades (Peak Velocity)</th>
<th>Saccades (Latency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS</td>
<td>-0.36 (-.001)</td>
<td>-0.41 (-.001)</td>
<td>0.19 (.05)</td>
</tr>
<tr>
<td>LBCRS</td>
<td>-0.17 (.09)</td>
<td>-0.31 (.001)</td>
<td>0.22 (.01)</td>
</tr>
<tr>
<td>King-Devick</td>
<td>-0.37 (.16)</td>
<td>-0.51 (.03)</td>
<td>-0.71 (.001)</td>
</tr>
<tr>
<td>Noise Pareidolia</td>
<td>0.32 (.003)</td>
<td>0.33 (.002)</td>
<td>-0.50 (&lt;.001)</td>
</tr>
</tbody>
</table>
Computerized Gait Analyses

- Develop a new metric of number of steps per standardized distance: Festination Index (FI).
- FI captures patients’ normal walking pattern over a 40’ distance
- A cut-off of 1.65 provides a sensitivity of 72.4% to detect individuals with cognitive impairment

<table>
<thead>
<tr>
<th>Cognitive Performance by Festination Index Cut-off of 1.65</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.65</td>
</tr>
<tr>
<td>MoCA</td>
</tr>
<tr>
<td>Numbers Forward</td>
</tr>
<tr>
<td>Numbers Backward</td>
</tr>
<tr>
<td>Animal Naming</td>
</tr>
<tr>
<td>15-item MINT</td>
</tr>
<tr>
<td>HVLT – Delay</td>
</tr>
<tr>
<td>HVLT – Recognition</td>
</tr>
<tr>
<td>Trails A, sec</td>
</tr>
<tr>
<td>Trails B, sec</td>
</tr>
<tr>
<td>Number-Symbol</td>
</tr>
<tr>
<td>Z-score</td>
</tr>
<tr>
<td>CDR-SB</td>
</tr>
</tbody>
</table>

CSF Synuclein

Mollenhauer et al, Exp Neurology 2008
**Synuclein-Amyloid Interactions**

![Graph showing mean selective recall test-free recall](image)

*Galvin JE, et al, Unpublished*

**Plasma Alpha-Synuclein**

![Graphs showing plasma alpha-synuclein levels](image)

*Data from MagQu Inc, Taiwan*
### Plasma Biomarkers

![Plasma Biomarkers Graph](Lin et al Front Aging Neurosci 2018)

### Clinical Predictors of LB Pathology

<table>
<thead>
<tr>
<th>Clinical Predictor</th>
<th>Present at any time</th>
<th>Present at 1st visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.50</td>
<td>1.01-2.38</td>
</tr>
<tr>
<td>Any EPS</td>
<td>2.50</td>
<td>1.64-3.82</td>
</tr>
<tr>
<td>Cognitive Fluctuation</td>
<td>4.98</td>
<td>1.63-15.15</td>
</tr>
<tr>
<td>Visual Hallucinations</td>
<td>8.93</td>
<td>2.31-34.50</td>
</tr>
<tr>
<td>Auditory Hallucination</td>
<td>11.76</td>
<td>1.66-83.30</td>
</tr>
<tr>
<td>Neuroleptic Sensitivity</td>
<td>3.75</td>
<td>1.05-13.30</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>3.90</td>
<td>1.27-12.05</td>
</tr>
<tr>
<td>Depression</td>
<td>1.81</td>
<td>1.16-2.82</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>1.98</td>
<td>1.33-2.94</td>
</tr>
</tbody>
</table>

Clinical features such as aphasia, apraxia, agnosia, ApoE not associated

Lewy Body Composite Risk Score

Please rate the following symptoms as being present or absent for at least 3 times over the past 6 months. Does the patient...

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have a loss of postural stability (balance) with or without frequent falls?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have a tremor at rest in any of the 4 extremities or head?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have episodes of illogical thinking or incoherent, random thoughts?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have frequent staring spells or periods of blank looks?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have visual hallucinations (see things not really there)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have orthostatic hypotension or other signs of autonomic insufficiency?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TOTAL SCORE

Copyright 2015 The Lewy Body Composite Risk Score James E. Galvin

Lewy Body Composite Risk Score

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=25)</th>
<th>AD (N=24)</th>
<th>LBD (N=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72.6 (6.4)</td>
<td>74.8 (6.8)</td>
<td>72.6 (8.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>28.0</td>
<td>58.3</td>
<td>70.0</td>
<td>.01</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.2 (1.9)</td>
<td>13.7 (2.9)</td>
<td>15.4 (2.7)</td>
<td>ns</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>.02 (.11)</td>
<td>3.4 (1.8)</td>
<td>3.9 (2.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.9 (1.2)</td>
<td>25.4 (3.2)</td>
<td>25.3 (3.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Global, z-score</td>
<td>.19 (.65)</td>
<td>-.85 (.78)</td>
<td>-.86 (.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Working, z-score</td>
<td>.13 (.81)</td>
<td>-.57 (.76)</td>
<td>-.56 (.67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visuospatial, z-score</td>
<td>.25 (.70)</td>
<td>-.56 (1.0)</td>
<td>-1.65 (1.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LBCR Score</td>
<td>0.8 (1.4)</td>
<td>1.0 (1.1)</td>
<td>5.8 (2.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

LBCR Score correlates to Cognitive Profiles:
- Global (r=-.563, p=.003)
- Visuospatial (r=-.529, p=.005)
- Working (r=-.369, p=.058)

AUC: 0.965 (95%CI: 0.91-1.0)
Using Cut-Off: 3
Sensitivity: 91%
Specificity: 89%

Karantoula S, Galvin JE, Clin Trans Gerontol 2013
Sample Characteristics

<table>
<thead>
<tr>
<th>Demographics and Global Ratings</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>Age, y</td>
<td>79.9 (7.9)</td>
</tr>
<tr>
<td>Gender, %M</td>
<td>37.4</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.2 (3.9)</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>5.9 (3.4)</td>
</tr>
<tr>
<td>CDR</td>
<td>0.9 (0.5)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>2.3 (1.3)</td>
</tr>
<tr>
<td>Systolic BP, sitting, mm Hg</td>
<td>133.4 (18.9)</td>
</tr>
<tr>
<td>Mean Arterial Pressure, sitting</td>
<td>94.5 (11.2)</td>
</tr>
<tr>
<td>Systolic BP, standing, mm Hg</td>
<td>133.2 (18.7)</td>
</tr>
<tr>
<td>Mean Arterial Pressure, standing</td>
<td>94.3 (11.1)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>25.0 (4.8)</td>
</tr>
<tr>
<td>Mini-PPT</td>
<td>9.8 (2.5)</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>7.5 (9.1)</td>
</tr>
<tr>
<td>Hoehn and Yahr Stage</td>
<td>0.5 (1.2)</td>
</tr>
<tr>
<td>FAQ</td>
<td>10.3 (8.7)</td>
</tr>
<tr>
<td>NPI-Q</td>
<td>7.7 (5.7)</td>
</tr>
<tr>
<td>Mayo Fluctuation Questionnaire</td>
<td>1.6 (3.1)</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>6.8 (4.8)</td>
</tr>
<tr>
<td>Alertness Rating</td>
<td>7.2 (2.0)</td>
</tr>
<tr>
<td>LBCRS</td>
<td>2.4 (1.3)</td>
</tr>
</tbody>
</table>

Cohen’s d (Effect Size correlation) = 2.17 (r=0.736)

LBD Module for NIA-Alzheimer Center Program

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
- Capture prodromal symptoms
- Instruments or measurements selected should be free of licensing fees or that an agreement is in place to make their use free
- Not burden sites
DIAMOND LEWY Toolkit

Assessment Toolkit for Dementia with Lewy Bodies

Questions to identify Symptoms of DLB

Cognitive Fluctuation (To cases)
1. Does the patient show extreme changes in their level of functioning during the day?
2. Between getting up in the morning and going to bed at night, does the patient spend more than one hour sleeping?
3. Is the patient usually less alert for more than one hour during the day?
4. Is it relatively easy to arouse the patient when they are in a drowsy state?

REM Sleep Disorder
(To cases - best partner)
5. Does the patient appear to “catnap” or fall asleep while the patient is sitting in the chair, studied or examined?
6. Answered affirmatively, then REM is highly likely to be present.

Visual Hallucinations
For the patient: Some people see things that other people cannot see.
1. Do you feel like your eyes play tricks on you?
2. Have you ever seen something or thought that other people could not see?
3. Does the patient have visual hallucinations sufficient to disturb their behavior?
4. Does the patient have visual hallucinations sufficient to disturb their behavior?

Other Diagnosis
Parkinsonian Dementia (PDS) (PD + 5+ behavior cognitive symptom)
Alzheimer’s Disease
Other Dementia
MCI

Assessment of Parkinsonism (Turner UPDRS)

FACIAL EXPRESSION

NORMAL

Right

Looking normal, reactive to sound and pain, smiling

Mild

Looking normal, reactive to sound and pain, smiling

Moderate

Looking normal, reactive to sound and pain, smiling

Severe

Looking normal, reactive to sound and pain, smiling

TORSO TREMOR

Normal

No tremor

Mild

Tremor is present but less than 1 cm in amplitude

Moderate

Tremor is present but less than 1 cm in amplitude

Severe

Tremor is present but less than 1 cm in amplitude

TORSO TORSION

Normal

No torsion

Mild

Torsion is present but less than 1 cm in amplitude

Moderate

Torsion is present but less than 1 cm in amplitude

Severe

Torsion is present but less than 1 cm in amplitude

PHASE IV: TORSION IN A STANDING POSITION

Normal

Right

No evidence of torsion

Mild

Torso is rotated 10° to right

Moderate

Torso is rotated 20° to right

Severe

Torso is rotated 30° to right


Treatment Options

Pharmacology

(nearly all options are off-label use of medication for DLB)

Cognitive Symptoms

Donepezil (approved for DLB in Japan/Italy)
Other cholinesterase inhibitors
Memantine (1)

Behavior

Antidepressants
Mirtazapine (2)
Venlafaxine (3)

Motor Symptoms

Carbidopa
Levodopa

Sleep

Melatonin
Clonazepam

Fluctuation Attention

Modafinil
Amodafinil

Autonomic

Fluoxetine/sertraline
Mirtazapine
Trihexyphenidyl

Overview of Change in MMSE Scores From Studies of Cholinesterase Inhibitors in PDD

Pharmacotherapy Options

<table>
<thead>
<tr>
<th>Symptom Domain</th>
<th>Treatment Option</th>
<th>Evidence in DLB/PDD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td>Cholinesterase inhibitors</td>
<td>Efficacious</td>
<td>• Rivastigmine, donepezil have class 1 efficacy in DLB. • Cochrane review showed overall positive effect of cholinesterase inhibitors in PD, PDD, and DLB.</td>
</tr>
<tr>
<td></td>
<td>Memantine</td>
<td>Insufficient evidence</td>
<td>• Evidence is inconsistent, but a small, significant improvement has been reported from RCTs.</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Cholinesterase inhibitors</td>
<td>Insufficient evidence</td>
<td>• No RCTs, but other evidence is positive.</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>DLB: Unlikely to be effective PDD: Mixed</td>
<td>• Few RCTs for DLB, evidence suggests only modest effects at best. • In PDD and PD, donepezil and rivastigmine are effective, olanzapine is not, and evidence for quetiapine is mixed.</td>
</tr>
<tr>
<td>Depression</td>
<td>Antidepressants</td>
<td>Insufficient evidence</td>
<td>• Evidence is mixed, some benefits seen with venlafaxine, paroxetine, and nortriptiline in PD.</td>
</tr>
<tr>
<td>RBD</td>
<td>Melatonin</td>
<td>Insufficient evidence</td>
<td>• Evidence from non-RCT in PD.</td>
</tr>
<tr>
<td></td>
<td>Clonazepam</td>
<td>Insufficient evidence</td>
<td>• Non-RCT evidence.</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>Moclobemide</td>
<td>Insufficient evidence</td>
<td>• RCT evidence for PD. • Non-RCT evidence for DLB.</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Levodopa</td>
<td>Insufficient evidence</td>
<td>• L-Dopa less effective in DLB than PD, probable increased risk of psychosis. Recent RCT showed zonisamide was effective as an adjunct to L-Dopa in DLB.</td>
</tr>
<tr>
<td>Autonomic Function</td>
<td>Fluoxetine</td>
<td>Insufficient evidence</td>
<td>• No RCTs, but other evidence is positive.</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial.


Ongoing Clinical Trials in LBD

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Phase/Location</th>
<th>Status/Timing</th>
<th>Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noclanserin</td>
<td>5-HT2A receptor inverse agonist</td>
<td>R</td>
<td>Completed – primary endpoint for RBD not met</td>
<td>NCT02700188</td>
</tr>
<tr>
<td>DLB</td>
<td>Interide</td>
<td>5-HT1A receptor antagonist</td>
<td>Phase 2/3, US</td>
<td>Extension terminated due to lack of efficacy in lead-in study</td>
</tr>
<tr>
<td>HTL0018318</td>
<td>M1 receptor agonist</td>
<td>Phase 2, US</td>
<td>Recruiting – estimated completion 2020</td>
<td>NCT03502862</td>
</tr>
<tr>
<td>E202T</td>
<td>PDE9 inhibitor</td>
<td>Phase 2, Japan</td>
<td>Recruiting – estimated completion 2020</td>
<td>NCT03407152</td>
</tr>
<tr>
<td>PDD</td>
<td>SYN120</td>
<td>5-HT2A,5-HT1A receptors antagonist</td>
<td>Phase 2, US</td>
<td>Completed – primary endpoint for cognition not met</td>
</tr>
<tr>
<td>RLR752</td>
<td>5-HT1a,5-HT3 receptors antagonist</td>
<td>Phase 2, Sweden/Finland</td>
<td>Completed – met primary endpoint for safety and tolerability</td>
<td>2017-001673-17</td>
</tr>
<tr>
<td>Ambroxol</td>
<td>Increase β-glucuronidase, reduce α-synuclein</td>
<td>Phase 2, Canada</td>
<td>Recruiting – estimated completion 2018</td>
<td>NCT03914366</td>
</tr>
<tr>
<td>LYS14207</td>
<td>D4 receptor positive allosteric modulator</td>
<td>Phase 2, Global</td>
<td>Recruiting – estimated completion 2019</td>
<td>NCT03305800</td>
</tr>
<tr>
<td>ANAVEX-2-73</td>
<td>α1 and M receptors agonist</td>
<td>Phase 2, Spain</td>
<td>Recruiting – estimated completion 2019</td>
<td>NCT03774459</td>
</tr>
<tr>
<td>Nictinib</td>
<td>Tyrosine kinase inhibitor</td>
<td>Phase 2, US</td>
<td>Active, not yet recruiting</td>
<td>NCT02954978</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Antibiotic</td>
<td>Phase 2, Taiwan</td>
<td>Active, not yet recruiting</td>
<td>NCT034133184</td>
</tr>
</tbody>
</table>
DLB Consortium

• U01 from NINDS (part of the PDBP)
• Cleveland Clinic is primary site
• FAU, Rush, UNC, UPenn, UPitt, UCSD, Thomas Jefferson, UWashington
• 5-Year Longitudinal Study
• Clinical-cognitivebehavioral evaluations
• MRI
• DAT
• LP
• Autopsy

LBD Research Centers of Excellence

• 25 research centers across the country
  • 17 States and District of Columbia
• Excellence in Clinical Care and Research
• Form Clinical Trials Network
• Mayo Clinic – Rochester is the Coordinating Center
• Cleveland Clinic, Cleveland ClinicLas Vegas, Columbia, Emory,
  Georgetown, Mass General, Johns Hopkins, Mayo ClinicJacksonville,
  Northwestern, Ohio State, Oregon, Rush, Stanford, Thomas Jefferson,
  UCSan Diego, UColorado, UFlorida, University of Miami, U
  Michigan, UNC-Chapel Hill, UPenn, U-Rochester, U-Virginia, U
  Washington
ARUK DLB (United Kingdom)

- Organized by ARUK
- Started February 2019
- Includes various centers across the UK: KCL (Aarsland, coordinating), Essex (Walker), Exeter (Ballard), Cambridge (O’Brien), Newcastle (Taylor), with additional centers joining
- Objectives
  - Identify CSF-based biomarkers to predict those with rapid decline
  - Explore disease mechanisms based on blood and CSF analyses
  - Establish a trial-ready cohort
- Methods
  - Leverage infrastructure to recruit and follow people with DLB for 5 years, focusing on imaging, blood, and CSF biomarker collection
  - Liaise with E-DLB (similar protocol) to create the world’s largest prospective DLB cohort

KCL = King’s College London.

DLB-SINdem (Italy)

- Organized by SINdem
- Includes 135 centers with 5624 DLB patients
- Objectives
  - Improve DLB identification by physicians working in dementia centers
  - Identify DLB cohorts available in Italy and develop an efficient method for data collection
  - Provide general guidelines and detailed recommendations for prospective cohort studies using appropriate biomarkers and clinical scales
  - Develop strategies to define and identify prodromal DLB
- Methods
  - Experts selected across the country via a semi-structured questionnaire will
    - Identify possible recruitment sources and bottlenecks
    - Identify best clinical scales to measure and assess parameters over time
    - Provide guidelines for selection of diagnostic and prognostic biomarkers
    - Perform genetic study to assess presence of genetic clusters in DLB populations

Progressive Supranuclear Palsy

- First described in 1963 by Richardson, Steele, and Olszewski
- Progressive parkinsonism (axial > appendicular) with early falls, postural instability, supranuclear ophthalmoplegia (vertical gaze), pseudobulbar dysfunction, and dementia
- Starts in mid-life, most commonly in mid-60’s, unheard of before age 40
- Prevalence: 5.8-6.5 per 100,000
- Incidence: 0.3-1.1 per 100,000
- Onset to death: 7 years
- Dementia is subcortical in nature
  - Executive and language with relative preservation of memory

PSP as a Neuropathological Entity

- The most common primary tauopathy
  - 4R tauopathy: 4 repeats in the microtubule binding domain
- The substantia nigra, subthalamic nucleus, globus pallidus interna, and pons are severely damaged.
- Additional pathology is frequently observed in the striatum, oculo-motor nucleus, medulla, and cerebellar dentate nucleus
- Increase in number of pathology confirmed cases over past 20 yrs
- Localization of tau is major driver of clinical phenotype
  - Brainstem predominant pathology results in pure akinesia
  - Cortical predominant pathology results in focal cortical syndromes
Clinical Findings

• Akinetic-rigid form of Parkinsonism (axial presentation)
  • Stiff and broad based gait, with quick pivots
  • Knees and trunk extended, Arms abducted
  • “Drunken sailor gait”
• Oculomotor findings
  • Supranuclear gaze palsy (only a minority of patients)
  • Impairment of vertical saccades
  • Downgaze before upgaze
  • Lateral eye movements may be preserved
  • Saccadic intrusions in fixation (square wave jerks)
  • Loss of optokinetic nystagmus
  • Blepharospasm
  • Eyelid opening apraxia

Clinical Findings

• Motor Involvement
  • Bradykinesia with marked micrographia
  • Rare blinking and facial dystonia (“perpetual surprise”)
  • Neck dystonia, typically retrocollis
  • Hyperreflexia and Babinski signs in 1/3 patients
  • Frontal release signs
  • Dysphonia
  • Dysarthria
  • Dysphagia

• Sleep Disturbances
  • Insomnia
  • Difficulty maintaining sleep
  • REM Sleep disorder exceedingly rare

Agarwal S, Gilbert R, StatPearls 2019
Cognitive-Behavioral Findings

- Frontal Lobe Dysfunction
  - Impaired executive function
  - Palilalia
  - Motor perseveration
  - Compulsive spitting
- Behavioral abnormalities
  - Apathy
  - Disinhibition
  - Depression
  - Anxiety
- Pseudobulbar palsy
- Ideomotor apraxia less common than CBS

Agarwal S, Gilbert R, StatPearls 2019

Variants

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Abbreviation</th>
<th>Description/key features</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSP-Richardson’s syndrome</td>
<td>PSP-RS</td>
<td>Vertical ocular motor dysfunction, early onset postural instability and falls</td>
</tr>
<tr>
<td>PSP-ocular motor</td>
<td>PSP-OM</td>
<td>Predominant ocular motor dysfunction</td>
</tr>
<tr>
<td>PSP-postural instability</td>
<td>PSP-PI</td>
<td>Predominant postural instability</td>
</tr>
<tr>
<td>PSP-parkinsonism</td>
<td>PSP-P</td>
<td>Clinical phenotype resembling Parkinson’s disease (later development of symptoms of PSP-RS)</td>
</tr>
<tr>
<td>PSP-frontal</td>
<td>PSP-F</td>
<td>Behavioral or frontal cognitive presentation (can be similar to behavioral variant frontotemporal dementia)</td>
</tr>
<tr>
<td>PSP-progressive gait freezing</td>
<td>PSP-PGF</td>
<td>Presentation with an isolated gait disorder with start hesitation and progressive freezing of gait</td>
</tr>
<tr>
<td>PSP-corticobasal syndrome</td>
<td>PSP-CBS</td>
<td>Corticobasal syndrome (1 movement disorder sign and 1 cortical sign)</td>
</tr>
<tr>
<td>PSP-speech/language disorder</td>
<td>PSP-SL</td>
<td>Progressive apraxia of speech and/or nonfluent/agrammatic primary progressive aphasia</td>
</tr>
<tr>
<td>PSP-primary lateral sclerosis</td>
<td>PSP-PLS</td>
<td>Primary lateral sclerosis</td>
</tr>
<tr>
<td>PSP-cerebellar ataxia</td>
<td>PSP-C</td>
<td>Cerebellar ataxia as initial and predominant symptom</td>
</tr>
</tbody>
</table>

Armstrong M, Curr Neurol Neurosci Rep 2018
Clinical Features of Different Variants

Clinical features of PSP-RS, PSP-P, PSP-PAGF, PSP-CBS, PSP-PNFA, PSP-bvFTD, PSP-C, Parkinson’s disease, and MSA-P

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>PSP-RS</th>
<th>PSP-P</th>
<th>PSP-PAGF</th>
<th>PSP-CBS</th>
<th>PSP-PNFA</th>
<th>PSP-bvFTD</th>
<th>PSP-C</th>
<th>Parkinson’s Disease</th>
<th>MSA-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigidity</td>
<td>Axial &gt; limb</td>
<td>Axial &gt; axial</td>
<td>Axial</td>
<td>Limb &gt; axial</td>
<td>+</td>
<td>+</td>
<td>Axial &gt; limb</td>
<td>Limb &gt; axial</td>
<td>Axial &gt; axial</td>
</tr>
<tr>
<td>Early postural instability and/or falls</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Early eye movement abnormalities</td>
<td>+++</td>
<td>++</td>
<td>&lt;=</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Early cognitive decline</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Early frontal behavior</td>
<td>--</td>
<td>-</td>
<td>-</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non-fluent aphasia and/or apraxia of speech</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>--</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Limb dystonia</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>(limb and truncal ataxia)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pyramidal and Babinski’s signs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Levedopa response</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>--</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

Pathology

Flame-shaped and globose neurofibrillary tangles and neuropil threads associated with neuronal loss.

Coiled Bodies

Tufted Astrocytes

Williams and Lees, Lancet Neurol 2009; Ling J Mov Disord 2016
Movement Disorder Society-PSP Criteria

MDS-PSP Criteria Core Clinical Features

<table>
<thead>
<tr>
<th>Functional domain</th>
<th>Lower certainty (Level 3)</th>
<th>(Level 2)</th>
<th>Higher certainty (Level 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular motor dysfunction</td>
<td>O3: Frequent macro square wave jerks or eyelid opening apraxia</td>
<td>O2: Slow velocity of vertical saccades</td>
<td>O1: Vertical supranuclear gaze palsy</td>
</tr>
<tr>
<td>Postural instability (within 3 years)</td>
<td>P3: Pull-test with &gt;2 steps backward</td>
<td>P2: Tendency to fall on the pull-test</td>
<td>P1: Repeated unprovoked falls</td>
</tr>
<tr>
<td>Akinesia</td>
<td>A3: Parkinsonism (with tremor +/- asymmetry +/- levodopa responsiveness)</td>
<td>A2: Levodopa-resistant, predominantly axial akinetic-rigid parkinsonism</td>
<td>A1: Progressive freezing of gait within 3 years</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>C3: Corticobasal syndrome</td>
<td>C2: Frontal cognitive/behavioral presentation</td>
<td>C1: Speech/ language disorder (naPPA or progressive AoS)</td>
</tr>
</tbody>
</table>
MRI: “Hummingbird Sign”


Midbrain to Pons Ratio

MTPR of less than 0.52 as a highly specific aid in the diagnosis of patients with PSP, with a positive predictive value of 100%

Owens E, et al Parkinsonism Relat Disord 2016
Treatment Options

- Largely symptomatic and supportive
- Limited benefit of L-DOPA in most PSP subtypes
  - May try Levodopa doses up to 1000 mg daily
- Anecdotal evidence for Zolipem for motor function, dysarthria, and ocular abnormalities
- SSRIs for depression, OCD, emotional lability
- Questionable benefit of Memantine for aphasia, no evidence for AChEi’s
- Botulinum toxin for blepharospasm and eyelid apraxia
- Deep brain stimulation not recommended outside of research settings

Corticobasal Syndrome

- Heterogeneous disorder
- At least 1 cortical symptom:
  - Apraxia, loss of cortical sensory function, alien limb phenomenon
- At least 1 extrapyramidal symptom:
  - Akinesia, rigidity, dystonia, myoclonus
- Frontal behavioral syndrome (executive, behavior, personality)
- Visuospatial deficits
- Progressive non-fluent aphasia

Parmera JB et al Dement Neuropsychol 2016
Imaging

- Generally asymmetric findings
- Posterior cortical atrophy
- Posterior hypometabolism
- PET findings may also include thalamus and striatum

Clinical Pearl: DDx Posterior Cortical Atrophy
1. Alzheimer’s disease
2. Lewy body dementia
3. Corticobasal syndrome
4. Creutzfeldt-Jacob disease

Neuropathology

- Asymmetric cortical atrophy
- Focal cortical neuronal loss
- Gliosis
- Superficial spongiosis
- Achromatic ballooned neurons
- Neurofibrillary tangles
- Astrocytic plaques and threads

Parmara JB et al Dement Neuropsychol 2016
Treatment Options

• Symptomatic and supportive
• L-DOPA modest benefit (35-56% cases)
• Botulinum toxin for focal dystonias
• Baclofen for dystonia
• Clonazepam for myoclonus
• Propanolol for action/postural tremor
• No good evidence for AChEI or Memantine

Parmera JB et al Dement Neuropsychol 2016

Nuclear Medicine Tracers in PSP and CBS

Progressive supranuclear palsy:
• $^{18}$F-FDG-PET - ↓ midline frontal structures, midbrain – „pimple sign“, cortical and subcortical motor areas hypometabolism
• SPECT- HMPAO – ↓ frontal hypoperfusion
• SPECT – IMP – ↓ prefrontal cortex hypoperfusion

Corticobasal syndrome:
• $^{18}$F-FDG-PET - ↓ cortical and subcortical regions (asymmetrically), asymmetrical parietal hypometabolism
• SPECT- HMPAO – ↓ contralateral asymmetrical hypoperfusion
• SPECT – IMP – ↓ basal ganglia, cortex of frontal and parietal lobe asymmetrical hypoperfusion

Alster P et al Front Neurol 2019
Differential Diagnosis

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Synucleinopathies</th>
<th>Tauopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliarial cytoplasmic</td>
<td>Multiple system</td>
<td>Tau body</td>
</tr>
<tr>
<td>inclusions</td>
<td>atrophy (MSA)</td>
<td>disease (LBD)</td>
</tr>
<tr>
<td></td>
<td>Lewy bodies</td>
<td>Progressive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>supranuclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>palsy (PSP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corticobasal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>degeneration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(CBD)</td>
</tr>
</tbody>
</table>

Levin et al. Dtsch Arztebl Int 2016

Imaging Differential Diagnosis

Levin et al. Dtsch Arztebl Int 2016
**Other Possibilities**

**Neurologic**
- Vascular Contributions to Cognitive Impairment and Dementia (VCID)
  - Vascular parkinsonism, apathy, abulia
- Frontotemporal Degeneration
  - FTDP-17 – parkinsonism, personality changes
- Normal Pressure Hydrocephalus
  - Lower extremity parkinsonism, gait abnormalities
- Prion Diseases
  - Visuoperceptual changes, parkinsonism, myoclonus
- Wernicke-Kosokoff Syndrome
  - Hallucinations and Confabulation

**Non-neurologic**
- Psychiatric Conditions
  - Depression: bradyphrenia, hallucinations, bradykinesia
- Multiple Medical Conditions
  - Hepatic or Renal dysfunction: Confusion, hallucinations, fluctuations
- Undetected Sleep Disordered Breathing and Obstructive Sleep Apnea
  - Thrashing about, moving about in sleep, snorting and gasping
- Medication-induced Psychosis
  - Dopamine agonists, amantadine

**Summary**
- The Parkinsonian dementias are distinct clinical syndromes that collectively represent the second most common cause of dementia
- The Lewy body dementias
  - PDD and DLB differ only by timing of movement disorder
  - While clinical criteria lack sensitivity, they are highly specific and correlated strongly with pathology
- The tauopathies
  - PSP is predominantly axial while CBS is predominantly asymmetric in presentation
  - Clinical criteria challenges with sensitivity, specificity and correspondence with neuropathology (particularly for CBS)
- Neuroimaging modalities may provide the greatest insights into the differential diagnosis and underlying mechanisms
- For the present time, treatments are largely symptomatic

*For Copies of Updated Presentation: jeg200@Miami.edu*
Assessment of Cognition in Clinical Practice

Alireza Atri, MD, PhD
Evaluation of Cognition in Clinical Practice

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Center for Brain/Mind Medicine
Department of Neurology
Brigham and Women’s Hospital, and
Harvard Medical School

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Disclosure/conflict of interest – Last 12 months

- I am not/have not been part of any speakers bureau

- Institutional Research Grants or clinical trials:
  - Alzheimer’s disease Consortia, Coordinating Research Institutes or Government Funding (ACTC, ADCS, ATRI, NIH), Indiana University (observational cohort), Johns Hopkins (clinical trial), Novartis (observational cohort study), Global Alzheimer’s Platform, Synexus (Brain Health Registry, observational cohort study)

- Scientific/Medical/Data Monitoring Advisory Board, Consultation, lectures/CME programs, or Work Groups/Committees:
  - Acadia, Alzheimer’s Association, Eisai, Grifols, Harvard Medical School Post-Graduate Continuing Education (HMS PGME), National Institutes of Health (NIH), Novo Nordisk, Roche/Genentech, Suven, Synexus

- Book/Authorship:
  - Oxford University Press (OUP)
Northwestern Care Pathway Model for Dementia

Executive/Attention
Symptoms: Similar to above (inability to plan, organize, multi-task, make goals/decisions, problem solve, complete tasks), forget why entered a room, daydream, easily distracted, less mentally efficient (more mental effort needed for some tasks)

Sympotms: Poor judgment, social disorganization, loss of empathy, new rituals and food preferences, apathy, inability to initiate, plan, organize, multi-task.

Slide courtesy of Dr. Lynn (Lili) Shaughnessy

Has there been a change, and in what domains - patient and care partner can complete separately (then can ask how long, fluctuating, progressive?)

COGNITIVE SYMPTOMS

Has there been a meaningful decline in your usual abilities for any of the following:

<table>
<thead>
<tr>
<th>First Symptom</th>
<th>Worst Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent or Short-term Memory</td>
<td>Yes</td>
</tr>
<tr>
<td>Long-term Memory</td>
<td>Yes</td>
</tr>
<tr>
<td>Attention/Concentration</td>
<td>Yes</td>
</tr>
<tr>
<td>Organization, Planning, Multi-tasking, completing tasks</td>
<td>Yes</td>
</tr>
<tr>
<td>Judgment, Reasoning or Problem Solving</td>
<td>Yes</td>
</tr>
<tr>
<td>Language</td>
<td>Yes</td>
</tr>
<tr>
<td>Orientation to day, date, time, timing of life events</td>
<td>Yes</td>
</tr>
<tr>
<td>Visuospatial Orientation &amp; Function</td>
<td>Yes</td>
</tr>
<tr>
<td>Other</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Search for NACC UDS forms (judgment of symptoms – modify to fit your practice and EMR or use AD-8 (Galvin 2005), IQ-CODE (Jorm 1994), CFI (Cognition Function Index) (Amariglio 2015), ADCQ (Murphy & Solomon 2009), etc.

CFI (Cognitive Function Index)

1. Compared to one year ago, do you feel that your memory has worsened generally?
   - Yes
   - No
   - Maybe

2. Do others tell you that you tend to repeat questions or lose things?
   - Yes
   - No
   - Maybe

3. Have you been having trouble with things more often?
   - Yes
   - No
   - Maybe

4. Do you find that it takes you longer to switch between tasks?
   - Yes
   - No
   - Maybe

5. Do you need more help from others to remember appointments, family events, or holidays?
   - Yes
   - No
   - Maybe

6. Do you have more trouble recalling names, finding the right word, or completing sentences?
   - Yes
   - No
   - Maybe

7. Do you have more trouble deciding about, or getting lost, when traveling?
   - Yes
   - No
   - Maybe

8. Compared to one year ago, do you have more difficulty in managing money (paying bills, managing change, completing tax forms)?
   - Yes
   - No
   - Maybe

9. Are you less involved in social activities?
   - Yes
   - No
   - Maybe

10. Have you worked in a job or volunteered significantly compared to one year ago?
    - Yes
    - No
    - Maybe

11. Do you have more trouble following the news, watching TV, or using your computer compared to one year ago?
    - Yes
    - No
    - Maybe

12. Are there any activities (e.g., hobbies, such as card games, crafts) that are substantially more difficult for you now compared to a year ago?
    - Yes
    - No
    - Maybe

13. Are you more likely to be confused or have trouble finding your way home from a place you know?
    - Yes
    - No
    - Maybe

14. Do you have more difficulty using household appliances (such as the washing machine, VCR, or computer)?
    - Yes
    - No
    - Maybe

See Amariglio RE, et al. JAMA Neurol 2015 for utility
● INTEGRATE:

● **Step 1: Is there something potentially wrong? Detection of potential Impairment [Delineate the Cognitive Functional Status]**
  - At what likely level: Cognitively unimpaired (CU), subjective cognitive impairment (SCD); Mild Cognitive Impairment (MCI), mild Dementia,?

● **Step 2: What is wrong? [ Syndromic Dx ]**
  - What are the characteristic of what is wrong
  - **Define the Cognitive-Behavioral Syndrome** (e.g. amnestic syndrome, PPA, PCA) and refine stage (e.g. Amnestic single MCI; multidomain amnestic and dysexecutive dementia in the mild stages; multidomain, non-amnestic, behavioral and language dementia in mild stages)

---

**Has there been a change, and in what domains - patient and care partner can complete separately (then can ask how long, fluctuating, progressive?)**

<table>
<thead>
<tr>
<th>Cognitive Symptoms</th>
<th>First Symptom (mark only one)</th>
<th>Worst Symptom (mark only one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent or Short-term Memory</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>(problems making new memories, forgetting recent events or conversations, losing/misplacing items)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term Memory</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>(remembering events from years/decades ago)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention/Concentration</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>(being more distractible, losing your train of thought, having short attention span)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organization, Planning, Multi-tasking, completing tasks</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>Judgment, Reasoning or Problem Solving</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>Language</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>(having hesitancy in speech; having difficulty with word finding, ability to communicate, reading, writing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orientation to day, date, time, timing of life events</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>(remembering the correct day, date, time relation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visuospatial Orientation &amp; Function</td>
<td>Yes</td>
<td>NO</td>
</tr>
<tr>
<td>(getting lost, finding way around, recognizing objects, not seeing things right in front of them)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Yes</td>
<td>NO</td>
</tr>
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</table>

Search for NACC UDS forms (judgment of symptoms – modify to fit your practice and EMR or use AD-8, IQ-CODE, CFI (Cognition Function Index), ADC-Q, etc.)
CFI (Cognitive Function Index)

1. Compared to one year ago, do you feel that your memory has declined substantially? □ Yes □ No □ Maybe
2. Do others tell you that you tend to repeat questions over and over? □ Yes □ No □ Maybe
3. Have you been simplifying things more often? □ Yes □ No □ Maybe
4. Do you find that family and friends notice changes in your abilities, such as speaking clearly or remembering recent events? □ Yes □ No □ Maybe
5. Do you need more help from others to remember important appointments, family occasions, or holidays? □ Yes □ No □ Maybe
6. Do you have more trouble recalling names, finding the right word, or completing sentences? □ Yes □ No □ Maybe
7. Do you have more trouble driving or, do you drive more slowly, have more trouble at night, tend to get lost, have accidents? □ Yes □ No □ Maybe
8. Compared to one year ago, do you have more difficulty managing money (e.g., paying bills, calculating change, completing tax forms)? □ Yes □ No □ Maybe
9. Are you involved in social activities? □ Yes □ No □ Maybe
10. Has your work performance (paid or volunteer) declined significantly compared to one year ago? □ Yes □ No □ Maybe
11. Do you have more trouble following the news, watching TV, movies, or reading? □ Yes □ No □ Maybe
12. Are there any problems (e.g., difficulty with memory, increased drowsiness) that are substantially more difficult for you now compared to one year ago? □ Yes □ No □ Maybe
13. Are you more likely to become disoriented, or get lost, for example when traveling to another city? □ Yes □ No □ Maybe
14. Do you have more difficulty using household appliances, such as the washing machine, VCR or computer? □ Yes □ No □ Maybe

See Amariglio RE, et al. JAMA Neurol 2015 for utility

Level of Arousal

- **Describe what you observe**

Common terms (e.g. “sleepy”) mean different things to different people – everything to awake and relatively alert to nearly comatose

The same goes for terms such as “arousable, sleepy, somnolent, obtunded, comatose”.

AAGP 2017_Dalla TX_Alzheimers 5
Orientation

- Context (situation)
- Person (s)
- Spatial location (place: state, city, hospital, bldg, floor)
- Temporal (year, season, month, day, date, time of day, exact time)

Memory

In different domains – verbal, visual, spatial

- Immediate: Registration/encoding (items, name & address, story, copying figures, asking for belongings or hiding objects in the room)
- Delayed Recall and Recognition - after a delay of at least 5 minutes
- Intermediate-term (recent events, conversations)
- Long-term
  - Autobiographical (where born, went to school, jobs, …)
  - Semantic – general knowledge (name of president, VP, year(s) of WWII)
- Current events -- Ask about their interests or if they have been following the news, and then ask them about something you know the answer to in those domains
- Their medications, what they are for, schedules and dosages
- Ask the names of their other health care providers
Language

Aphasia: disorder of communication

- Fluency
- Comprehension
  - "If a lion and a tiger fight and the tiger eats the lion, which animal is still alive?" or
  - A multi-step command, preferably across midline: "Please take your left thumb, touch your right ear, and then point to the door"

- Reading
- Writing (sentence with subject and verb)
- Repeating ("The Bruins scored two touchdowns in the fourth quarter to beat the Trojans")
- Naming (go from high frequency to low frequency)

Visuospatial Cognition

Perception, integration of details into a whole, structure, and spatial relations

- Copying a cube or intersecting pentagons
- Construction and mental manipulation of objects
- Drawing a clock-face and the hands of the clock to a specified time ("Please draw a large round clock face with all the numbers in place; now draw the hands of the clock for it to show ten minutes past 11")
- Counting different arrangements of dots without touching them (9, 7, 8, 10 dots)
- Perceiving overlapping or degraded letters
Specialized Mental Functions/ Multimodal Dysfunction

- Calculations
- Reasoning/Problem Solving
- Abstraction
- Insight
- Judgment
- Neglect
- Agnosia
- Apraxia

Calculation, Reasoning, Problem Solving, Abstraction

- # of quarters in $6.75; $3.25; $2; $1
- Calculate tip: 15% of $120 bill
- Word problems:
  - “If a dozen eggs cost $1.20 how much would 3 eggs. Cost?”
  - “If it takes 4 workers to complete a job in 6 hours, how many workers would you need to complete the job in ½ hour?”
- Similarities and differences
  - Similarity between: train & bicycle, desk & book case, clock & ruler
  - Difference between: lie & mistake, river & canal
Praxis

- **Apraxia** - loss of the ability to execute or carry out learned purposeful movements, despite having the desire and the physical ability to perform the movements
  
  - *Ideomotor* (inability to carry out a motor command, for example, “act as if you are brushing your teeth” or “salute”) – most common form, is usually caused by lesions of (language) dominant hemisphere
    - *limb apraxia* when movements of the arms and legs are involved,
    - *nonverbal-oral or buccofacial* (inability to carry out facial movements on command, e.g., lick lips, whistle, cough, or wink)
  
  - *Ideational* (inability to create a plan for or idea of a specific movement, for example, "pick up this pen and write down your name") – most commonly encountered during encephalopathy (delirium, confusional state)

---

**Need to Assess Multiple Domains in Evaluation of Suspected CI/Dementia**

Changes or Problems with Cognition, Daily Living Function, Neuropsychiatric symptoms/Behavior, Global Function, can impact QoL for affected individuals, their loved ones and their community

### Representative Assessment Scales

<table>
<thead>
<tr>
<th>Domain</th>
<th>Considerations</th>
<th>Example Scale(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td>• Key change of interest in dementia</td>
<td>MoCA, MMSE, SLUMS, SIB* GP-Cog, ADAS-cog*, BDS-IMC</td>
</tr>
<tr>
<td>Daily Living Function</td>
<td>• Ability to carry out ADL</td>
<td>ADCS-ADL, FAQ, IADL</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>• Often referred to as BPSD</td>
<td>NPI</td>
</tr>
<tr>
<td>Function/Behavior</td>
<td>• Can be hazardous; related to institutionalization and caregiver stress</td>
<td>ADCS-ADL, FAQ, IADL</td>
</tr>
<tr>
<td>Staging/Severity</td>
<td>• Staging of dementia</td>
<td>QDRS, CDR, GDS, FAST</td>
</tr>
<tr>
<td>Quality of life</td>
<td>• Multidimensional; reflects patient’s perception of impact of illness on everyday functioning</td>
<td>ADRQL, PDS</td>
</tr>
<tr>
<td>Depression</td>
<td>• Common symptom, but can be challenging to assess</td>
<td>Cornell Depression in Dementia Scale</td>
</tr>
<tr>
<td>Caregiver burden</td>
<td>• Major issue in dementia</td>
<td>General Health Questionnaire ZBI Caregiver Burden Interview (ZBI)</td>
</tr>
<tr>
<td>Global Impression</td>
<td>• Designed to assign an overall level and assess changes in patient’s condition</td>
<td>ADCS-CGIC*, CIBIS/CIBIC-Plus*</td>
</tr>
</tbody>
</table>

---

### Validated Brief Cognitive Test Instruments

<table>
<thead>
<tr>
<th>Cognitive Screen</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Mini Mental State Examination (MMSE)** | • Still widely used; copyright (~$1.23 per use required)  
  • Has norms for age, ethnicity, education  
  • Takes 7–10 minutes  
  • Limited executive-function assessment  
| **Montreal Cognitive Assessment (MoCA)** | • Most accessible/multiple languages; Blind MoCA  
  • Excellent sensitivity for MCI; more difficult than MMSE  
  • Takes 10-15 minutes  
| **St. Louis University Mental Status Examination (SLUMS)** | • Less utilized; mostly studied in VA population  
  • Take 7–10 minutes  
  • Good sensitivity for MCI; more difficult than MMSE  
| **Mini-Cog** | • Simple: consists of clock draw (for executive function) and recall of 3 words  
  • Good sensitivity for dementia (equivalent or better than MMSE); unclear for MCI  

---

Validated Brief Cognitive Test Instruments

<table>
<thead>
<tr>
<th>Test Instrument</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-Minute Screen (7MS)</td>
<td>10-15</td>
<td>Developed and suited for detection of AD/dementia; components test memory (enhanced free and cued recall), temporal orientation, semantic (animal category) verbal fluency and a 7-point CDT; administration and scoring may be better suited for specialty setting</td>
</tr>
<tr>
<td>Short Test of Mental Status (STMS)</td>
<td>10-15</td>
<td>Robust test for assessing several domains to detect and track MCI and dementia; validated in primary care, administration and scoring may be better suited for specialty setting</td>
</tr>
<tr>
<td>Blessed Dementia Scale Information-Memory-Concentration Test (BDS-IMC)</td>
<td>10-15</td>
<td>Well-validated for AD neuropathology and detecting and tracking AD dementia progression from mild through very severe stages. Not sensitive for non-amnestic MCI. Verbal test (no writing/copying) with emphasis on memory and information (limited executive function and no visuospatial component).</td>
</tr>
<tr>
<td>Cambridge Cognitive Examination (CAM-Cog)</td>
<td>20-25</td>
<td>Suited for specialty settings, provides multiple cognitive domain scores</td>
</tr>
<tr>
<td>Addenbrooke's Cognitive Exam (ACE-III)</td>
<td>20-30</td>
<td>Suited for specialty settings; provides multiple cognitive domain scores</td>
</tr>
<tr>
<td>Frontal Assessment Battery (FAB)</td>
<td>10</td>
<td>Suited for specialty settings; provides a structured examination of frontal systems function</td>
</tr>
</tbody>
</table>

Blessed (BDS–IMC)

- Based on total errors
- Range = 0-37 errors
- Rule of thumb 0-3 errors is within non-impaired range for older individuals (beware of the pattern – e.g. if all three errors are on memory then it’s not normal!)
- Address delayed recall should be 5 minutes
- Generally regarded as a better tool for tracking decline in dementia, less sensitive to early change
MOCA

Scored out of 30
Cut off for Impairment: <26*  
(high specificity but impacted by low education)
*Add 1 point if ≤ 12 yrs education
- multiple versions
- available in multiple languages
- visually impaired version scored out of 22 (skips top two panels) → can be administered remotely

www.mocatest.org
**MOCA Cued Recall**

<table>
<thead>
<tr>
<th></th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category cue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple choice cue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MOCA Multiple Choice Recognition**

- **FACE**: category cue: part of the body
  - multiple choice: nose, face, hand
- **VELVET**: category cue: type of fabric
  - multiple choice: denim, cotton, velvet
- **CHURCH**: category cue: type of building
  - multiple choice: church, school, hospital
- **DAISY**: category cue: type of flower
  - multiple choice: rose, daisy, tulip
- **RED**: category cue: a color
  - multiple choice: red, blue, green
**MoCA Memory Index Score (MoCA-MIS)**

<table>
<thead>
<tr>
<th>Montreal Cognitive Assessment</th>
<th>MoCA-MIS (Memory Index Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Word</td>
<td>Free recall (3 points each correct)</td>
</tr>
<tr>
<td>Face</td>
<td></td>
</tr>
<tr>
<td>Velvet</td>
<td></td>
</tr>
<tr>
<td>Church</td>
<td></td>
</tr>
<tr>
<td>Daisy</td>
<td></td>
</tr>
<tr>
<td>Red</td>
<td></td>
</tr>
<tr>
<td>Subscores</td>
<td>(0-15)</td>
</tr>
</tbody>
</table>

**MIS Total Score (range 0-15)**


---

**MOCA Index Scores**

**The Memory Index Score (0–15 points)**
Number of words recalled in delayed free, category-cued, and multiple-choice conditions, multiplied by 3, 2, and 1, respectively.

**The Executive Index Score (0–13 points)**

**The Visuospatial Index (0–7 points)**
Cube Copy, Clock, and Naming.

**The Language Index Score (0–6 points)**
Naming, Sentence Repetition, and Letter Fluency.

**The Attention Index Score (0–18 points)**
Digit Span, Letter A Tapping, Serial 7 Subtraction, Sentence Repetition, and Words Recalled in Both Immediate Recall Trials.

**Orientation Index Score (0–6 points)**
All Orientation items
# Case 1, Dr. AA: 64 yo RHWM employed executive

- **Chief complaint:** “some changes at work … finding it more stressful …”
- **History:** AA states – working in a fast-paced and demanding environment and noticing more work stress and mild changes in his work efficiency. He is sleeping less and waking early concerned about work. Wife states (did not accompany AA, I called her on the phone) -- AA seems more stressed, has forgotten or misremembered some conversations & and context and timing of life events, some repetitiveness in statements.
- **Structured multidomain review of cognition, daily function, behavior/neuropsychiatric symptoms, sensorimotor function**
- **Structure review of Cognitive domains/symptoms:** (Scale for below: 0 = wnl, Tr = subtle/very mild, 1+ = mild, 2+ = moderate , 3+ = severe)
  - **Memory:** 1+
    - Repetitive, misremembering
  - **Attention:** 2+ (“always been that way to some degree”)
  - **Executive Function:** 1-2+
  - **Language:** 0
  - **Behavior:** 1-2+
    - Judgment and interaction issues with team at work, considered to be more aloof and less sensitive and dismissive, anxious, mildly less motivated

---

# Case 1: 64 yo RHWM employed executive

- **Daily Function:** independent with subtle decline
  - FAQ 5/30 (bill paying, taxes, shopping, current events, remembering appts)

- **Behavior/Neuropsychiatric Symptoms:**
  - NPIQ severity = 7 (irritability, anxiety depression/dysphoria, disinhibition, lability, night-time behaviors)
  - NPIQ distress = 9 (mild distress)
  - Geriatric Depression Scale (GDS) = 3 (not suggestive)

- **Sensorimotor:** none
Case 1: 64 yo RHWM employed executive

- Risk Factors for Cognitive-Behavioral Impairment/Dementia: none (parents alive and well) except one minor “concussion” age 14 playing baseball (no LOC)
- Safety: okay
- PMH: “borderline” hypertension – no meds
- Meds: none
- Supplements: multivitamin
- Developmental Hx: no issues; could be inattentive “or absent-minded in a professorial way”, BS/PhD from elite universities
- SHx: married x37 yrs, working as high level executive, adult children
- Health Related Behavior: rare EtOH, good exercise in past less now
- Caregiver: Zarit like scale moderate burden

Case 1: 64 yo RHWM employed executive

- Medical & Elemental Neurologic Exam: Unremarkable
- Neurobehavioral Status Exam:
  - Appropriate, attentive to examiner
  - MoCA = 27/30
  - Pattern of points missed: - 3 on recall
  - Encoding of 5 words: 5/5 first trial; 5/5 second trial
  - Recall: MoCA MIS (Memory Index Score 0-15) = 7/15 (0/3 with cue, 1/3 from multiple choice)
Montreal Cognitive Assessment  MoCA-MIS (Memory Index Score)

<table>
<thead>
<tr>
<th>Word</th>
<th>Free recall (3 points each)</th>
<th>Cued recall (2 points each)</th>
<th>Multiple Choice Recognition (1 point each)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>+ (3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Velvet</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Church</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Daisy</td>
<td>-</td>
<td>-</td>
<td>+ (1)</td>
</tr>
<tr>
<td>Red</td>
<td>+ (3)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Subscores 6 0 1

MIS Total Score (range 0-15) 7


Case 1: 64 yo RHWM employed executive

- Medical & Elemental Neurologic Exam: Unremarkable
- Neurobehavioral Status Exam:
  - Awake and alert, no fluctuations, appropriate, attentive to examiner
  - MoCA = 27/30
  - Pattern of points missed: - 3 on recall
  - Encoding of 5 words: 5/5 first trial; 5/5 second trial
  - Recall: MoCA MIS (Memory Index Score 0-15) = 7/15 (0/3 with cue, 1/3 from multiple choice)
- Letter Fluency (F) in 60 sec = 25
- Animal Fluency in 60 sec = 14
- Naming (from ACE-R): 12/12 (Very occasional word-finding hesitation)
- Appeared to give good effort on testing
- Denied depression and significant anxiety → mood/affect congruent and not suggestive of clinical depression or anxiety
Case 1: 64 yo RHWM employed executive

- Good case to refer for formal neuropsychological evaluation → need more nuanced information and sensitive cognitive testing befitting of Dr. A’s estimated pre-morbid level of functioning!

Cognitive Behavioral Syndromes and DDx of Neuropathological Cause – connection between syndrome and cause(s) (etiology) are probabilistic not deterministic associations

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cognitive-behavioral major characteristics</th>
<th>Differential Diagnosis of Neuropathological Cause(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive amnestic syndrome</td>
<td>Difficulty learning and remembering new information; often accompanied by executive dysfunction, depression, or anxiety</td>
<td>Usually due to AD; sometimes due to DLB or ADHDS, occasionally due to CBD; very rarely due to FTD or CBD</td>
</tr>
<tr>
<td>(single- or multi-domain)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive aphasic syndrome/primary progressive aphasia</td>
<td>Speech and language impairment, e.g., word-finding difficulty, anomia, speech sound errors, impaired repetition (often due to impaired auditory-verbal working memory), alexia, agraphia</td>
<td>Common causes of primary progressive aphasia are AD, semantic dementia, and primary progressive aphasia (PPA), but AD is the most common.</td>
</tr>
<tr>
<td>Progressive visuospatial dysfunction/posterior cortical atrophy</td>
<td>Difficulty with visual/spatial perception/cognition, often with limb apraxia, ideomotor apraxia, and related cognitive dysfunction localizable to posterior cortical regions</td>
<td>Usually due to AD; occasionally due to DLB or ADHDS; occasionally due to CBD; very rarely due to FTD or CBD</td>
</tr>
<tr>
<td>Progressive behavioral/frontal/dysexecutive syndrome</td>
<td>Changes in comportment, personality, and social/interpersonal/emotional behavior; often includes early difficulty with executive function (judgment, problem-solving, reasoning, and distress)</td>
<td>Usually due to FTD-related pathology (FTLD-tau or FTLD-TDP-43); not uncommonly a presentation of young onset AD; or due to CBD, mixed AD-CBD; sometimes due to DBB, PS-CBD</td>
</tr>
<tr>
<td>Primary FTD-spectrum syndrome with cognitive features/primary somatoform/motor cortical-related syndrome</td>
<td>Elements of FTD-spectrum syndromes (e.g., motor dysfunction); some FTD-spectrum syndromes are related to motor systems; motor behaviors may resemble motor symptoms of AD; also difficulty in speaking, eating, and swallowing</td>
<td>LBD (manifest as DLB or PDD) or mixed LBD with AD and VBD; sometimes PS-TD, CBD, MSA; rarely AD (sometimes AD in DBB)</td>
</tr>
</tbody>
</table>

* Atri, 2019; Shaughnessy et al. 2019
Conclusions

“Where there is no hope, there can be no endeavour” ~ Samuel Johnson

THANK YOU!

Twitter: @TheDrAtri
Providing Practical Compensatory Strategies for Cognitive Decline

Lynn W. Shaughnessy, PsyD, ABPP/CN
Providing Practical Compensatory Strategies for Cognitive Decline

Lynn Shaughnessy, PsyD, ABPP/CN
Director, Neuropsychology
Department of Neurology
Beth Israel Deaconess Medical Center
Harvard Medical School

Disclosures

None
Overview

1. Goals of Neuropsychology
2. Psychosocial Model of Dementia Care
3. Compensatory Strategies Based on Cognitive Findings
   • Memory
   • Visuospatial
   • Language
   • Executive/Behavioral
   • Executive/Attention

Goals of Neuropsychology

1. To define the cognitive behavioral syndrome and level of impairment/magnitude of cognitive change
2. To provide insights into differential diagnosis
3. To monitor cognitive status or trajectory of disease progression over time through repeat evaluation
4. To characterize the profile with regard to both cognitive strengths and weaknesses, as well as functional changes
5. To provide personalized recommendations surrounding potential treatments and/or interventions that can help patients and care partners, and inform capacity for managing instrumental activities of daily living (eg, finances, medication, appointments, driving).
Dementia Care Models

- Psychosocial models of dementia care and intervention often focus on a clinical diagnosis, without specific attention to the presenting symptoms or their magnitude.
- This approach may lead to care based solely upon dementia diagnosis, and may not take into account overall suitability for the intervention.
- This may apply to approaches designed for patient or caregiver.

Northwestern Care Pathway Model for Dementia (CARE-D)™

Provide psychoeducation and connect them to resources...

- Alzheimer’s Assoc. - https://www.alz.org/
- The Assoc. for Frontotemporal Degeneration - https://www.theaftd.org/
- Lewy Body Dementia Assoc. - https://www.lbda.org/
- National Aphasia Assoc - https://www.aphasia.org/aphasia-resources/primary-progressive-aphasia/
- Alz Assoc. Care Navigation - https://www.alzheimersnavigator.org/
Memory: Forgets appointments, names, recent events, meds, misplaces items, repeats the same question

**Internal Strategies**

- Mnemonics
- Connect new information with information you already know (make associations, create context)
- Rhyming
- Clustering – grouping similar information together allows you to remember more (categories, numbers)
- Repeat, Reframe, Associate

**External Strategies**

- Pillbox to help manage medication
- Memory table
- To-do lists
- Calendar and daily planner
- Alarms
- Memory notebook
- Reminders and post-it notes (e.g., on the front door to remember something before leaving)
- Use simple labels on a few of the most-used drawers and cabinets
- White board
Memory: Forgets appointments, names, recent events, meds, misplaces items, repeats the same question

• External Strategies

Use of Technology (Apps)
• Find Items: Tile, TrackR
• Med Management: MediSafe, Round Health
• To-do Lists: Microsoft To-Do, Google Keep, Any.do, It’s Done!
• Note Taking: Evernote, Google Keep
Visuospatial: Poor depth perception, trouble locating objects, easily lost, reading, cannot see the ‘bigger picture’

- Use other sense systems, such as touch, words, or smell, to obtain and communicate information
- Work with only one object at a time
- Keep things simple and organized

Visuospatial: Poor depth perception, trouble locating objects, easily lost, reading, cannot see the ‘bigger picture’

- Environmental Modifications
  - Decrease clutter (store only a few things together)
  - Use proper lighting (even lighting, night lights)
  - Mark stairs with alternating colored tape to provide better visual contrast for safety
  - Reflective tape can mark changes in floor levels
  - Decals applied to sliding glass doors can make them more visible.
  - Reduce glare
**Visuospatial:** Poor depth perception, trouble locating objects, easily lost, reading, cannot see the ‘bigger picture’

Use of Technology

• Talking watches, alarms, large numbered phone, voice activated tools
• Audio books
• GPS technology
• MedicAlert® + Alzheimer's Association Safe Return® Program (https://www.alz.org/help-support/caregiving/safety/medicalert-with-24-7-wandering-support)
**Language: Reduced word finding, comprehension, spelling, reading**

- Create a communication-friendly environment
- Quiet, one-on-one conversations
- Simple sentences
- Modified community activities (e.g., volunteer work that does not rely on communication – dog walking)
- Script rehearsal for telephone or social contexts
- Checking for understanding

**Language: Reduced word finding, comprehension, spelling, reading**

Encourage Alternate Communication

- Hand signals or movements
- Pointing to objects
- Drawing or showing pictures
- Speech and language pathology can help with further compensatory recommendations (e.g., communication board or wallet with commonly used words or pictures)
Executive/Behavioral: Poor judgement, social disinhibition, apathy, difficulty initiating, planning, organizing, multitasking

- Communication tips for family (e.g., 3 R's – Repeat, Reassure, Redirect)
- Written cues to decrease perseveration and increase initiation of questions during conversation
- Increase organization/structure, create a daily schedule
- Respite care for primary caregiver
**Executive/Behavioral:** Poor judgement, social disinhibition, apathy, difficulty initiating, planning, organizing, multitasking

Modifications
- Limit access to bank accounts
- Reduce access to unhealthy foods and beverages
- Limit access to potentially dangerous items
- Carry a card that briefly explains the condition and typical features (e.g., limited judgement, withdrawal, or inappropriate behavior) - (https://www.theaftd.org/living-with-ftd/resources/)

Safety devices
- GPS
- Home monitor device (e.g., nest)

---

**Executive/Attention:** Easily distracted, may drift off in conversation, ‘daydreamer’, may have trouble learning

- Encourage active attention
- In conversation, face directly toward someone and make eye contact
- Slow down and engage the senses
- Take time to notice the details of the environment
- Practice mindfulness
- Work in a quiet, distraction-free environment
- Stay organized and use routines
Finally…

• Practical compensatory strategies can be tailored to each patient based on their particular strengths and weaknesses.
• Maintaining independence as much as possible supports quality of life.
• These strategies can be mixed and matched to create the ideal treatment plan.
• Involve the caregivers.

Thank You!

And… Because one of the most common memory complaints is trouble remembering names, I leave you with this…
Assessment of Daily Function and Neuropsychiatric Symptoms/Behavior and Staging of Dementia in Practice

Bradford C. Dickerson, MD, MMSc
Dementia: A Comprehensive Update
Assessment of daily function & neuropsychiatric symptoms of dementia in practice
Bradford C. Dickerson, M.D.
Associate Professor of Neurology, Harvard Medical School
Director, Frontotemporal Disorders Unit, Mass General Hospital
Martinos Center for Biomedical Imaging
brad.dickerson@mgh.harvard.edu

Disclosures

Data Safety Monitoring Board:
Merck

Consulting:
Arkuda, Axovant, Biogen, Lilly, Novartis, Wave LifeSciences
Med Learning Group, @PointofCare
Best Doctors.com, GrandRounds.com

Royalties:
Oxford University Press (Dementia: Comprehensive Principles and Practice, 2014)
Cambridge University Press (Hodges’ Frontotemporal Dementia, 2016)
Elsevier (Editor in Chief, Neuroimage: Clinical; Behavioral Neurology Section Editor, Cortex)
Independent function and quality of life

<table>
<thead>
<tr>
<th>Cognitive Functional Status</th>
<th>1. Cognitive Functional Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cognitively normal, Subjective Cognitive Decline, Mild Cognitive/Behavioral Impairment, Dementia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPA, bvFTD, Amnesic MCI, PCA, Amnesic &amp; Dysexecutive dementia, etc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>History from patient, informant(s)</td>
<td>Office based cognitive testing, neurologic exam, psychiatric interview, neuropsychological testing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurodegenerative Brain Disease</th>
<th>3. Neurodegenerative Brain Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTLD, AD, LBD, etc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal in Brain Structure?</th>
<th>Abnormal Brain Function?</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Glucose PET, SPECT, EEG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Molecular Brain Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid or Tau PET, CSF, etc.</td>
</tr>
</tbody>
</table>

Dickerson et al., CNS Spectrums 2017; Wong & Dickerson, Neurodegener Dis Mgmt 2019
Overall Cognitive Functional Status (Staging)

defined by loss of independent function due to cognitive or behavioral impairment

<table>
<thead>
<tr>
<th>Staging</th>
<th>Cognitive Normal</th>
<th>Subjective Cognitive Decline</th>
<th>Mild Cognitive Impairment (MC1)</th>
<th>Very Mild Dementia</th>
<th>Mild Dementia</th>
<th>Moderate Dementia</th>
<th>Severe Dementia</th>
<th>Advanced Dementia</th>
</tr>
</thead>
</table>

Levels of independent function

- **Advanced activities of daily living**
  - Performing at work (if not retired) or volunteer position, or performing mental tasks involved in former primary job
  - Handling complex finances (e.g., assembling tax records, business affairs, investment decisions)
  - Ability to hold positions of leadership in community organizations
  - Actively paying attention to and understanding a movie, TV program, book, or magazine
  - Participating in complex games (e.g., scrabble, crossword puzzles)
  - Navigating to unfamiliar areas
  - Keeping mail and papers organized
  - Developing a schedule in advance of anticipated events
  - Fixing things or starting and finishing projects (e.g., painting, repairing furniture, fixing appliances, plumbing work, yard work)
  - Using technology (Navigating an automated phone menu, Using automated teller services (ATM), Using a cell phone, Using a computer)

- **Instrumental activities of daily living**
  - Responsibility for own medications, ability to handle basic household finances, getting from one familiar place to another (transportation), food preparation, shopping, ability to use telephone, housekeeping, laundry

- **Basic activities of daily living**
  - eating, dressing, grooming/dental care, physical ambulation, bathing, toileting
Why is it important to establish the patient’s Cognitive Functional Status?

• A major goal of care planning for people with cognitive impairment or dementia is to help people maximize independence while maintaining safety
  • Cognitive Functional Status provides important information relevant for safety and care planning
• Adaptations and supports are critical and need to be re-evaluated regularly
  • Relates to symptoms affecting cognition and mood/behavior but ultimately their impact on independent function
• Many patients with dementia lack insight (understanding and appreciation of illness)
  • This worsens with worsening dementia status (stage)
• Creative approaches are often necessary to implement care plans
  • Relates to cognitive functional status and specific symptoms (especially insight and executive function, but also memory)

What to measure
How to measure

There are many widely used scales, many do not have well-established psychometric properties.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Content validity</th>
<th>Internal consistency</th>
<th>Criterion validity</th>
<th>Construct validity</th>
<th>Reproducibility</th>
<th>Response- ness</th>
<th>Floor or ceiling effect</th>
<th>Interpretability</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCS-ADL</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ADCS-ADL-Dev</td>
<td>-</td>
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<td>NA</td>
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<tr>
<td>ADL-PS</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
</tr>
<tr>
<td>ADL-PS</td>
<td>#</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>ADLQ</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bayer ADL</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bristol ADL</td>
<td>#</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Blessed DRS</td>
<td>?</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Crandall ADL</td>
<td>?</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
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<td>NA</td>
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<td>NA</td>
<td>?</td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lawton IADL</td>
<td>-(a)/(NA)(b)</td>
<td>(a)/(b)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
## How to measure – traditional measures

### Functional activities questionnaire

**Form D1.** Indicate the level of performance for each activity by circling the appropriate response.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Not applicable</th>
<th>Normal</th>
<th>No difficulty, but does it at all?</th>
<th>Requires assistance</th>
<th>Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Writing checks, paying bills, or balancing a checkbook</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Assembling tax records, business affairs, or other papers</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Shopping, care for clothes, household accessories, or groceries</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Playing a game of skill such as bridge or chess, working on a hobby</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Heating water, making a cup of coffee, turning the stove</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Preparing a balanced meal</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Keeping track of current events</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Paying attention to and understanding a TV program, book, or newspaper</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Remembering appointments, family occasions, holidays, milestones</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. Travelling out of the neighborhood, driving, or arranging to take public transportation</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Pfeffer, Kuroski, Harrah et al. J Geront (1982)**

### How to measure – traditional measures

ADCS FAQ is used in many trials

| 24-30 normal | 20-23 mild impairment | 10-19 moderate impairment | 1-9 severe impairment | 0 profound |

#### Questions:

4. In the past 4 weeks, did [S] clean a living, eating, or family room?
   - Yes
   - No
   - Don't Know

5. In the past 4 weeks, did [S] balance his/her checkbook or a credit card statement?
   - Yes
   - No
   - Don't Know

6. In the past 4 weeks, did [S] ever write things down?
   - Yes
   - No
   - Don't Know

   **Note:** If [S] wrote things only after encouragement or with help, the response should still be 'yes.'

   - Yes, which best describes the most complicated things that he/she wrote:
     - Without supervision or help
     - With supervision
     - With physical help

7. In the past 4 weeks, did [S] clean a load of laundry?
   - Yes
   - No
   - Don't Know

   - Yes, which best describes how he/she usually performed:
     - Without supervision or help
     - With supervision
     - With physical help

**Galasko et al 1997**
How to measure – new measures
Amsterdam IADL

Proxy (spouse, child, friend) completes the questionnaire
Adaptive content
Administration time: 10 minutes short version / 20 minutes long version

Case example
FAQ vs. Amsterdam IADL

Man (57), business support manager who presents with a detailed description of his memory problems and word finding difficulties
Spouse: progressive forgetfulness since age 54, problems with complex daily tasks, increasingly insecure doing activities that used to be second nature
Cognitive testing: MMSE 24/30, MoCA 19/30
FAQ: 8/30 (>6 is usually consistent with mild dementia)
Amsterdam IADL questionnaire: 39/100 (>50 is usually consistent with mild dementia)
How to measure – new measures

The Harvard Automated Phone Task (APT)
Navigating an interactive voice response system

Cognitive Functioning Instrument (CFI)
Self-report as an early marker of cognitive decline

1. Cognitive Functional Status
   Cognitively normal, Subjective Cognitive Decline, Mild Cognitive/Behavioral Impairment, Dementia

2. Cognitive-Behavioral Syndrome
   PPA, bvFTD, Amnesic MCI, PCA, Amnesic & Dysexecutive dementia, etc.

   Symptoms
   History from patient, informant(s)

   Signs
   Office based cognitive testing, neurologic exam, psychiatric interview, neuropsychological testing

3. Neurodegenerative Brain Disease
   FTLD, AD, LBD, etc.

   Abnormal in Brain Structure?
   MRI

   Abnormal Brain Function?
   Glucose PET, SPECT, EEG

   Molecular Brain Pathology
   Amyloid or Tau PET, CSF, etc.
Diagnostic formulation
Cognitive-behavioral syndrome – specifying behavioral symptoms

Billing codes: Dementia with or without behavioral symptoms

Descriptive codes, examples:
- MCI, amnesic and dysexecutive syndrome with depression & irritability
- Dementia, dysexecutive and aphasic syndrome with apathy
- Dementia, bvFTD; executive dysfunction with predominant disinhibition, hyperorality

Behavioral-neuropsychiatric symptom assessment: general instruments

Behavioral Pathology in AD Rating Scale (BEHAVE-AD) (B Reisberg 1987; 2014)
Neuropsychiatric Inventory (Cummings 1994)
Cambridge Behavioral Inventory (J Hodges 2000)
### Cambridge Behavioral Inventory

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory and Orientation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has poor day-to-day memory</td>
<td>(e.g. about conversations, trips etc.)</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Asks the same questions over and over again</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Loses or misplaces things</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Forgets the names of familiar people</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Forgets the names of objects and things</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Shows poor concentration when reading or watching television</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Forgets what day it is</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Becomes confused or muddled in unusual surroundings</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td><strong>Everyday Skills</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has difficulties using electrical appliances (e.g. TV, radio, cooker, washing machine)</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Has difficulties writing (letters, Christmas cards, lists etc.)</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Has difficulties using the telephone</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Has difficulties making a hot drink (e.g. tea/coffee)</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Has problems handling money or paying bills</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td><strong>Self Care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has difficulties grooming self (e.g. shaving or putting on make-up)</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Has difficulties dressing self</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Has problems feeding self without assistance</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Has problems bathing or showering self</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td><strong>Abnormal Behaviour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finds humour or laughs at things others do not find funny</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Has temper outbursts</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Is uncooperative when asked to do something</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Shows socially embarrassing behaviour</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Makes tactless or suggestive remarks</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Acts impulsively without thinking</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cries</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Appears sad or depressed</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Is very restless or agitated</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Is very irritable</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td><strong>Beliefs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sees things that are not really there (visual hallucinations)</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Hears voices that are not really there (auditory hallucinations)</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Has odd or bizarre ideas that cannot be true</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td><strong>Eating Habits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefers sweet foods more than before</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Wants to eat the same foods repeatedly</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Her/his appetite is greater, s/he eats more than before</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Table manners are declining e.g. stuffing food into mouth</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td><strong>Sleep</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep is disturbed at night</td>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Sleeps more by day than before (cat naps etc.)</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td><strong>Stereotypic and Motor Behaviours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is rigid and fixed in her/his ideas and opinions</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Develops routines from which s/he cannot easily be discouraged e.g. wanting to eat or go for walks at fixed times</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Clock watches or appears pre-occupied with time</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Repeatedly uses the same expression or catch phrase</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td><strong>Motivation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shows less enthusiasm for his or her usual interests</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Shows little interest in doing new things</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Fails to maintain motivation to keep in contact with friends or family</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Appears indifferent to the worries and concerns of family members</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>Shows reduced affection</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
</tbody>
</table>

Cambridge Behavioral Inventory


Neuropsychiatric Inventory

Circle “Yes” only if the symptom(s) has been present in the last month. Otherwise, circle “No”. For each item marked “Yes”:

a) Rate the SEVERITY of the symptom (how it affects the patient):
   1 = Mild (Noticeable, but not a significant change)
   2 = Moderate (Significant, but not a dramatic change)
   3 = Severe (Very marked or prominent; a dramatic change)

b) Rate the DISTRESS you experience due to the symptom (how it affects you):
   0 = Not distressing at all
   1 = Mild (Slightly distressing, not a problem to cope with)
   2 = Moderate (Not very distressing, generally easy to cope with)
   3 = Severe (Fairly distressing, not always easy to cope with)
   4 = Extreme or Very Severe (extremely distressing, unable to cope with)

Please answer each question carefully. Ask for assistance if you have any questions.

Delusions

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEVERITY</td>
<td>2 3</td>
</tr>
</tbody>
</table>

DISTRESS: 0 1 2 3 4 5

Cummings JL et al., Neurology, 1994
# Neuropsychiatric Inventory

Please answer each question carefully. Ask for assistance if you have any questions.

<table>
<thead>
<tr>
<th>Item</th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>Does the patient have false beliefs, such as thinking that others are stealing from him/her or planning to harm him/her in some way?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Does the patient have hallucinations such as false visions or voices? Does he or she seem to hear or see things that are not present?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation/Aggression</td>
<td>Is the patient resistant to help from others at times, or hard to handle?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression/Dysphoria</td>
<td>Does the patient seem sad or say that he/she is depressed?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>Does the patient become upset when separated from you? Does he/she have any other signs of nervousness such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elation/Euphoria</td>
<td>Does the patient appear to feel too good or act excessively happy?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apathy/Indifference</td>
<td>Does the patient seem less interested in his/her usual activities or in the activities and plans of others?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>Does the patient seem to act impulsively, for example, talking to strangers as if he/she knows them, or saying things that may hurt people’s feelings?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability/Lability</td>
<td>Is the patient impatient or cranky? Does he/she have difficulty coping with delays or waiting for planned activities?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Disturbance</td>
<td>Does the patient engage in repetitive activities such as pacing around the house, handling buttons, wrapping string, or doing other things repetitively?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime Behaviors</td>
<td>Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite/Eating</td>
<td>Has the patient lost or gained weight, or had a change in the type of food he/she likes?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SEVERITY: 2 3 DISTRESS: 0 1 2 3 4 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Developed by Daniel Kado, MD. Final Version 3.0. All rights reserved. Jeffrey L. Cummings, MD. NP1-Q-2.

Cummings JL et al., Neurology, 1994
Neuropsychiatric symptoms before MCI or dementia

Data included in this study were collected for NACC Uniform Data Set visits conducted between August 2005 and January 2017. The sample was limited to cognitively normal individuals aged ≥60 years at their first visit, with at least one follow-up visit at which they were adjudicated to have MCI or dementia. Neuropsychiatric symptoms on participants were assessed approximately annually by the Neuropsychiatric Inventory Questionnaire (NPI-Q)

1998 cognitively normal participants who progressed to MCI or dementia (with or without MCI). 80% of participants had > 3 visits

Wise EA, Lyketsos, et al., ADAD, 2019
Neuropsychiatric symptoms before MCI or dementia

A majority developed neuropsychiatric symptoms before diagnosis of cognitive disorder.

Depression and irritability were most common NPSs before diagnosis.

Apathy, agitation, hallucinations, and delusions were rare before cognitive decline.

Wise EA, Lyketsos, et al., ADAD, 2019
Mild Behavioral Impairment

ISTAART research diagnostic criteria for MBI

1. Changes in behavior or personality observed by the patient, informant, or clinician, starting later in life (age ≥50 years) and persisting at least intermittently for at least 6 months. These represent clear change from the person’s usual behavior or personality as evidenced by at least one of the following:
   a. Decreased motivation (e.g., apathy, apsomania, indifference)
   b. Affective dysregulation (e.g., anxiety, dysphoria, changeability, euphoria, irritability)
   c. Impulse dyscontrol (e.g., agitation, disinhibition, gambling, obsessions, behavioral perseveration, stimulus bind)
   d. Social inappropriateness (e.g., lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits)
   e. Abnormal perception or thought content (e.g., delusions, hallucinations)

2. Behaviors are of sufficient severity to produce at least minimal impairment in at least one of the following areas:
   a. Interpersonal relationships
   b. Other aspects of social functioning
   c. Ability to perform in the workplace
   d. The patient should generally maintain his/her independence of function in daily life, with minimal aids or assistance.

3. Although comorbid conditions may be present, the behavioral or personality changes are not attributable to another current psychiatric disorder (e.g., generalized anxiety disorder, major depression, manic or psychotic disorders), traumatic or general medical causes, or the physiological effects of a substance or medication.

4. The patient does not meet criteria for a dementia syndrome (e.g., Alzheimer’s disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia). MCI can be concurrently diagnosed with MBI.

Ismail Z et al, Alz & Dementia 2016 ; https://mbitest.org

Mild Behavioral Impairment checklist

Please rate severity: 1 = Mild (noticeable, but not a significant change); 2 = Moderate (significant, but not a dramatic change); 3 = Severe (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

<table>
<thead>
<tr>
<th>This domain describes interest, motivation, and drive</th>
<th>YES</th>
<th>NO</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person lost interest in friends, family, or home activities?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does the person lack curiosity in topics that would usually have attracted her/his interest?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Has the person lost motivation to act on her/his obligations or interests?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Does she/he no longer care about anything?</td>
<td>Yes</td>
<td>No</td>
<td>1 2 3</td>
</tr>
</tbody>
</table>

Ismail Z et al, Alz & Dementia 2016 ; https://mbitest.org
# Mild Behavioral Impairment checklist

**This domain describes mood or anxiety symptoms**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Has the person become less able to experience pleasure?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Has the person become discouraged about their future or feel that she/he is a failure?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Does the person view herself/himself as a burden to family?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person become agitated, aggressive, irritable, or temperamental?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Has she/he become unreasonably or uncharacteristically argumentative?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Has the person become more impulsive, seeming to act without</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>considering things?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**This domain describes following societal norms and having social graces, tact, and empathy**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person become less concerned about how her/his words or actions affect others? Has she/he become insensitive to others’ feelings?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Has the person started talking openly about very personal or private matters not usually discussed in public?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Does the person seem to lack the social judgement she/he previously had about what to say or how to behave in public or private?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Does the person now talk to strangers as if familiar, or intrude on their activities?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**This domain describes strongly held beliefs and sensory experiences**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Has the person developed suspiciousness about the intentions or motives of other people?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Does she/he have unrealistic beliefs about her/his power, wealth or skills?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Does the person describe hearing voices or does she/he talk to imaginary people or “spirits”?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Does the person report or complain about, or act as if seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others?</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Ismail Z et al, Alz & Dementia 2016 ; https://mbitest.org
In-depth assessments

Depression: Geriatric Depression Scale (UDS); Cornell Scale for Depression in Dementia
Anxiety: Rating Anxiety in Dementia Scale (Shankar KK, 1999)
Agitation: Cohen-Mansfield Agitation Inventory
Apathy: Dimensional Apathy Scale (S Abrahams), Starkstein Apathy Scale, Apathy Evaluation Scale
Sleep: Mayo Sleep Questionnaire, Scales for Outcomes in PD-Sleep Scale (both in UDS LBD module), Pittsburgh Sleep Quality Index

Empathy & Perspective Taking: Interpersonal Reactivity Index (UDS)
Socio-Emotional Expressiveness & Flexibility: Revised Self-Monitoring Scale (UDS)
Social perception, affiliation, aversion: Social Impairment Rating Scale (Bickart & Dickerson, JNNP 2014)

NACC UDS: https://www.alz.washington.edu
NIMH Research Domain Criteria (RDoC) Domains and Constructs

Negative valence systems
Positive valence systems
Systems for social processes
Arousal/regulatory systems
Cognitive systems
Sensorimotor systems

https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/

RDoC Domains and Constructs
Negative valence

Negative valence systems (e.g.)
   Acute threat (fear)
   Potential threat (anxiety)
   Sustained threat
   Loss
   Frustrated non-reward

https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/
RDoC Domains and Constructs
Positive valence

Positive valence systems (e.g.)
- Reward responsiveness
  - anticipation, initial response, satiation
- Reward learning
  - reinforcement learning, habit formation
- Reward valuation
  - Ambiguity/risk, delay, effort

https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/

RDoC Domains and Constructs
Arousal/regulatory systems
- arousal
- sleep-wakefulness
- circadian rhythms

https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/
Cased-based Assessment and Application of Biomarkers in Dementia Clinical Practice

Alireza Atri, MD, PhD
Bradford C. Dickerson, MD, MMSc
Janet C. Sherman, PhD
David Wolk, MD
Case-based Assessment and Application of Biomarkers in Dementia Clinical Practice

Janet Sherman, PhD (neuropsychology)
David Wolk, MD (behavioral neurology)
Alireza Atri, MD, PhD (behavioral neurology)
Brad Dickerson, MD (behavioral neurology)

1. Cognitive-Functional Status
   Cognitively normal, Subjective Cognitive Concern, Mild Cognitive Impairment, Dementia

2. Cognitive-Behavioral Syndrome
   PCA, PPA, Amnesic MCI, bvFTD, Amnesic & Dysexecutive dementia, etc.

   Symptoms
   History from patient, informant(s)

   Signs
   Office based cognitive testing, neurologic exam, psychiatric interview, neuropsychological testing

3. Likely Neurodegenerative (or other) Brain Disease or contributing condition
   AD, FTLD, CVD, LBD, etc.

   Abnormal in Brain Structure?
   CT, MRI

   Abnormal Brain Function?
   Glucose PET, SPECT, EEG

   Molecular Brain Pathology
   Amyloid or Tau PET, CSF, etc.
The attorney who forgot the Superbowl

- 72 year old man, retired tax attorney
- Gradually increasing forgetfulness over past 2 years
  - Did not remember the “whole evening” of Superbowl party the next week; frequently argues with family about memory lapses
- Does family taxes but takes longer, serves on local housing community board, plays golf, engaged in other routine activities
- Wife/daughter prompted clinic visit

- PMH: HTN, HL
- Office cognitive testing:
  - MMSE: 29/30 (didn’t know name of hospital)
  - Good effort on testing, normal comportment
  - Speech and language including naming, reading, writing: normal
  - Verbal fluency: 11 F-words; 8 animals.
  - 7-item word list learning: 4, 5, 5 word encoding; 10’ delayed free recall 2, addition 3 with cues, 1 of remaining 2 with multiple choice

The attorney who forgot the Superbowl

- High average to superior premorbid intelligence
- Memory difficulties:
  - Difficulty encoding and retrieving verbal and visual information regardless of whether structured or not; memory not aided by cues or recognition format.
  - Subtle difficulty with aspects of executive functioning, including mildly weak speeded information processing, category fluency, and category switching. In contrast, working memory and set shifting (Trails B) intact.
  - Average verbal comprehension and visuospatial skills.
Cognitive-functional status?

1. Cognitively normal
2. Subjective cognitive concerns
3. Mild cognitive impairment/mild neurocognitive disorder
4. Dementia/major neurocognitive disorder

Cognitive-behavioral syndrome?

1. Amnesic MCI syndrome
2. Posterior cortical atrophy syndrome
3. Behavioral variant FTD syndrome
4. Primary progressive aphasia syndrome
5. Dysexecutive-predominant MCI syndrome
 Likely pathology (etiology)

1. Alzheimer’s disease (plaques, tangles, etc)
2. Cerebrovascular disease
3. Lewy body disease
4. Frontotemporal lobar degeneration
5. Mixed AD/cerebrovascular
6. No specific pathology
7. Not confident yet

MRI
Likely pathology (etiology)

1. Alzheimer’s disease (plaques, tangles, etc)
2. Cerebrovascular disease
3. Lewy body disease
4. Frontotemporal lobar degeneration
5. Mixed AD/cerebrovascular
6. No specific pathology
7. Not confident yet
The attorney who forgot the Superbowl

ALZHEIMER DISEASE NEUROPATHOLOGIC CHANGE [ADNC]:

Thal stage 5 of 5 for amyloid deposition Braak and Braak tangle stage: V of VI.

CERAD age related plaque score: Abundant

NIA-Alzheimer association score: A3B3C3

High probability of cognitive impairment due to Alzheimer Disease

CEREBROVASCULAR DISEASE: Hypertensive vasculopathy, moderate

The professor who got lost

• 80y F former English professor
  – Past 5 years, wasn’t seeing things she should have, missed turns; felt like “mind wandering”: chose to stop driving out of self-identified safety concerns
  – Noticed other visual problems; sought out ophthalmology appt to see if glasses prescription should be changed
  – Due to visual problems, difficulty with:
    • Finding things; looking for purse multiple times/day
    • Spatial orientation, even in familiar places
    • Map reading
    • Finding letters on keyboard: “no tactile memory”
    • Signing her name (“hard due to similarity of letters”)
    • Writing a check – uncertain as to what goes where
    • Dressing (putting t-shirts on backwards)
    • Color discrimination
    • ”The thing I’m worst at is drawing”
The professor who got lost

- Greater difficulty with aspects of executive functioning
  - Keeping track of points she is trying to make
  - Keeping track of appointments
  - Timing of dishes when cooking, now making simpler meals
  - Making even simple plans
- Increased anxiety: unsure if cause or effect of her increased visual difficulties

Primary care screening prior to presentation

Age 78
March 2013 MOCA: 28/30

Age 79
October 2014 MOCA: 29/30

Age 80
March 2015 MOCA: 22/30
Neuropsychological evaluation

Behavioral observations

– Very insightful, highly articulate, occasional wfd
– Intact attention and effort; gave up somewhat easily on figure copy tasks
– Most notable for visual perception difficulties:
  • Left hemi-neglect and some tendency to neglect bottom half of stimuli on a page; scanned from r to l
  • Visual search slow and inefficient
  • Difficulty following instructions for visual tasks; unable to complete rating forms due to visual confusion
  • Overwhelmed when attempting copy tasks and written math problems

Evaluation results

Intellectual functioning

• Superior estimated premorbid intellect
  – TOPF = 131; 98th %ile
• Superior Verbal Comprehension (98th %ile)
• Low Average Perceptual Reasoning (18th %ile)
• Cognitive screens:
  – MMSE: 27/30 (county, repetition, figure copy)
    ACE-R: Impaired only in visuospatial domain (-5)
Weak visuospatial functioning

• Visual construction:
  – Block Design: 16th %ile
  – Visuomotor integration: 2nd %ile

• Visuoperception:
  – Visual Form Discrimination: Severely Defective
  – Visual reasoning: 25th %ile
  – Accurate identification of nonoverlapping letter triplets, but impaired accuracy for overlapping letters (8/18)

[Diagram of a clock showing a time of 10:12]
Spatial dyscalculia

- Difficulty attending to multiple columns of numbers

\[
\begin{array}{c}
96 \\
53 \\
28 \\
+ 17
\end{array}
\quad +
\begin{array}{c}
589 \\
234 \\
+ 163
\end{array}
\]
Attention/Executive Functioning

– Average attention span and working memory
– Letter > category fluency
  • FAS: 55 words, 1 SL, 5 repetitions (95th %ile)
  • 11 animals (10th %ile), 12 vegetables (32nd %ile)
  • Intact category switching 12 fruit-furniture (75th %ile)
– Verbal reasoning > visual reasoning
  • Similarities: >99th %ile
  • Matrix reasoning: 25th %ile
– Slow visual tracking
  • Coding: 16th %ile
  • Trails A: 120", <1st %ile (accurate)
  • Trails B: 159": 25th %ile (2 SL errors)
– Retrieval-based difficulties (evident in naming, memory)

Memory performances

• Some difficulty with remote memory (e.g., failed to remember JFK)
• High average story memory at all stages vs. below average word list learning and impaired retrieval, though with average recognition
• Low average memory for visual information (designs) at all stages
• On an associative learning and memory task, both free and cued recall well wnl, without evidence for retentive memory difficulty.
Impressions

• Predominant problems with visuoperception and visual construction. Difficulties attending to, and processing visual information, especially when more complex.
  • Visual difficulties impact ADLs
• Preserved verbal abilities
• Preserved memory retention
• Variable exec. fx, in part due to visual processing difficulties

Neurological assessment

• PMH: asthma, hypothyroidism, breast carcinoma fully treated, no past neuropsychiatric history
• MoCA 26/30 (missed 4 items related to drawing)
• Neuro exam:
  – Extinction to double simultaneous stimulation in visual and somatosensory domains, mild simultanagnosia
  – Difficulty with face identification
  – Remainder of neuro exam unremarkable; no evidence of parkinsonism
Cognitive-functional status?

1. Cognitively normal
2. Subjective cognitive concerns
3. Mild cognitive impairment/mild neurocognitive disorder
4. Dementia/major neurocognitive disorder

Cognitive-behavioral syndrome?

1. Amnesic MCI syndrome
2. Posterior cortical atrophy syndrome
3. Behavioral variant FTD syndrome
4. Primary progressive aphasia syndrome
5. Dysexecutive-predominant MCI syndrome
Likely pathology (etiology)

1. Alzheimer’s disease (plaques, tangles, etc)
2. Cerebrovascular disease
3. Lewy body disease
4. Frontotemporal lobar degeneration
5. Mixed AD/cerebrovascular
6. Focal brain lesion (e.g., possible metastasis?)
7. Exacerbation of hypothyroidism
8. Not confident yet
Likely pathology (etiology)

1. Alzheimer’s disease (plaques, tangles, etc)
2. Cerebrovascular disease
3. Lewy body disease
4. Frontotemporal lobar degeneration
5. Mixed AD/cerebrovascular
6. Focal brain lesion (e.g., possible metastasis?)
7. Exacerbation of hypothyroidism
8. Not confident yet

Formulation

Mild cognitive impairment/very mild dementia,
Posterior cortical atrophy (PCA) syndrome,
likely due to atypical Alzheimer’s disease pathology
The man who forgot he had performed in a choir

76 y with PMHx of CABG, HTN, DM, hyperlipidemia

2-3 years of increasing forgetfulness
- Started missing appointments
- Forgot he had a performance in choir the day before
- Geographic disorientation

Now defers to wife for important decisions
- Mistakes with finances; wife has taken over
- Driving without problems
- Decreased motivation and interest

---

Neurologic/cognitive exam

Exam normal except slightly brisk reflexes

29/30 on MMSE (2/3 on recall)

Impaired Trails A, but normal Trails B
29/30 on Boston Naming Test (BNT)
Verbal Fluency:
- 13 Animals
- 14 F-words
Cognitive exam

Limited details of current events
3/5 delayed recall of a 5-element address;
recognized other 2 with multiple choice
10 item word-list
   Immediate Trial 1: 2/10 words
   Immediate Trial 2: 3/10 words
   Immediate Trial 3: 6/10 words
Delayed recall: 3/10 words
Recognition: 10 hits, 0 false alarms (100%)
Cognitive-functional status?

1. Cognitively normal
2. Subjective cognitive concerns
3. Mild cognitive impairment/mild neurocognitive disorder
4. Dementia/major neurocognitive disorder
Cognitive-behavioral syndrome?

1. Amnesic syndrome
2. Posterior cortical atrophy syndrome
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Likely pathology (etiology)

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Likely pathology (etiology)

1. Alzheimer’s disease (plaques, tangles, etc)
2. Cerebrovascular disease
3. Lewy body disease
4. Frontotemporal lobar degeneration
5. Mixed AD/cerebrovascular
6. No specific pathology
7. Not confident yet
Amyloid PET (florbetaben)

This case

Amyloid PET (florbetaben)

Comparison “negative” case
Amyloid PET Scan

Likely pathology (etiology)

1. Alzheimer’s disease (plaques, tangles, etc)
2. Cerebrovascular disease
3. Lewy body disease
4. Frontotemporal lobar degeneration
5. Mixed AD/cerebrovascular
6. No specific pathology
7. Not confident yet
Dementia due to Cerebrovascular Disease

- Autopsy
  - Severe atherosclerosis
  - Braak Stage 2
  - Sparse amyloid plaques
  - Low AD neuropathic change