UT Southwestern Medical Center

Variants of Alzheimer's Dementia

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Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.

Objectives

- Define Alzheimer’s disease (AD)
- Review the common amnestic presentation of AD
- Identify the non-amnestic variants of AD
  - Language
  - Visuospatial
  - Dysexecutive
  - Behavioral

Defining Alzheimer's Disease

Diagnostic criteria over the years

Clinical diagnosis of Alzheimer's disease:
Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

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Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup

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1984 — 2011 — 2018 — 2024

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

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2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

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2024 Revised criteria for diagnosis and staging of Alzheimer's disease

- Defined as a biological process beginning with appearance of AD neuropathologic change and progression to later appearance of clinical symptoms
- Core 1 biomarkers are sufficient to establish AD diagnosis
- Core 2 biomarkers aid prognosis and increase confidence

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T_2 (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments[a]	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD copathology		
V vascular brain injury		Infarction on MRI or CT, WMH
S α-synuclein	αSyn-SAA[a]	

Jack, C.R., et al., (2024). *Alzheimer's Dement.*

Clinical staging of Alzheimer's disease

Stage 0 Asymptomatic, deterministic gene[a]

No evidence of clinical change. Biomarkers in normal range.

Stage 1 Asymptomatic, biomarker evidence only

Performance within expected range on objective cognitive tests.

No evidence of recent cognitive decline or new symptoms.

Stage 2 Transitional decline: mild detectable change, but minimal impact on daily function

Normal performance within expected range on objective cognitive tests.

Decline from previous level of cognitive or neurobehavioral function that represents a change from individual baseline within the past 1 to 3 years, and has been persistent for at least 6 months.

May be documented by evidence of subtle decline on longitudinal cognitive testing, which may involve memory or other cognitive domains but performance still within normal range.

May be documented through subjective report of cognitive decline.

May be documented with recent-onset change in mood, anxiety, motivation not explained by life events.

Remains fully independent with no or minimal functional impact on activities of daily living (ADLs)

Stage 3 Cognitive impairment with early functional impact

Performance in the impaired/abnormal range on objective cognitive tests.

Evidence of decline from baseline, documented by the individual's report or by an observer's (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral assessments.

Performs daily life activities independently but cognitive difficulty may result in detectable functional impact on complex ADLs (i.e., may take more time or be less efficient but still can complete—either self-reported or corroborated by an observer).

Stage 4 Dementia with mild functional impairment

Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.

Stage 5 Dementia with moderate functional impairment

Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.

Stage 6 Dementia with severe functional impairment

Progressive cognitive and functional impairment, and complete dependence for basic ADLs.

Jack, C.R., et al., (2024). *Alzheimer's Dement.*

Amnestic Variant Alzheimer's Disease

Amnestic variant AD

- Most common presentation
- Complaints
  - Memory loss
  - Forgetfulness
- Manifestations
  - Repetition
  - Forgetting details
  - Misplacing items
- Other cognitive domains can be involved at the same time or later in the disease course
- Broad differential
  - Medical conditions
  - Psychiatric conditions
  - Neurologic/neurodegenerative conditions

Non-Amnestic Variants of Alzheimer's Disease

Non-amnestic variants of AD

- Defined by the cognitive domain most impaired at onset
- Diagnosed as AD by biomarkers
  - Similarly diffuse amyloid PET distribution
  - FDG-PET and tau PET reflect regions involved
  - Less hippocampal atrophy
- Often occur with younger age at onset
- Diagnosis delayed or missed
- More aggressive clinical course
- Broad differential when considering alternative or co-pathology

Graff-Radford, J., et al.,(2022). *Lancet Neurol.*

Language Variant Alzheimer's Disease

Primary progressive aphasia (PPA)

- Language difficulties are:
  - The most prominent feature
  - The principal cause of impairment
  - The most prominent deficit at onset and initial phases of the disease

- Not PPA if
  - Better accounted for by
    - Other neurologic disorder
    - Medical disorder
    - Psychiatric disorder
  - Prominent initial impairment in
    - Episodic memory
    - Visual memory
    - Visuoperceptual impairments
  - Prominent, initial behavioral disturbance

Gorno-Tempini, M.L., et al.,(2011). *Neurology.*

Logopenic variant PPA

- Impaired
  - Word retrieval when speaking and naming
  - Sentence/phrase repetition
- 3+ of:
  - Speech (phonologic) errors
  - Spared word comprehension and object knowledge
  - Spared motor speech
  - Absence of agrammatism

Gorno-Tempini, M.L., et al.,(2011). *Neurology.*

Language variant AD

- Complaints
  - Word-finding difficulties
  - “Tip of the tongue”
- Manifestations:
  - Describing objects rather than using the exact word/name
  - Fluent, but with word-finding pauses
  - Words don’t sound right (phonemic paraphasic errors)

- Examination
  - Listen to their speech
  - Confrontational naming
  - Preserved object and word knowledge
  - Impaired sentence repetition

Repeat: The caring grandmother sent groceries over a week ago.

Nonfluent/agrammatic variant PPA

- Either
  - Agrammatism
  - Effortful, halting speech with inconsistent speech sound errors and distortion (apraxia of speech)
- 2+ of:
  - Impaired comprehension of syntactically complex sentences
  - Spared word comprehension
  - Spared object knowledge

The lion was eaten by the tiger.
- Which animal is still alive?
The car that the truck hit was green.
- Which vehicle was hit?

Gorno-Tempini, M.L., et al.,(2011). *Neurology.*

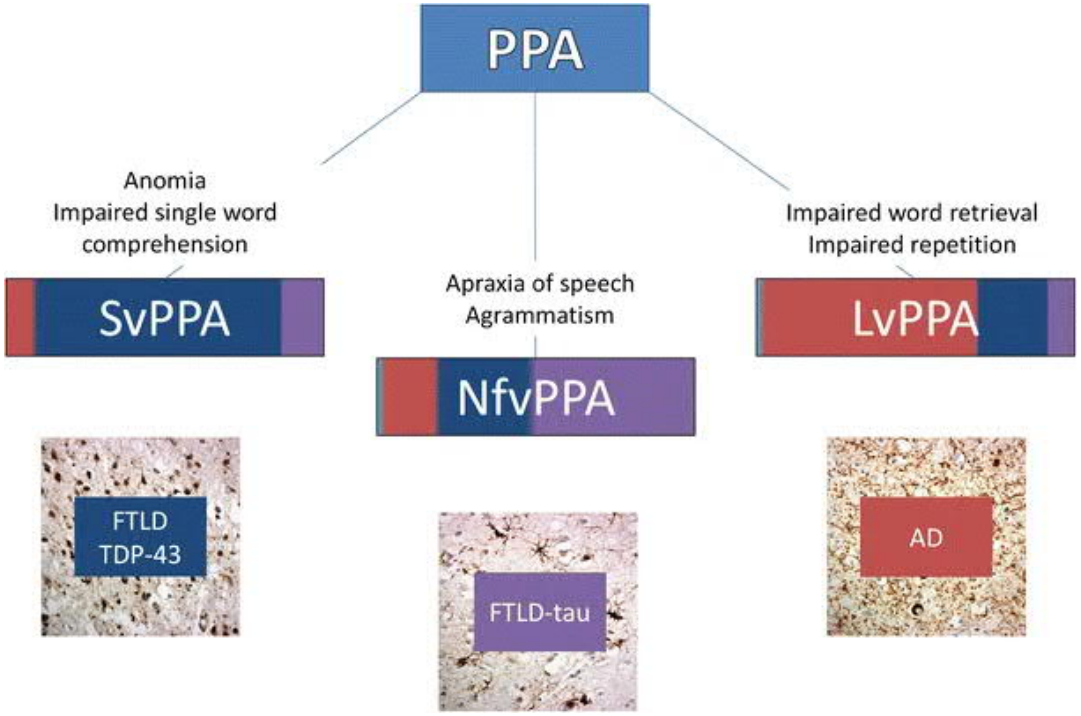
Semantic variant PPA

- Both
  - Impaired confrontational naming
  - Impaired word comprehension
- 3+ of:
  - Impaired object knowledge
  - Surface dyslexia or dysgraphia
  - Spared repetition
  - Spared speech production

COLONEL	*PINT*
BLOOD	*DENY*
YACHT	*TOMB*

Gorno-Tempini, M.L., et al.,(2011). *Neurology.*

Other PPA variants



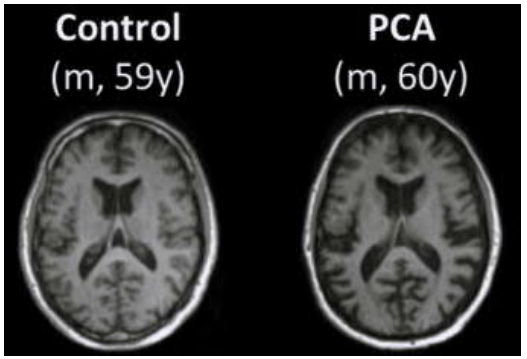
Harris, J.M. and Jones, M., (2016). *Curr Neurol Neurosci Rep.*

Visual Variant Alzheimer's Disease

Posterior Cortical Atrophy (PCA)

- Prominent early disturbance of visual +/- other posterior cognitive functions (3+*)
- Relatively spared functioning in other domains

- Neuroimaging evidence of atrophy, hypometabolism or hypoperfusion of
  - Occipitoparietal region
  - Occipitotemporal region



Crutch, S.J., et al.,(2017). *Alzheimer's & Dementia.*

*PCA cognitive features

- Space perception deficit
- Simultanagnosia
- Object perception deficit
- Constructional dyspraxia
- Environmental agnosia
- Oculomotor apraxia
- Dressing apraxia
- Optic ataxia
- Alexia
- Left/right disorientation
- Acalculia
- Limb apraxia
- Apperceptive prosopagnosia
- Agraphia
- Homonymous visual field defect
- Finger agnosia

Crutch, S.J., et al.,(2017). *Alzheimer's & Dementia.*

Syndromes associated with PCA

Balint Syndrome

- Simultanagnosia
- Oculomotor apraxia
- Optic ataxia
- Localization: bilateral parietal and occipital lobes

Gerstmann Syndrome

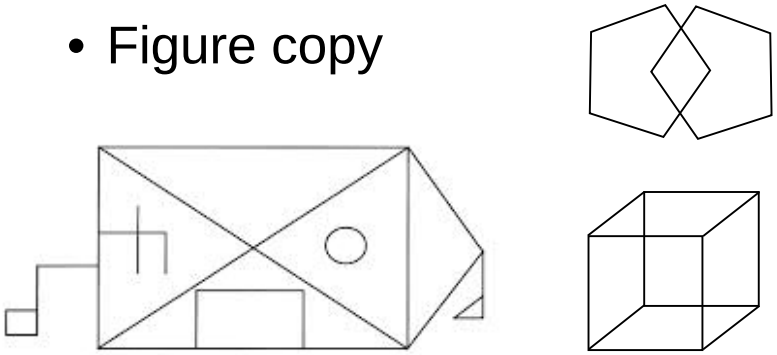
- Left/right disorientation
- Acalculia
- Agraphia
- Finger agnosia
- Localization: dominant angular gyrus

Visual variant AD

- Complaints
  - Vision problems
  - Troubles seeing
  - Clumsiness
  - Navigation problems
- Manifestations – difficulties:
  - Reading
  - Putting things together
  - Driving (!)
  - Finding items (right in front)
  - “Seeing the forest for the trees”

Examining Visuospatial Abilities

- Figure copy



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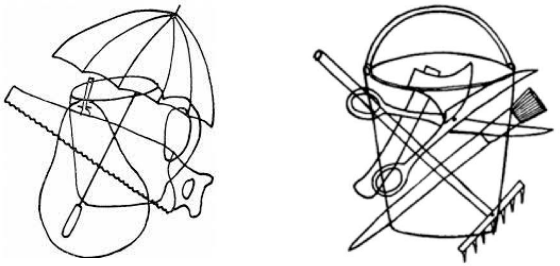

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AAAAA      DD    DD
AA         DD    DD
AAAAA      DDDDDD
AA         DD    DD
AAAAA      DD    DD
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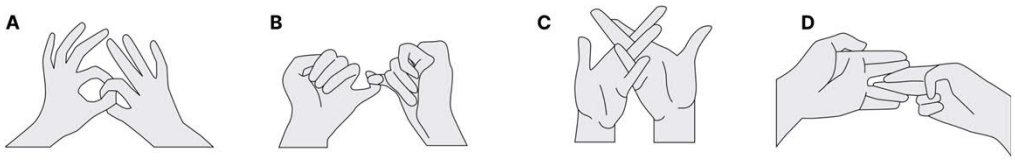
- Interlocking fingers



Moo, et al.,(2003). *J. Neurol. Neurosurg. Psychiatry.*

Differential: other causes of PCA

- Lewy body disease
- Corticobasal syndrome
- Creutzfeldt-Jakob disease

Dysexecutive Variant Alzheimer's Disease

Progressive dysexecutive syndrome: proposed diagnostic criteria

- Persistent, predominant and progressive decline for over 6 months in any core executive function
  - Working memory – monitoring existing and updating incoming information
  - Cognitive flexibility – incorporating simultaneous streams of information and shifting between tasks
  - Inhibition – suppress irrelevant information
- Absence of predominant behavioral features
- Excludes a history of sudden onset or other medical conditions

Townley, R.A., et al.,(2020). *Brain Communications.*

Dysexecutive variant AD

- Complaints
  - “Memory troubles”
  - Troubles
    - Planning and organization
    - Multi-tasking
    - Multi-step processes
- Manifestations – difficulties:
  - Playing board games
  - Following directions, recipes
  - Projects at home or work

- Examination
  - Similarities
  - Proverbs
  - Luria motor sequence
  - “Go-No Go” tasks
- Exclude
  - Primary psychiatric disorders
  - Cerebrovascular disease
  - Medical (infectious, toxic, inflammatory, metabolic)

Townley, R.A., et al.,(2020). *Brain Communications.*

Behavioral Variant Alzheimer's Disease

Behavioral variant AD: research criteria for clinical bvAD

- Early, persistent, predominant, and progressive change in at least 2 of:
  - Behavioral disinhibition
  - Apathy or inertia
  - Loss of empathy or sympathy
  - Perseverative, stereotyped, or compulsive or ritualistic behavior
  - Hyperorality and dietary change
- Impaired executive and/or episodic memory, with relatively preserved language and visuospatial abilities
- Not caused by other neurologic, medical or psychiatric comorbidity

Ossenkoppe, R., et al.,(2022). *JAMA Neurol.*

Behavioral variant AD: additional research criteria

- Possible bvAD
  - Amyloid PET or CSF
  - CSF or plasma tau
- Probable bvAD: tau PET

- Definite bvAD
  - Histopathology on biopsy or autopsy
  - Known genetic variant associated with familial AD

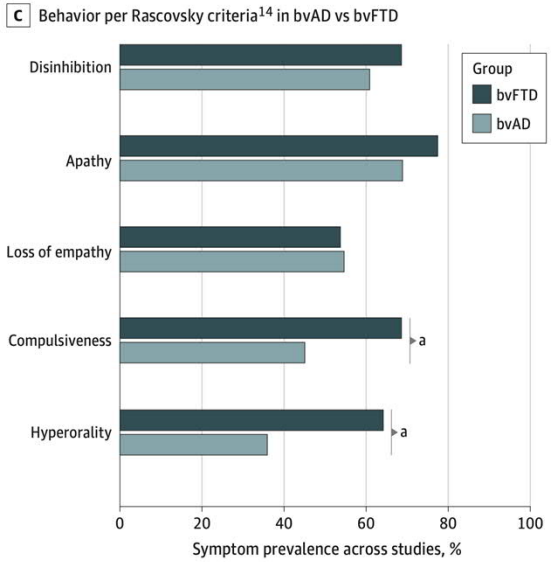
Ossenkoppe, R., et al.,(2022). *JAMA Neurol.*

Behavioral variant AD

- Complaints
  - “Not the same person”
  - Personality change
  - Odd behaviors
  - No motivation
- Manifestations
  - Inappropriate behaviors in public
  - Impulsive or rash actions
  - Lack of drive or initiative
  - Diminished response to others
  - Compulsive/repetitive behaviors
  - Particular food preferences

Behavioral variant AD versus FTD

- Less common in bvAD
  - Compulsive/repetitive behaviors
  - Hyperorality



- More common in bvAD
  - Agitation
  - Hallucinations
  - Delusions
  - Worse memory function
  - Early cognitive impairment

Ossenkoppe, R., et al.,(2022). *JAMA Neurol.*

Treatment

Treatment of AD variants

- Similar to amnestic AD
  - Cholinesterase inhibitors
  - NMDA receptor antagonists
- Psychiatric medications
- Therapies
- Caregiver resources
- Social work

- Anti-amyloid monoclonal antibody therapies
  - Appropriate use recommendations allow for inclusion of PCA, lvPPA, dysexecutive AD
  - Clinical trials primarily assessed amnestic AD

Cummings, J., et al.,(2023). *J Prev Alzheimers Dis*.; Rabinovici, G.D., et al., (2025). *J Prev Alzheimers Dis.*

Conclusion

Variants of Alzheimer's Disease

- Defined by early prominent non-amnestic cognitive impairment with biomarker evidence indicating AD
- Language variant AD (logopenic PPA) can be differentiated from PPA variants that typically have non-AD pathology
- Look for signs of other diseases when considering visuospatial variant AD (posterior cortical atrophy)
- Executive and behavioral variant AD are becoming increasingly recognized
- Treatment options are similar to those for amnestic AD

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