Patterns of Cognitive Impairment in Dementia

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Objectives

(1) Review current diagnostic criteria for Alzheimer's disease and other common dementia syndromes

(2) Describe assessment methods and neuropsychological impairments observed in Alzheimer's disease and other dementia syndromes

(3) Discuss challenges in differential diagnosis including reversible conditions that mimic dementia and factors that may influence cognitive test performance
What is dementia?

National Institute on Aging-Alzheimer’s Association criteria (2011)

- Presence of cognitive or behavioral symptoms that:
  - Interfere with ability to function at work or at usual activities
  - Represent a decline from previous levels of functioning
  - Is not explained by delirium or major psychiatric disorder
  - Cognitive impairment is detected through a combination of
    - (1) history-taking from the patient and a knowledgeable informant and
    - (2) objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing

  Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

- Cognitive or behavioral impairment involves a minimum of two of the following domains:

  Note: DSM-5 criteria for major neurocognitive disorder identical except impairment in one or more domains

McKhann et al., 2011, Alzheimer’s & Dementia
What is dementia?
National Institute on Aging-Alzheimer’s Association criteria (2011)

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>• Repetitive questions or conversations, misplacing personal belongings,</td>
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<tr>
<td></td>
<td>forgetting events or appointments, getting lost on a familiar route</td>
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<tr>
<td>Executive Functioning</td>
<td>• Poor understanding of safety risks, difficulty managing finances, poor</td>
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<td></td>
<td>decision-making ability, inability to plan complex or sequential</td>
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<tr>
<td></td>
<td>activities</td>
</tr>
<tr>
<td>Visuospatial abilities</td>
<td>• Inability to recognize faces or common objects, difficulty putting on</td>
</tr>
<tr>
<td></td>
<td>clothing</td>
</tr>
<tr>
<td>Language</td>
<td>• Word-finding difficulties, speech, spelling, or writing errors</td>
</tr>
<tr>
<td>Personality, behavior, or comportment</td>
<td>• Agitation, impaired motivation, apathy, loss of drive, social</td>
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<tr>
<td></td>
<td>withdrawal, loss of empathy, socially inappropriate behaviors,</td>
</tr>
<tr>
<td></td>
<td>obsessive or compulsive behaviors</td>
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</tbody>
</table>

Note: DSM-5 criteria for major neurocognitive disorder identical except also includes domains of complex attention and perceptual-motor

McKhann et al., 2011, Alzheimer’s & Dementia
What is dementia?
National Institute on Aging-Alzheimer’s Association criteria (2011)

Differentiation of dementia from MCI

“Determination of whether or not there is significant interference in the ability to function at work or in usual daily activities”

This is inherently a clinical judgment made by a skilled clinician on the basis of the individual circumstances of the patient and the description of daily affairs obtained from the patient and from a knowledgeable informant

McKhann et al., 2011, Alzheimer’s & Dementia
### Cognitive Domains and Assessment

<table>
<thead>
<tr>
<th>LANGUAGE</th>
<th>VISUOSPATIAL ABILITIES</th>
<th>ATTENTION/WORKING MEMORY</th>
<th>PROCESSING/MOTOR SPEED</th>
<th>LEARNING</th>
<th>MEMORY</th>
<th>EXECUTIVE FUNCTIONING</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRAT-4 Reading</td>
<td>Figure Copy (Rey-O, WMS VR, BVMT)</td>
<td>Digit Span Forward</td>
<td>Trailmaking Test A</td>
<td>Word List Immediate Recall</td>
<td>Word List Delayed Recall</td>
<td>Trailmaking Test B</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>Judgment of Line Orientation</td>
<td>Letter-Number Sequencing</td>
<td>Digit Symbol/Coding</td>
<td>Story Immediate Recall</td>
<td>Story Delayed Recall</td>
<td>Wisconsin Card Sorting Test</td>
</tr>
<tr>
<td>Semantic Fluency</td>
<td>Clock Drawing</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Block Design</td>
<td></td>
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</tbody>
</table>

- WRAT-4: Reading
- Boston Naming Test
- Semantic Fluency
- Block Design
- Digit Span Forward
- Trailmaking Test A
- Digit Symbol/Coding
- Word List Immediate Recall
- Word List Delayed Recall
- Trailmaking Test B
- Judgment of Line Orientation
- Letter-Number Sequencing
- Clock Drawing

**Test Examples:**
- **Semantic Fluency**
- **Digit Symbol/Coding**
- **Word List Immediate Recall**
- **Story Immediate Recall**
- **Word List Delayed Recall**
- **Story Delayed Recall**
- **Trailmaking Test B**
- **Wisconsin Card Sorting Test**
- **Figure Delayed Recall**
What is “Impaired”? 

68% of population fall within 1 SD
95% of population fall within 2 SD

Important to consider expected baseline for each individual

Increase in certainty of impairment:
- Greater the impairment
- More tests that are impaired

<table>
<thead>
<tr>
<th>Score Type</th>
<th>Percentile rank</th>
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<tbody>
<tr>
<td>Standard</td>
<td>≤2\text{nd}</td>
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<tr>
<td>Scale</td>
<td>3-9\text{th}</td>
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<tr>
<td>T score</td>
<td>10-25\text{th}</td>
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<tr>
<td></td>
<td>25\text{th}-75\text{th}</td>
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<tr>
<td></td>
<td>75-90\text{th}</td>
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<td></td>
<td>&gt;90\text{th}</td>
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- Impaired
- Borderline/
  Mildly Impaired
- Low Average
- Average
- High Average
- Superior to Very Superior
## Dementia due to Alzheimer’s disease

<table>
<thead>
<tr>
<th>Probable AD</th>
<th>Possible AD</th>
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<tbody>
<tr>
<td>• Dementia has the following characteristics:</td>
<td>• Atypical course (e.g., sudden onset or no evidence of progressive decline)</td>
</tr>
<tr>
<td>• Insidious onset - Gradual onset over months to years not sudden over hours or days</td>
<td>• Etiologically mixed presentation</td>
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<tr>
<td>• Clear-cut history of worsening of cognition by report or observation</td>
<td>• Concomitant cerebrovascular disease (e.g., history of stroke temporally related to cognitive impairment, presence of multiple or extensive infarcts or severe white matter hyperintensity burden)</td>
</tr>
<tr>
<td>• Initial and most prominent cognitive deficits are evidence on history and exam in memory</td>
<td>• Features of dementia with lewy bodies</td>
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<tr>
<td>• Does not meet criteria for other neurodegenerative disorder (e.g., VaD, DLB, FTD)</td>
<td>• Another neurological disease or medical conditions/medications that could substantially effect cognition</td>
</tr>
<tr>
<td>• OR (per DSM-5) has evidence of a causative Alzheimer’s disease genetic mutation from family history or genetic testing (e.g., presinilin 1 or 2 or APP)</td>
<td>McKhann et al., 2011, Alzheimer’s &amp; Dementia</td>
</tr>
</tbody>
</table>
Memory impairment in AD – “Cortical pattern”

PRESENTATION

IMMEDIATE RECALL (IMPAIRED)
LEARNING/ENCODING NEW INFORMATION

DELAYED RECALL (IMPAIRED)
RETENTION/STORAGE OF INFORMATION

RECOGNITION (IMPAIRED)
RETRIEVAL OF INFORMATION FROM STORAGE

1. RAPID FORGETTING
2. INFORMATION STILL NOT ACCESSIBLE EVEN WHEN REDUCE RETRIEVAL DEMANDS VIA RECOGNITION TEST
3. REDUCED PRIMACY EFFECT (E.G., MORE DIFFICULTY RECALLING BEGINNING OF WORD LIST)
4. MORE LIKELY TO PRODUCE INTRUSION ERRORS
Memory impairment in non-AD – “Subcortical pattern”

1. ABLE TO LEARN AND STORE INFORMATION, BUT DIFFICULTY RETRIEVING FROM STORAGE RESULTING IN DELAYED RECALL IMPAIRMENT
2. INFORMATION IS ACCESSIBLE WHEN REDUCE RETRIEVAL DEMANDS VIA RECOGNITION TEST

Frontal-subcortical circuit disruption
Semantic memory and executive functioning impairments in typical AD

**SEMANTIC MEMORY**
- Loss of general knowledge
- Language impairment

**EXECUTIVE FUNCTIONING**
- Set-shifting
- Novel problem-solving

- Confrontation naming
  - Semantic, superordinate errors common
  - e.g., animal for camel
- Category fluency
  - More impaired than letter fluency
- Difficulty recalling overlearned information

Deficits in attention and visuospatial abilities are usually less salient and not observed until later in the disease

Clinical case example

- 81 year-old gentleman diagnosed with a mild neurocognitive disorder (mild cognitive impairment) 1.5 years ago with deficits in delayed memory, but only mild functional changes (e.g., needs reminders for medications).
  - Had a brain injury a few months prior to that evaluation during an MVA resulting in subarachnoid and frontal-temporal lobe hemorrhage and contusions
  - However, wife reported concern about memory loss prior to the injury
  - Recommended to return for follow-up evaluation to assess progression of symptoms

- At the current appointment, patient denied any problems with memory or other cognitive abilities. This was in contrast to his wife who reported continued cognitive and functional decline during the past 1.5 years, including frequent repetitive statements, forgetting to pay bills, unable to use new appliances, wearing the same clothes and not showering regularly, and increased sleeping. He had difficulty describing what he does in a typical day, just noting that he takes a short nap in the afternoon.
Cognitive Profile

Mildly impaired semantic fluency performance

Average to superior performances on measures of attention, visuospatial, and executive functioning

Severely impaired delayed memory including impaired recall & recognition performance

Borderline (<10%) Impaired (<2%)
Clinical case example

• Summary: Patient’s continued cognitive and functional decline are consistent with a major neurocognitive disorder (dementia). Although the prior brain injury may have exacerbated symptoms, his progressive worsening of symptoms during the past 1.5 years provides evidence for an underlying neurodegenerative disorder. His cognitive profile of rapid forgetting are suggestive of Alzheimer's disease.
**Dementia with Lewy Bodies (DLB)**

4th consensus report of the DLB consortium (McKeith et al., 2017)

<table>
<thead>
<tr>
<th>CORE CLINICAL FEATURES</th>
<th>Probable DLB:</th>
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<tbody>
<tr>
<td>Fluctuating cognition with pronounced variations in attention and alertness.</td>
<td>• 2 or more core clinical features</td>
</tr>
<tr>
<td>Recurrent visual hallucinations that are typically well formed and detailed.</td>
<td>• 1 core clinical feature + ≥1 indicative biomarker*</td>
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<tr>
<td>REM sleep behavior disorder, which may precede cognitive decline.</td>
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<tr>
<td>One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.</td>
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<thead>
<tr>
<th>SUPPORTING CLINICAL FEATURES</th>
<th>Possible DLB:</th>
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<tbody>
<tr>
<td>Severe sensitivity to antipsychotic agents</td>
<td>• 1 core clinical feature or 1 indicative biomarker* is present</td>
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<tr>
<td>Postural instability; repeated falls; syncope or other transient episodes of unresponsiveness</td>
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<tr>
<td>Severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence</td>
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<tr>
<td>Hypersomnia; hyposmia</td>
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<tr>
<td>Hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression</td>
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*(1) Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET. (2) Abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy. (3) Polysomnographic confirmation of REM sleep without atonia.
FLUCTUATIONS IN COGNITION

• Delirium-like, occurring as spontaneous alterations in cognition, attention, and arousal.
  • Waxing and waning episodes of behavioral inconsistency
  • Incoherent speech
  • Variable attention
  • Altered consciousness that involves staring or zoning out

• Questions of an informant about daytime drowsiness, lethargy, staring into space, or episodes of disorganized speech help to discriminate from other dementias.

• Fluctuations may also occur in advanced stages of other dementias, so they best predict DLB when they are present early.

McKeith et al. (2017) Neurology
COGNITIVE PATTERNS IN DLB

“Although dementia screens such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment are useful to characterize global impairment in DLB, neuropsychological assessment should include tests covering the full range of cognitive domains potentially affected. Disproportionate attentional, executive function, and visual processing deficits relative to memory and naming are typical.”  

McKeith et al. (2017) Neurology

ATTENTION/EXECUTIVE FUNCTIONING

- Compared to AD, disproportionately severe deficits in attention and executive functions
- Include tests of processing speed and divided/alternating attention
  - Stroop tasks, trailmaking tasks, letter fluency, and computerized tasks of reaction time

Frontal-subcortical circuits may be affected in two ways in DLB
- Direct neocortical Lewy body pathology in the association areas of the frontal lobes
- Substantia nigra pathology that interrupts dopaminergic projections to the striatum
- When superimposed on AD pathology that is also often present in the frontal cortex, these pathological changes may result in disproportionately severe deficits in executive function and attention.

COGNITIVE PATTERNS IN DLB

VISUOSPATIAL FUNCTIONS

- Disproportionately severe visuospatial and visuo-constructive deficit in patients with DLB compared to those with AD
- The spatial and perceptual difficulties of DLB often occur early
- Useful tasks may include:
  - Figure copy (e.g., intersecting pentagons, complex figure copy)
  - Visual assembly (e.g., block design, puzzle tasks)
  - Spatial matching (e.g., line orientation, size matching tasks)
  - Perceptual discrimination (e.g., incomplete figures, incomplete letters)

FDG-PET occipital hypometabolism correlates with visual cortex neuropathology in DLB. Larger studies, earlier in disease, suggest sensitivity (70%) and specificity (74%) slightly lower than needed for an indicative biomarker.

COGNITIVE PATTERNS IN DLB

MEMORY AND LANGUAGE

- Memory and object naming tend to be less affected in DLB, although some patients’ difficulties may be secondary to speed or retrieval task demands.
- Best evaluated through story recall, verbal list learning, and confrontation naming tasks

Relative preservation of medial temporal lobe in DLB

A. MRI

Vascular Dementia (VaD) – Diagnostic Criteria

**Vascular Dementia**

NINDS-AIREN (1993)

1. Memory impairment + at least one other domain
2. IADL impairment
3. Evidence of CVD
4. Causal relationship between dementia & CVD (onset within 3 months of stroke and/or acute onset)

**Vascular Dementia**

AHA/ASA (2011)

1. Evidence of stroke or subclinical vascular injury
2. ≥ 2 cognitive domains + IADL impairment

**PROBABLE VAD:**

- IMAGING EVIDENCE
- TEMPORAL RELATIONSHIP OR RELATIONSHIP IN SEVERITY/PATTERN OF IMPAIRMENT AND PRESENCE OF DIFFUSE, SUBCORTICAL CVD
- NO GRADUALLY PROGRESSIVE DEFICITS BEFORE OR AFTER STROKE

**Major vascular neurocognitive disorder**

DSM-5 (2013)

1. Major neurocognitive disorder criteria met
2. **Onset of deficits temporally related to cerebrovascular event** OR Evidence for decline prominent in complex attention (including processing speed) and frontal-executive dysfunction
3. Evidence of CVD from history, physical exam, and/or **neuroimaging** sufficient to account for neurocognitive deficits

**PROBABLE VAD: AT LEAST ONE OF 3 FEATURES**

Both clinical and genetic evidence of CVD is present
Proposed mechanisms of cause:
Cerebral amyloid angiopathy
Mixed dementia
White matter hyperintensities
Microbleeds/microhemorrhages
Microinfarcts
Arteritis/vasculitis
PATTERN OF COGNITIVE IMPAIRMENT IN VAD

• Heterogeneous syndrome
  • Depends on location/nature of pathology
  • No uniform pattern of NP performance will characterize all patients with VaD

• Most common pattern (due to common disruptions to deep frontal white matter, frontal-subcortical circuits, and basal ganglia)
  • Executive dysfunction
  • Slowed processing speed
  • Attention deficits

• More frequent and earlier impairments in mobility, incontinence and depression
• May have greater functional impairment than AD when level of cognitive impairment is equal
Reed et al., 2007; BRAIN

Memory more impaired than executive function in mild to moderate AD

Two domains may be equally affected in VaD

VaD:
Executive function not significantly lower than memory scores

AD:
Memory scores 1 SD lower than executive function scores
- Correlations between memory tests and neuropathology ~ .50

AD/VaD mixed cases were neuropsychologically similar to AD

N = 62 autopsied cases
Clinical Case Example

- 85 year-old retired mechanic presenting to the clinic due to memory decline that has been particularly noticeable during the past year.
- Several vascular risk factors including history of TIAs (x3 w/ left hand numbness), atrial fibrillation, AAA, cerebral atherosclerosis, iliac artery aneurysm, carotid stenosis, hyperlipidemia, COPD. He has gait ataxia and tremor that are thought to be related to vascular disease per Neurology evaluation.
- MRI head imaging showed stable (since 2015) generalized mild to moderate parenchymal volume loss, mild chronic microangiopathic change, and old microhemorrhage in the right mid temporal lobe.
Cognitive Profile

Severely impaired performances on attention, processing/motor speed and executive functioning

Severely impaired learning, but no accelerated forgetting

Language measures with executive functioning component (e.g., semantic fluency) were impaired, whereas other language measures (e.g., reading, object naming) were within normal expectations.

MMSE = 27/30 – orientation intact
Clinical Case Example

• Diagnostic impression = Major vascular neurocognitive disorder (VaD)

• His cognitive impairment likely reflects a decline from his prior level of functioning, interferes with his ability to perform everyday activities independently, and therefore is consistent with a diagnosis of major neurocognitive disorder. His cognitive profile of impaired attention and executive functioning with milder memory deficits, as well as the presence of significant vascular risk factors and cerebrovascular disease noted on MRI is most consistent with an etiology of cerebrovascular disease (e.g., vascular dementia).
Mixed pathologies are more common than single pathologies

- In persons with probable AD, vascular disease is present in approximately 90% and other degenerative diseases in about 65%

Kapasi, DeCarli, Schneider, 2017; Acta Neuropathologica

N=1078 autopsied subjects from the Religious Orders Study and Memory & Aging Project (Rush)
Reversible causes of cognitive impairment

- Depression
- Delirium
- Thyroid dysfunction
- Vitamin deficiencies – B12
- Infections
- Medication side effects
  - Anticholinergics
- Sleep disorders (e.g., sleep apnea, insomnia)
- Alcohol abuse
- Chronic pain

Brain dysfunction

Individual test scores → “Impaired” → Brain dysfunction

- Educational quality
- Socioeconomic status
- Cultural experience
- Preferred language
- Familiarity with cognitive testing
- Normative sample of tests

Other factors that can influence cognitive test scores

- Effort
- Mood
- Pain
### Summary

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>DLB</th>
<th>VaD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Gradual</td>
<td>Gradual</td>
<td>Temporally related to stroke, or gradual if related to SVD</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>Gradual</td>
<td>Gradual</td>
<td>“Stepwise” or gradual</td>
</tr>
</tbody>
</table>
| **Cognitive pattern** | • Memory more impaired than other domains (both recall & recognition)  
• Semantic/language and executive dysfunction | • Visuospatial  
• Attention  
• Executive Function | • Similar level of impairment on memory and executive functioning measures (intact recognition)  
• Slowed processing speed |
| **Additional features that may be present** | • Visual hallucinations  
• Parkinsonism  
• REM sleep behavior disorder | | • More frequent and earlier impairments in mobility, incontinence and depression |
| **Neuropathology** | • Beta-amyloid plaques  
• Neurofibrillary tangles | • Alpha-synuclein deposits | • Infarcts, hemorrhages, atherosclerosis, cerebral amyloid angiopathy, hypoperfusion |
Summary

• Although most dementia results from a mixed pathology, evidence suggests there are distinct cognitive patterns across syndromes which may help determine the most prominent etiology.

• Cognitive patterns may assist with differential diagnosis, determining severity of overall cognitive impairment, and providing evidence of strengths and weaknesses that may be useful in advance care planning for those with dementia.

• When determining presence and severity of cognitive impairment, important to consider:
  • Premorbid intellectual functioning level of individual patient – is this a decline?
  • Is the normative sample for tests representative of the patient – similar demographics?
  • Are there any other factors may explain impairment on cognitive tests?
Thank You!
Questions?

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