Neuropsychology of Aging and Dementia

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Clinical Core Director,
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1. Concepts of cognitive aging
2. Neurodegenerative dementia: a large-scale neurocognitive network disorder
3. Role of neuropsychology in diagnosis: assessment principles
4. Neuropsychological profiles of dementia: Amnestic, Aphasic, Visuospatial, Compromtental
1. Concepts of cognitive aging

2. Neurodegenerative dementia is a large-scale neurocognitive network disorder

3. Role of neuropsychology in diagnosis

4. Neuropsychological profiles of dementia:
   - Amnestic
   - Aphasic
   - Visuospatial
   - Comportmental

Assessment principles
That is average for age (SS=10) age 16-89
WMS-III Raw Score Immediate Story Memory
AVERAGE VS PERSONAL TRAJECTORIES
COGNITIVE DECLINE WITH AGING:
A Race Against Time
PATHWAYS OF AGE-RELATED COGNITIVE CHANGE

A Race Against Time

LEVEL OF FUNCTIONING

90+ Years

40 Years

- Normal Aging
- Mid-Cognitive Impairment
- Mild Cognitive Impairment
- SuperAging®
- Better Than Average:
- "SuperAging®"
- Not able to function without assistance due to cognitive loss
- Normal ability to function in routine activities
- Abnormal Aging: Dementia

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1. Changing concepts of cognitive aging
2. Neurodegenerative dementia: a large-scale neurocognitive network disorder
3. Role of neuropsychology in diagnosis: assessment principles
4. Neuropsychological profiles of dementia: Amnestic, Aphasic, Visuospatial, Comportmental
Dementia: A Clinical Syndrome

• Progressive DECLINE from a prior level
• Due to brain disease
• Causes dependence, alienation, interference with customary activities and social relationships, memory, reasoning, language, visual processes, executive functions, social-interpersonal behaviors, compoartment, personality
• Causes dependence, alienation, interference with customary activities and social relationships, memory, reasoning, language, visual processes, executive functions, social-interpersonal behaviors, compoartment, personality

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WHAT CAUSES DEMENTIA?

- Neurodegenerative: NERVE CELL DEATH that is selective for cognitive networks
- Non Alzheimer’s Disease
  - TDP-43 Proteinopathies
  - Frontotemporal Lobar Degeneration
  - Tauopathies (e.g. Pick disease, CBD, PSP, others)
- Amyloid Plaques, Tau Tangles
- VASCULAR
  - Others
  - FUS, other
- Alzheimers Disease
- Prion Diseases
- Others

Irreversible
Reversible
Toxic Metabolic
Mixed pathologies
There is evidence for mixed pathologies
Frontotemporal Lobar Degeneration
With TDP-43 Proteinopathy

Frontotemporal Lobar Degeneration
With FUS Inclusions

Cortical Lewy Body Disease

"Alzheimer's Disease"
Plaques and Tangles

Normal Brain Tissue

Plaques and Tangles

Alzheimer's Disease

Types of Neuropathology Diagnosed at Brain Autopsy

That Cause Clinical Dementia Syndromes
Neuropathologically

LATE STAGE

Neuropathologically

Early Stage

POST 1980 = EARLY DETECTION

PRE 1980 = LATE DETECTION

Can Neurodegenerative Brain Disease Cause Focal Clinical Deficits?
3 LEVELS OF DEMENTIA CHARACTERIZATION

CLINICAL SYNDROME – THE DEMENTIA

NEUROPATHOLOGIC TISSUE DISEASE

CELLULAR AND MOLECULAR ABNORMALITIES FOUND AT POST MORTEM AUTOPSY

REGIONAL PHYSIOLOGICAL DYSFUNCTION (FDG-PET)
ATROPHY (MRI)
NEUROANATOMICAL SIGNATURE – NETWORKS

COGNITIVE AND BEHAVIORAL SYMPTOMS

THE DEMENTIA SYNDROME – THE DEMENTIA
How are the levels related?

Neuropathologic probabilities of disease predicts neuropathologic network predicts neuropsychological profile
EARLY PROFILE: AMNESIA

- Retentive memory loss; rapid forgetting
- Executive dysfunction
- Constructional
- Anomia
- Apathy
- Personality changes very late

OVER TIME:
- Additional cognitive/behavioral deficits

DEMENTIA AKA "Dementia of the AD type"

NEUROANATOMY
NEUROPATHOLOGIC RELATIONSHIPS IN DEMENTIA
NEUROPSYCHOLOGICAL, NEUROANATOMIC, AND

NEUROPATHOLOGY

5-10-FTLD

5-10-OTHER

Cortical Lewy Body

EARKY PROFILE: AMNESIA

AKA "Dementia of the AD type"

DISEASE
EARLY PROFILE:

- Aphasia, amnesia later
- Executive dysfunction

OVER TIME:

- Additional cognitive/behavioral deficits
- Impaired judgment, social cognition

EARLY PERSONALITY CHANGE

DEMENTIA

NEUROANATOMY

BEH VARIANT FRONTOTEMPORAL DEMENTIA

EXECUTIVE/COMPORTMENTAL

EARLY PROFILE:
EARLY PROFILE:
Beh Variant Frontotemporal dementia
Executive/comportmental

80% FTLD
Neuropathology

20% AD, X% OTHER

DISEASE

NEUROPATHOLOGIC RELATIONSHIPS IN DEMENTIA
NEUROPSYCHOLOGICAL, NEUROANATOMIC AND
Primary Progressive Aphasia

EARLY PROFILE: APHASIA

DEMENTIA

NEUROANATOMY

Anomia, other language deficits (syntax, semantics, phonology, orthography, morphology)

Additional cognitive/behavioral deficits over time:

- Behavioral changes later
- Other cognitive impairment late
Early Profile: Aphasia
Primary Progressive Aphasia

60-70% FTD

Neuropathology

30-40% AD

Neuropathology

1-2% OTHER

CJD, Cortical Lewy Body

Diseases in Demenitia

Neuropathologic, Neuropyschologic and Neuroanatomic Relationships in Demenitia

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Early Profile:

- Progressive Visuospatial Dysfunction
- AKA Posterior Cortical Atrophy

Additional cognitive/behavioral deficits over time:

- Amnesia
- Anomia
- Visuospatial deficits (Balint's, neglect)

Over time:
EARLY PROFILE:
Progressive Visual-Spatial Dysfunction
AKA Posterior Cortical Atrophy

DEMENTIA

70% AD

CBD, LBD, CJD, FFI
30% Other

AD (n = 13), AD + PD (n = 1), Lewy Body Disease (n = 2), Corticobasal Degeneration (n = 2), and prion-associated diseases (CJD, FFI) (n=2) (Renner et al, Neurology, 2004)
1. Changing concepts of cognitive aging

2. Neurodegenerative dementia is a large-scale neurocognitive network disorder

3. Role of neuropsychology in diagnosis: assessment principles

4. Neuropsychological Profiles of Dementia: Amnestic, Aphasic, Visuospatial, Comportamental
Neuropsychological assessment provides:

Beyond Biomarkers

- Caregiver education
- Blueprint for management and patient/caregiver education
- Differential diagnosis
- Magnitude of change and rate of decline
- Early detection - Preclinical? Subclinical?
- The only objective marker of THE DEMENTIA Sx
1. Is there change from a prior level of functioning?
2. Is change interfering with routine activities of daily living? How?
3. What is the stage of dementia?
4. What domain(s) is the most salient?
1. Is there change from a prior level of functioning?

ESTIMATED PRIOR ABILITY:

• Usual emotional reactions
• Hobbies/recreation
• Accomplishments
• Career/home/civic/social
• IQ/Reading scores

Is there change?
<table>
<thead>
<tr>
<th>Activity</th>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Self-Care</td>
<td>0-3</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>4-6</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>7-9</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Mild=0-33%; Moderate=34-66%; Severe=>66%


3. What is the stage of dementia?

Mild, Moderate, Severe

Staging TESTS:
- Montreal Cognitive Assessment
- Mattis Dementia Rating Scale (BDS)
- Blessed Dementia Scale (BDS)
- MMSE
- RBANS

Observer RATINGS:
- Clinical Dementia Rating (CDR)

Mild, Moderate, Severe
Useful to track stages of dementia

Mini Mental State Examination

http://www.mocatest.org/

Caveat: mixed findings in low education

Sensitive to mild impairment

Montreal Cognitive Assessment

Mild, Moderate, Severe

Staging Dementia Severity
Montreal Cognitive Assessment Memory Index Score (0-6):

- 3x N free recall + 2x N cued recall + 1x N recognition

Orientation Index Score (0-6):

- cube + clock + naming + sentence repetition + letter fluency

Visuospatial Index Score (0-6):

- cube + clock + naming + sentence repetition + letter fluency

Language Index Score (0-6):

- naming + sentence repetition + letter fluency

Executive Index Score (0-13):

- Trails A + serial 7s + digit span FB + letter A + serial 7s + letter fluency + abstraction

Attention/Concentration (0-18):

- language + cube + clock + digits FB + Trails A + serial 7s + letter A + serial 7s + letter fluency + abstraction

Memory Index Score (0-15):

- 3x N free recall + 2x N cued recall + 1x N recognition

and Ziad S. Nasreddine, MD, JACG, 2014

Parkynou Julayanont, MD, Melanie Brassenna, SWT, Howard Chernkow, MD, Natalie Phillips, PhD,

Alzheimer’s Disease

Predictor of Conversion from Mild Cognitive Impairment to Montreal Cognitive Assessment Memory Index Score (Moca-MIS) as a
Osher et al, 2007

**MMSE Penalizes Patients with PPA Due to Its Emphasis on Verbal Skills**

<table>
<thead>
<tr>
<th>Condition</th>
<th>MMSE</th>
<th>ADLQ</th>
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<tbody>
<tr>
<td>FTD</td>
<td>-25%</td>
<td>-10%</td>
</tr>
<tr>
<td>PPA</td>
<td>-25%</td>
<td>-15%</td>
</tr>
</tbody>
</table>

Osher et al, 2007

**Annualized Percent Change in MMSE Score**

VS Activities of Daily Living Score

* * p < .05
Derive profile of deficits and strengths to aid in clinical dementia characterization and in clinical differential diagnosis.

Use the profile to generate targeted educational materials and interventions for patients and caregivers.

4. What domain(s) is the most salient?
In late stages of dementia, all domains are affected; profiles cannot be discerned.
Aka Posterior Cortical Atrophy
Early Profile of Progressive Visuospatial Dysfunction
Principles Of Assessment

• Select “pure” measures
• Choose tests appropriate for patient demographics
• Cover all domains, but be brief
• Identify PRIMARY DOMAIN Of Deficit
• Identify “Secondary” symptoms- i.e., word list memory test failed due to aphasia
Amnesia in DAT is abnormal, all recognition is abnormal of words and shapes and delayed recall of shapes and delayed recall with effortless encoding of PPA and DAT patients.

Phineas (PPA) patient
Primary Progressive Aphasia
Amnesia in PPA interferes with effortless encoding and delayed retrieval of words but not shapes and delayed retrieval of shapes and effortless encoding of shapes.

Type (DAT) patient
Dementia of the AD
Amnesia in DAT interferes with effortless encoding of shapes and delayed recall of words and shapes and all recognition is abnormal.

Weintraub et al., Beh Neurol, 2013

Aphasia: The Three Words-Three Shapes Test
Verbal and Nonverbal Memory in Primary Progressive Aphasia

Delayed Recall
Acquisition
Encodine/Effortful

Effortless
Encodine

Copy
Stimulus (form 2)

Primary Progressive Aphasia (PPA) patient
Dementia of the AD Type (DAT) patient

www.brain.northwestern.edu

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Kielb et al, JAMA Neurology, 2016

PPA With and Without AD Neuropathology

3W3S Errors in Learning, Retrieval, and Retention in...
<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Word</th>
<th>Hits/False</th>
<th>Recognition</th>
<th>Delayed Recall</th>
<th>Learning Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoe</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pencil</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dress</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Horse</td>
<td>✓</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Truck</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Window</td>
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<td>Machine</td>
<td>✓</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Park</td>
<td>✓</td>
<td></td>
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</tr>
</tbody>
</table>

- 1. Learns quickly because attention is normal
- 2. Remembers if not distracted
- 3. Loses information if distracted
- 4. Loses information over time
- 5. Fails to recognize old items
- 6. Makes false positive errors

Drilled Word Span Memory Test
Dementia of the Alzheimer Type (Amnestic)
### Stimulus Word Span Memory Test

#### Acute Confusional State

<table>
<thead>
<tr>
<th>Learning Trials</th>
<th>Delayed Recall</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

- **Stimulus Word**
  - 1. **Learning Trials**
  - 2. **Delay Recall**

### Drilled Word Recall Table

<table>
<thead>
<tr>
<th>Word</th>
<th>Hits/False</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>60''</th>
<th>60''-dis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>x</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orange</td>
<td>✓</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pencil</td>
<td>x</td>
<td></td>
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<td></td>
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<tr>
<td>Shoe</td>
<td>✓</td>
<td>✓</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Truck</td>
<td>✓</td>
<td>✓</td>
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<td></td>
<td></td>
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<tr>
<td>Window</td>
<td>✓</td>
<td>✓</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Horse</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>Dress</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Park</td>
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<td>✓</td>
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<td></td>
<td></td>
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<tr>
<td>Machine</td>
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<td>✓</td>
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<td></td>
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<td>✓</td>
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</tr>
</tbody>
</table>

- **1. Learns slowly**
- **2. Loses train of thought without distraction**
- **3. Distraction does not eliminate learned material**
- **4. No information loss over time - inconsistent recall**
- **5. Recognizes all old items**
- **6. No false positive errors**
1. Changing concepts of cognitive aging
2. Neurodegenerative dementia is a large-scale neurocognitive network disorder
3. Role of neuropsychology in the diagnostic process: assessment principles
4. Neuropsychological Profiles Of Dementia: Amnestic, Aphasic, Visuospatial, Comportamental
<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>MMSE</th>
<th>ADL Scale</th>
<th>Geriatric Depression Scale</th>
<th>Word List Delayed Learning</th>
<th>Word List Recognition</th>
<th>Story Recall Immediate</th>
<th>Story Recall Delayed</th>
<th>Judgment Of Line Orientation</th>
<th>Boston Naming Test</th>
<th>Visual Verbal Test</th>
<th>Word List Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
<td></td>
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<tr>
<td></td>
<td>Average</td>
<td>Normal</td>
<td>Superior</td>
<td>Average</td>
<td>Average</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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</tbody>
</table>

Case 1

- 81 yo male
- retired M.D.
- insidious onset
- progressive, 4y
- repetitive, losing belongings
- allergies, asthma
- PMH: CAD
- CT unremarkable
- Dementia? Yes
- Memory abn? Yes
- Other abn? EF
- Profile: Amnesia
- DX Dementia of the Alzheimer Type
- Profile: Amnesia

PMH: CAD

Word List Generation

Visual Verbal Test

Boston Naming Test

Judgment Of Line Orientation

Story Recall Immediate

Story Recall Delayed

Word List Recognition

Word List Delayed Learning

TRAIL MAKING B

Geriatric Depression Scale

ADL Scale

MMSE

Level
Case 2, Weintraub et al., 1990

FH: Learning disabilities (spelling, writing)

PMH: Breast cancer

PMH:

Auditory EPs - abn, L temporal

MRI: Non specific bilateral atrophy, L>R

Word-finding difficulty; agrammatic

Progressive, 2 y

46 yo, woman, PhD, nurse; insidious onset,
Case 3, Weintraub et al., 1990

Percent Change in Test Scores Over 2 Years
### Case 2

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia?</td>
<td>YES</td>
</tr>
<tr>
<td>Memory impaired?</td>
<td>NO</td>
</tr>
<tr>
<td>Other cog/beh deficits?</td>
<td>NO</td>
</tr>
<tr>
<td>Neurocognitive Profile</td>
<td>Agrammatic Aphasia</td>
</tr>
<tr>
<td>Neuroanatomy</td>
<td>L Perisylvian</td>
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<tr>
<td>DX</td>
<td>Primary Progressive Aphasia</td>
</tr>
<tr>
<td>Cause?</td>
<td>FTLD-Tau</td>
</tr>
</tbody>
</table>

Case 3, Weintraub et al, 1990
M. K. PPA. Female, onset at age 44. Died 16 years after disease onset.

PATH DX: PICK'S DISEASE
Multilingual Naming Test (MINT)

"axle"

"parachute"

"candle"

"wig"
### Case 3

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests</th>
<th>Level</th>
<th>ADL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasoning</td>
<td>DRS Conceptionalization</td>
<td>Normal</td>
<td>Mattis DRS Total</td>
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<tr>
<td>Memory</td>
<td>DRS Memory</td>
<td>Normal</td>
<td>Mattis DRS Total</td>
</tr>
<tr>
<td>Language</td>
<td>Speech</td>
<td>Abn</td>
<td>Mattis DRS Total</td>
</tr>
<tr>
<td>Calculations</td>
<td>Verbal Fluency</td>
<td>Abn</td>
<td>Mattis DRS Total</td>
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<tr>
<td>Visuospatial</td>
<td>Cube Copy</td>
<td>Abn</td>
<td>Mattis DRS Total</td>
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<tr>
<td></td>
<td>DRS Constructions</td>
<td>Abn</td>
<td>Mattis DRS Total</td>
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<tr>
<td></td>
<td>DRS Initiations</td>
<td>Abn</td>
<td>Mattis DRS Total</td>
</tr>
<tr>
<td></td>
<td>DRS Attention</td>
<td>Abn</td>
<td>Mattis DRS Total</td>
</tr>
</tbody>
</table>

- **61 yo man, professional landscaper**
- **Insidious onset**
- **Progressive, 5 y**
- **Trouble seeing**
- **PMH: none**

- **CT, MRI, EEG normal**
- **PMH: none**
- **Trouble "seeing"**
- **Progressive, 5 y**
- **Insidious onset**
- **Landscaper**

- **Dementia? Yes**
- **Memory abnormal? No**
- **Other abnormal? Yes**
- **Dementia? Yes**
- **Pathology: AD vs LBD**
- **Anatomy: Parietal; Profile: Visuospatial**

- **BNT**
- **Verbal fluency**
- **Digit Span**

- **Abn**
- **Normal**
- **Abn**
- **Abn**
- **Abn**
- **Abn**
- **Abn**

- **Normal**
- **Abn**
- **Abn**
- **Abn**
- **Abn**
- **Abn**

- **Borderline**
- **Impaired**
- **Impaired**
- **Impaired**
- **Impaired**
- **Impaired**
- **Impaired**
From Weintraub and Mesulam, 2000
Case 4

• 61 yo woman, assembly line worker
• Insidious onset
• Progressive, 2 y
• Dwelling on her birth mother, inattentive, bizarre
• PMH: none
• Other ABN? Yes
• Memory abn? No
• Pathology: FTLD
• Anatomy: Frontotemporal
• Profile: Exec/Comportm
• CT, EEG normal
• Profile: Exec/Comportm
• Memory: ND

<table>
<thead>
<tr>
<th>Domain / Tests</th>
<th>cut scores</th>
<th>Domain / Tests</th>
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<tbody>
<tr>
<td>ADL</td>
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<td>DRS Concept</td>
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<td>DRS Construct</td>
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<td>WAIS VIQ/PIQ</td>
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Visual-Verbal Test (Feldman & Drasgow, 1959)
NEUROPSYCHOLOGICAL PROFILE:
PROGRESSIVE COMPORMENTAL/EXECUTIVE DYSFUNCTION
1. MMSE is normal in an individual with complaints.

2. Is there cognitive decline beyond age/personal best?

3. Are there character changes without explanation?

4. What is the rate of decline?

5. What level of care is needed?

6. Is treatment having an effect?

**Referrals for Neuropsychological Examination**

**GET A BASELINE**

1. MMSE is normal in an individual with complaints.
7. Are cognitive/behavioral changes under age 65 signs of young onset dementia?

8. Can delirium be differentiated from dementia?

9. Is the patient safe/able to live alone? To drive?

10. What can the patient/family do to address cognitive/behavioral symptoms?
ADL Problems to target:
- Word finding, comprehension, object recognition problems
- Problems locating or misreaching for objects, trouble judging distance
- Poor judgment, disinhibition, loss of empathy, apathy
- Problems with short term memory, forgetting names, places
- Forgetting personal belonging
- Misperception of objects, trouble judging distance
- Misplacing personal belonging
- Memory problems with short term memory

Language

Visuospatial

Memory

Emotion/Behavior

Neuropsychological Profile

NORTHWESTERN CARE PATHWAYS PROGRAM FOR DEMENTIA (CARE-D)™:
TRANSLATIONAL NEUROPSYCHOLOGICAL RESEARCH

MORHARDT ET AL., 2016
CONCLUSION

- Dementia identification occurs at earlier stages than in the past.
- Different symptoms require different approaches.
- Neurropsychological evaluation contributes to diagnosis, staging, management, and prediction.
- Stages of disease occur at earlier ages.