



Neurocognitive Disorders: Clinical Principles and Bedside Assessment

Medical Psychiatry: A Comprehensive Update 2026

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Disclosures

- I do not have any relevant financial relationships with any commercial interests.

Goals

- To recognize the value of localization and time course in the process of diagnosing neurocognitive disorders
- To understand distinguishing features of common conditions in the differential diagnoses of: (1) acute/subacute onset cognitive dysfunction; and (2) insidious onset cognitive dysfunction.
- To review the value of differentiating between syndrome, severity and neuropathology in neurodegenerative conditions causing cognitive dysfunction.

Instant Cognitive Neurologist

Onset/Course		1° Attention/Executive	1° Other Cognitive Domain [Episodic memory, language, visual/spatial, higher somatosensory/motor, social cognition]
Acute/Subacute	Fluctuating	Delirium	Recurrent transient neurological condition*
	Progressive	Rapidly progressive dementia	

*Focal seizure, spreading cortical depression (eg, migraine aura, subarachnoid hemorrhage, CAA), cerebral ischemia

Distinguishing Subacute Conditions

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Etiologies	- Frequently general medical conditions, medications, substance intoxication/withdrawal - Less frequently 1° neurological (diffuse or right-hemispheric lesions, focal status epilepticus)	- Autoimmune/inflammatory, prion disease, non-prion degenerative, CNS vascular, infection, neoplasm, toxic/metabolic	- Focal seizures, spreading cortical depression, ischemia

* aphasia, apraxia, alexia, agraphia, acalculia, agnosia, cortical sensory signs, neglect

Distinguishing Subacute Conditions

Time efficient bedside neurological examination: context-specific

- Screening exam:
 - MSE to survey cognitive domains, with emphasis on establishing whether impaired attention is the primary and/or exclusive domain affected. Assess for “cortical” signs (aphasia, apraxia, agnosia, neglect, etc).
 - General neuro exam to survey cranial nerves, motor, sensory, and cerebellar systems for localizing findings. Assess for non-localizing motor signs (e.g., myoclonus, asterixis) and localizing signs (pyramidal, extrapyramidal, cerebellar).
- Initial exam with localizing signs present: delineate nature, extent, severity of signs and screen for findings in other parts of the nervous system.
- Follow-up exams: assess for interval changes in established signs. Repeat screening for other signs where appropriate.

Distinguishing Subacute Conditions

Standard workup

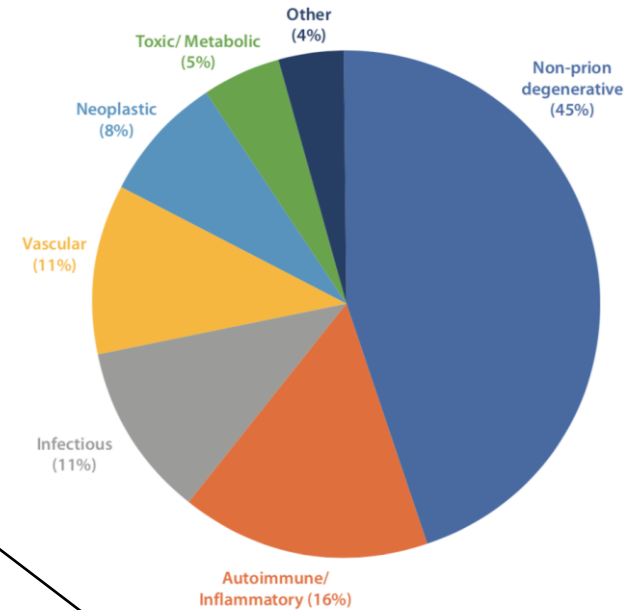
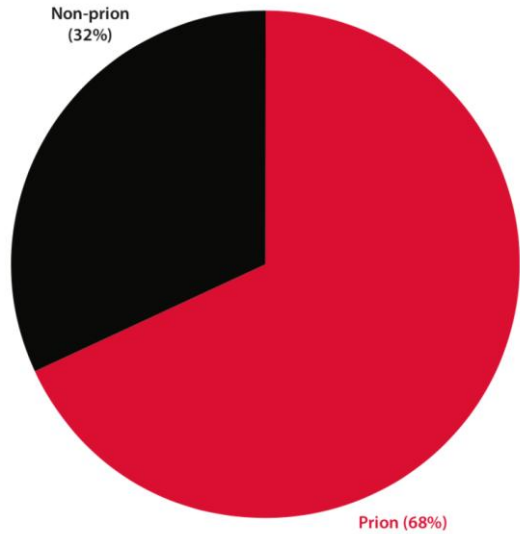
- Labs: comprehensive metabolic profile, B12, TSH, CBC, UA/culture, toxicology screens, drug levels are appropriate in most contexts.
- Studies: ECG, chest x-ray

Contextual and/or extended workup for atypical or unexplained delirium

- Structural neuroimaging (head CT, MRI brain)
- EEG
- LP:
 - Fever, nuchal rigidity, suspected infection with unknown source.
 - Potential autoimmune encephalitis.
 - Potential neoplasm (e.g., CNS lymphoma, leptomeningeal metastases).
 - Potential degenerative disease (JCD, AD).

Rapidly Progressive Dementia

Acute/subacute onset (days, weeks)



Infection

Autoimmune

Toxic /
Metabolic

Neoplasm

Other
degen.

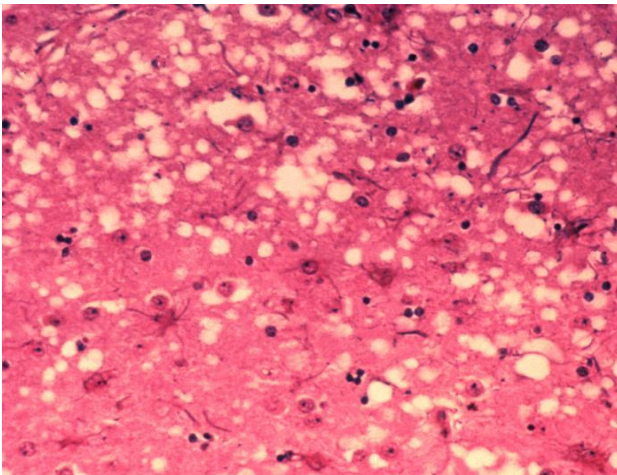
Vascular

Prion

1° Central Nervous System Process

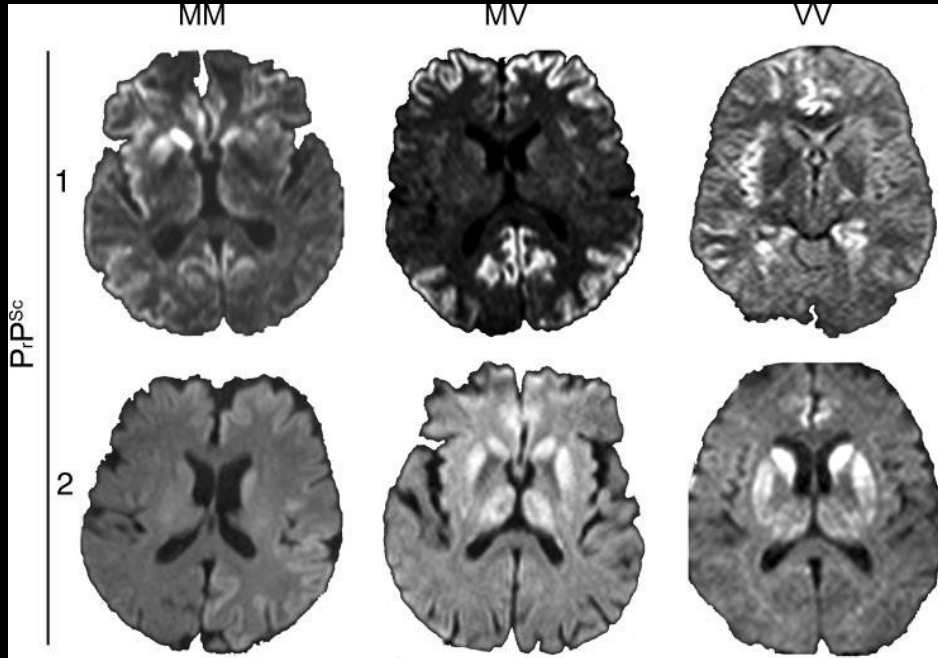
Prion disease

- Sporadic Creutzfeldt-Jakob disease (sJCD) is the most common; incidence 1-2 per 1,000,000 per year.
- Rapidly progressive deterioration in cognition and behavior with higher cortical signs; myoclonus occurs in >90% of cases; pyramidal or extrapyramidal motor signs (>50%), cerebellar signs (>50%) are also common.
- Neuropsychiatric features: apathy → akinetic mutism, depression; less commonly euphoria, emotional lability, anxiety, psychotic features.
- Molecular variants defined by amino acid at codon 129 of prion protein gene (M or V) and type of pathological prion (1 or 2) influence clinical presentation.

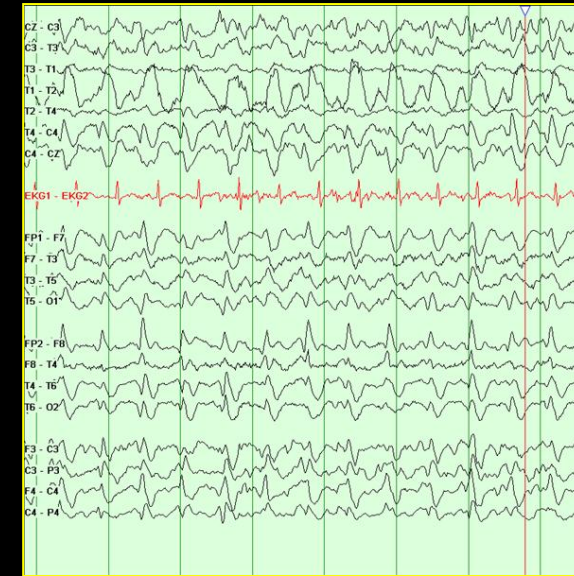


CJD biomarkers

DWI restriction ~90-95% sensitive, ~90-99% specific



Periodic sharp wave complexes ~65% sensitive, ~90% specific



- Real-time quaking-induced conversion (RT-QuIC) assay amplifies detection of PrP(CJD); CSF or olfactory mucosa brushings; sensitivity ~90-96%, specificity ~99-100%
- Supportive but non-specific: elevated CSF 14-3-3 protein; highly elevated CSF total tau

Instant Cognitive Neurologist

		1° Attention/Executive	1° Other Cognitive Domain
Insidious	Static	Multifactorial (non-neurological)	Prior monophasic injury or developmental disorder
	Progressive	Degenerative and/or Vascular	Degenerative ± Vascular

Initial Assessment: Questions

Has the patient experienced a meaningful change in cognitive functioning?

[history, exam]

Yes

Is the primary underlying etiology neurodegenerative?

[history, exam, structural imaging]

Yes

What neurodegenerative syndrome best captures the presentation?

[history, exam, structural imaging]

How far along in the course of disease is the patient?

[history, exam]

What underlying neuropathology do I predict?

[history, exam, structural imaging ± biomarkers]

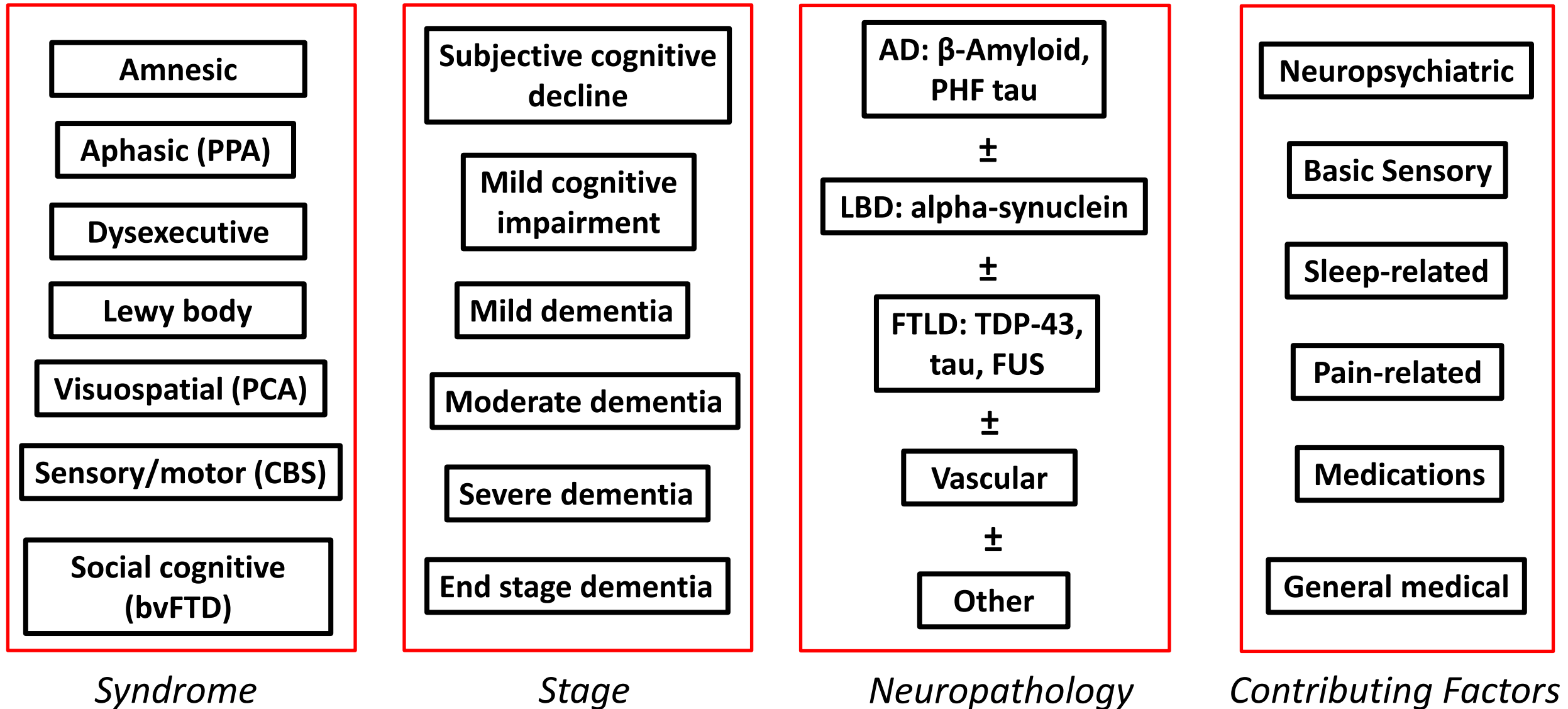
No

What additional factors might be contributing to cognitive dysfunction?

+

[history, exam, structural imaging, labs]

Formulation: Degenerative Cognitive Disorders



Initial Assessment: Questions

Has the patient experienced a meaningful change in cognitive functioning?

Is the cognitive profile characteristic of a neurodegenerative syndrome?

History
Cognitive Exam

Is the time course gradually progressive?

Are there additional features suggestive of a neurodegenerative syndrome and/or evidence of non-degenerative factors contributing to cognitive dysfunction?

Pertinent ROS
Elemental neuro exam

Is there biomarker evidence to suggest a neurodegenerative condition and/or non-degenerative factors?

Laboratory evaluation
Structural MRI or CT
Additional studies as indicated

Is the primary underlying etiology neurodegenerative?

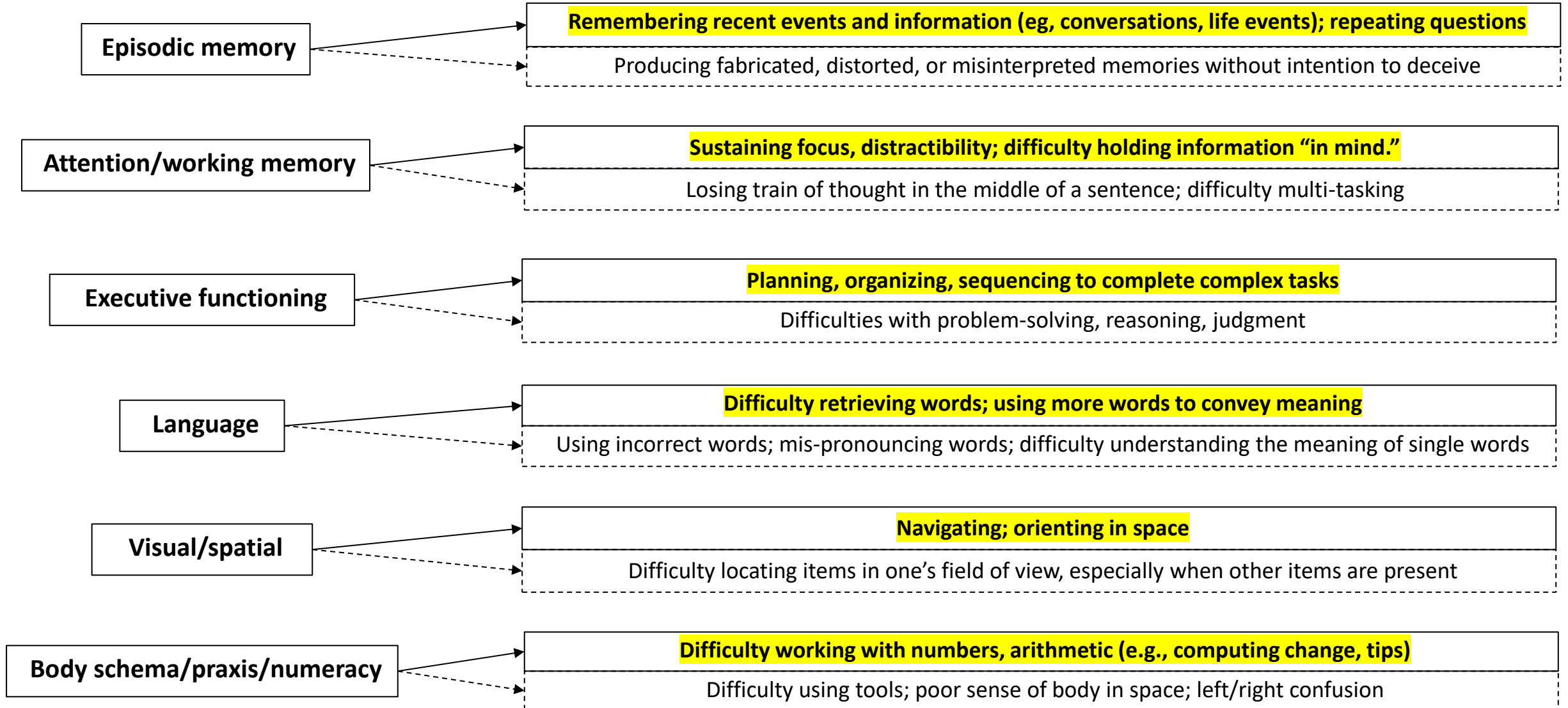
History: Process

- **Assess source reliability, comfort (patient, informant); optimize setting**
- **Localize based on symptoms**
 - Develop and refine an understanding of how reported symptoms relate to cognitive processes and domains
 - Obtain examples; clarify; recognize patterns
- **Manage time proactively**
 - Allocate sufficient time (typically 60 ± 15 minutes for initial history and exam)
 - Open-ended → directed questioning
 - Stay organized, prioritize
 - Use validated questionnaires where appropriate
 - Obtain information from EMR, where available
 - Parallel processing: examination; preliminary cognitive profile, plan

History: Content

- **History of the Present Illness**
 - Cognitive symptoms
 - Usual activities
 - Behavioral/emotional symptoms
 - Sleep/fluctuations
 - Motor/sensory
 - Autonomic/pain
- **Neurological, Psychiatric, Medical and Surgical History**
- **Developmental, Educational, Occupational History**
- **Social History**
- **Family History**

HPI: Cognitive Symptoms



HPI: Usual Activities

Type	Elements/Examples
Advanced ADLs Compromised in MCI	Performance at work Participating in group/community activities Leisure activities (intellectual, social)
Instrumental ADLs Loss of independence in mild dementia	Driving (and other forms of transportation in the community) Taking prescribed medications Managing finances Shopping for groceries and completing errands in the community Completing household chores, preparing meals Using the telephone and computer
Basic ADLs Loss of independence in moderate and severe dementia	Tending to personal hygiene and grooming Bathing and/or showering Dressing Toileting Functional mobility Self-feeding

Recommended scale: **Activities of Daily Living Questionnaire** (Johnson et al. *Alzheimer Dis Assoc Disord* 2004;18:223-30)

HPI: Other Features

Behavioral/Emotional Symptoms

Neuropsychiatric Inventory-Questionnaire (Kaufer 2000)

Mood; ability to derive pleasure from usual sources; motivation; anxiety; appetite

False beliefs; bipolar-spectrum symptoms; PTSD-spectrum symptoms; disinhibition, obsessive-compulsive or perseverative behaviors, sympathy/empathy, food behaviors

Sleep/Fluctuations

Mayo Sleep Questionnaire (Boeve 2011)
Mayo Fluctuations Scale (Fermin 2004)

Schedule; insomnia (early, middle, late); snoring/breathing; dream enactment; daytime energy level; napping, dozing; episodes of prolonged staring and/or disorganized speech

Restless legs symptoms; other movements in sleep; vivid dreams

Motor/Sensory

Queen Square Visual Hallucinations Inventory (Williams 2008)

Walking, balance; tremors; fine manual dexterity; basic vision, hearing, smell/taste; visual hallucinations, illusions

Speech, swallowing; handwriting; stiffness; eye movements; episodic muscle contractions; fasciculations; extracampine (presence) hallucinations; motion hallucinations; auditory or tactile hallucinations

Autonomic/Pain

NACC/UDS Autonomic Symptoms Checklist

Orthostatic lightheadedness; constipation, loose stools; urinary frequency, urgency; pain

Rhinorrhea; excessive salivation, sweating; temperature regulation; erectile function

Cognitive Examination: Goals

- Goal of determining whether there are **changes above and beyond those attributable to normal aging**, considering baseline intellect/education.
 1. Survey major cognitive domains, testing hypotheses generated from the history (MMSE alone is not sufficient; MoCA, SLUMS, ACE-III may be sufficient in 'typical' cases, particularly if supplemented).
 2. Standard evaluation is geared towards discriminating between common conditions and identifying atypical features, corroborating evidence from history.
 3. Flexible evaluations employed in specific atypical situations (e.g., primary dysfunction in a domain other than memory, attention/executive functioning).
 4. Global scores on selected measures can provide a gauge of severity but should always be considered with functional status.
- Billing possible using Medicare CPT code 96116, neurobehavioral status exam

If time doesn't permit a detailed cognitive examination/interpretation, refer to a specialist (e.g., neuropsychologist or cognitive neurologist) for initial assessment.

Brief Cognitive Instruments: Comparison

	MoCA	MMSE	ACE-III	SLUMS
Memory	++	+	++	++
Attention/Executive	++	+	+	+
Language	+	+	++	+
Visual/Spatial	++	+	+++	++
Time efficiency	++	+++	+	++
Typical range: MCI*	~18-25	~24-27	~72-86	~21-26
Typical range: Mild dementia*	~15-22	~21-25	~61-82	~11-20

*Most applicable in typical (amnesic) Alzheimer disease

The Rowland Universal Dementia Assessment Scale: A Multicultural Cognitive Assessment Scale. (Storey, Rowland, Basic, Conforti & Dickson, 2004). *International Psychogeriatrics*, 16 (1), 13-31

Date: / / Patient Name:

RUDAS

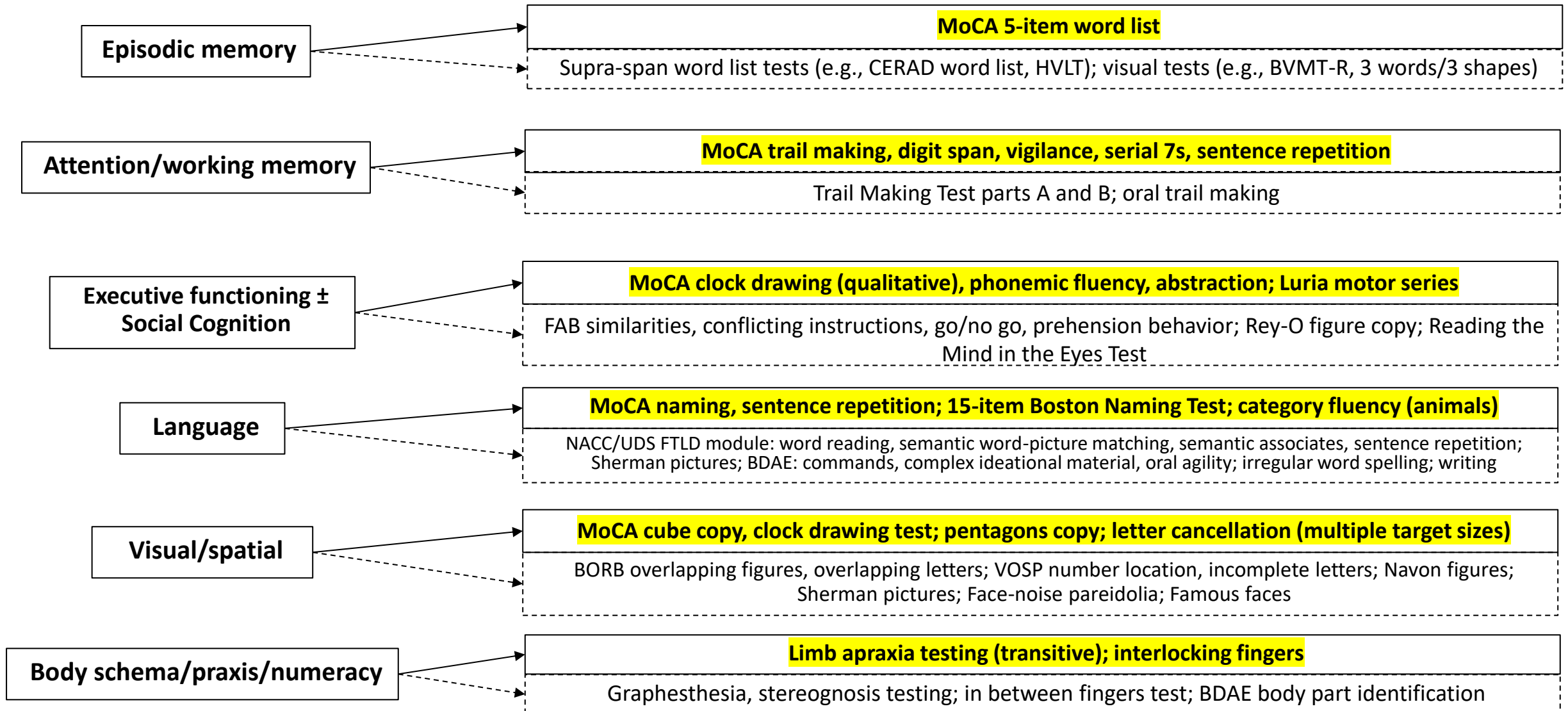
Item	Max Score
Memory 1. (Instructions) I want you to imagine that we are going shopping. Here is a list of grocery items. I would like you to remember the following items which we need to get from the shop. When we get to the shop in about 5 mins. time I will ask you what it is that we have to buy. You must remember the list for me. Tea, Cooking Oil, Eggs, Soap Please repeat this list for me (ask person to repeat the list 3 times). (If person did not repeat all four words, repeat the list until the person has learned them and can repeat them, or, up to a maximum of five times.)	
Visuospatial Orientation 2. I am going to ask you to identify/show me different parts of the body. (Correct = 1). Once the person correctly answers 5 parts of this question, do not continue as the maximum score is 5. (1) show me your right foot 1 (2) show me your left hand 1 (3) with your right hand touch your left shoulder 1 (4) with your left hand touch your right ear 1 (5) which is (indicate/point to) my left knee 1 (6) which is (indicate/point to) my right elbow 1 (7) with your right hand indicate/point to my left eye 1 (8) with your left hand indicate/point to my left foot 1	5
Praxis 3. I am going to show you an action/exercise with my hands. I want you to watch me and copy what I do. Copy me when I do this ... (One hand in fist, the other palm down on table - alternate simultaneously.) Now do it with me: Now I would like you to keep doing this action at this pace until I tell you to stop - approximately 10 seconds. (Demonstrate at moderate walking pace). Score as: Normal = 2 (very few if any errors; self-corrected, progressively better; good maintenance; only very slight lack of synchrony between hands) Partially Adequate = 1 (noticeable errors with some attempt to self-correct; some attempt at maintenance; poor synchrony) Failed = 0 (cannot do the task; no maintenance; no attempt whatsoever)	2
Visuoconstructional Drawing 4. Please draw this picture exactly as it looks to you (Show cube on back of page). (Yes = 1) Score as: (1) Has person drawn a picture based on a square? 1 (2) Do all internal lines appear in person's drawing? 1  (3) Do all external lines appear in person's drawing? 1 	3
Judgment 5. You are standing on the side of a busy street. There is no pedestrian crossing and no traffic lights. Tell me what you would do to get across to the other side of the road safely. (If person gives incomplete response that does not address both parts of answer, use prompt: "Is there anything else you would do?") Record exactly what patient says and circle all parts of response which were prompted. Score as: Did person indicate that they would look for traffic? (YES = 2; YES PROMPTED = 1; NO = 0) 2 Did person make any additional safety proposals? (YES = 2; YES PROMPTED = 1; NO = 0) 2	4

Memory Recall 1. (Recall) We have just arrived at the shop. Can you remember the list of groceries we need to buy? (Prompt: If person cannot recall any of the list, say "The first one was 'tea'." (Score 2 points each for any item recalled which was not prompted – use only 'tea' as a prompt.) Tea 2 Cooking Oil 2 Eggs 2 Soap 2 Language 6. I am going to time you for one minute. In that one minute, I would like you to tell me the names of as many different animals as you can. We'll see how many different animals you can name in one minute. (Repeat instructions if necessary). Maximum score for this item is 8. If person names 8 new animals in less than one minute there is no need to continue. 1. 5. 2. 6. 3. 7. 4. 8.		
TOTAL SCORE =		

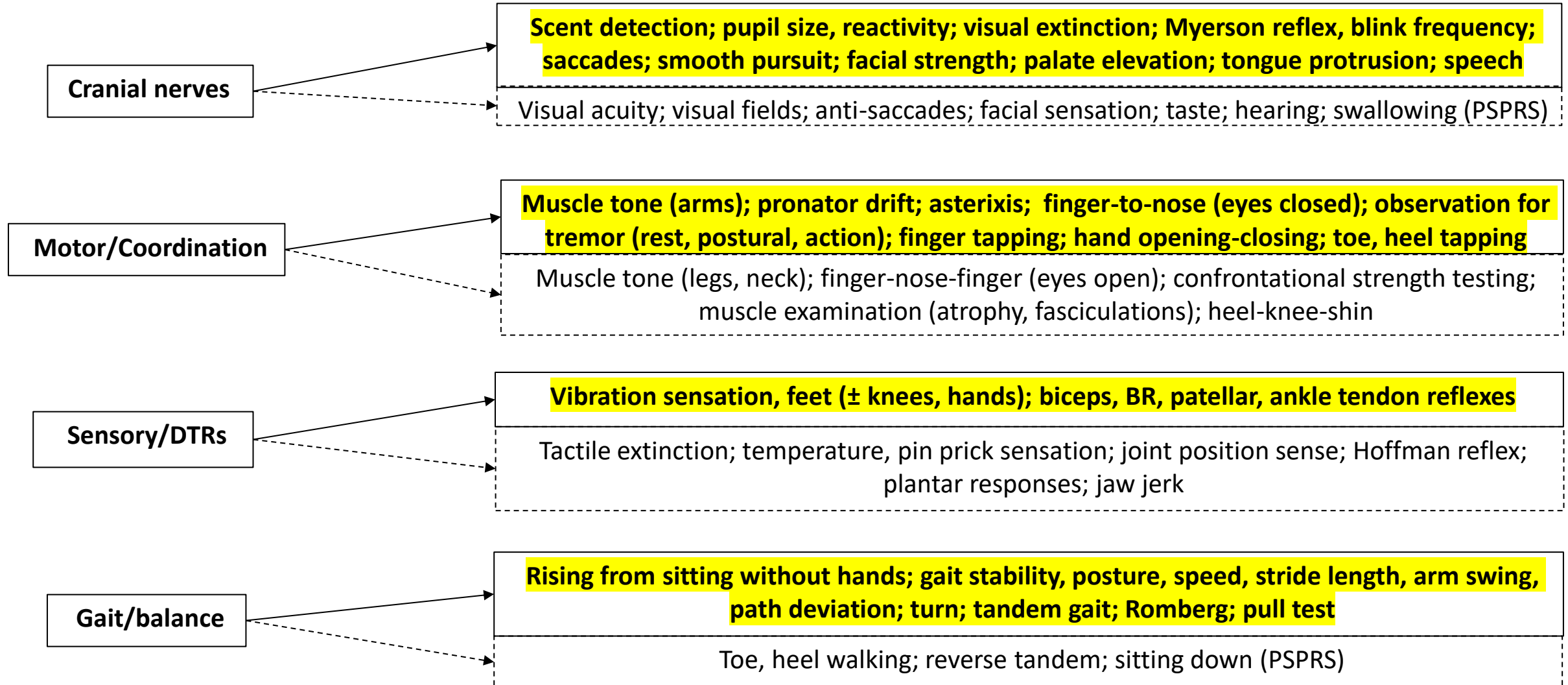
Relative strengths:

- Superior to other measures in multicultural populations, and/or patients with limited education or low literacy.

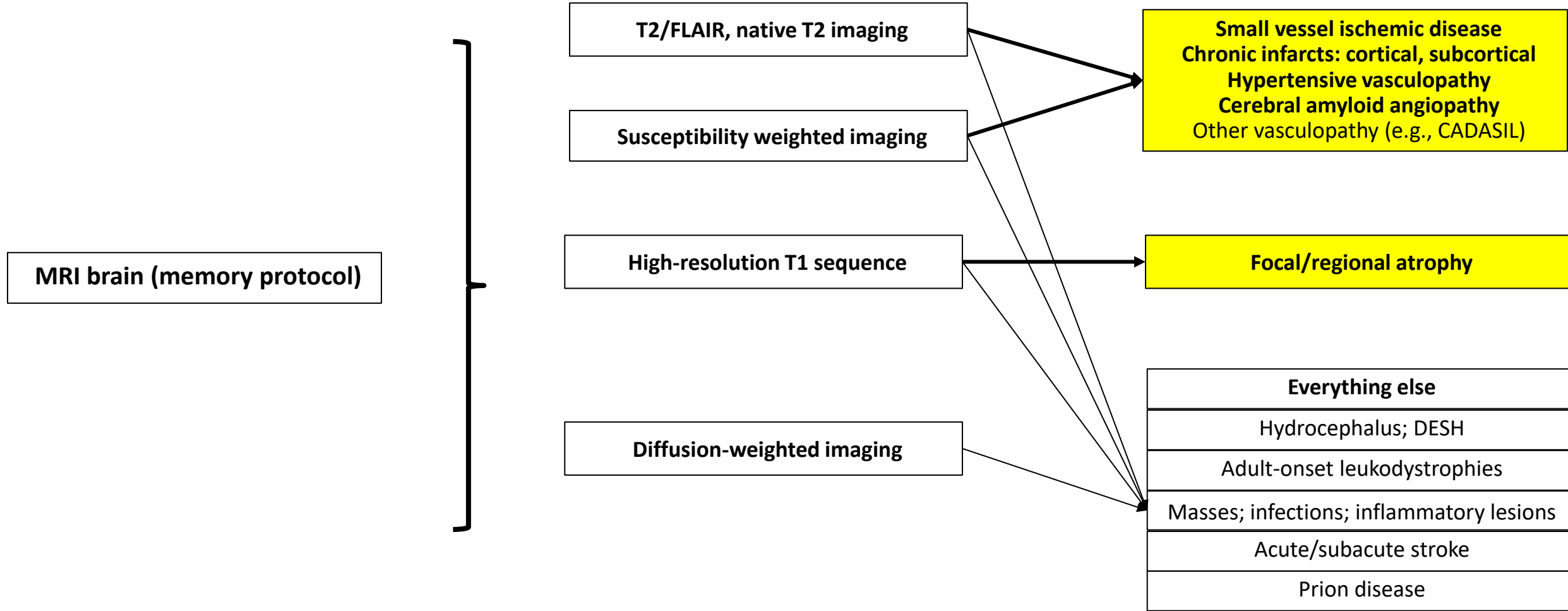
Standard and Flexible Cognitive Examination



General Neurological Examination



Standard Imaging

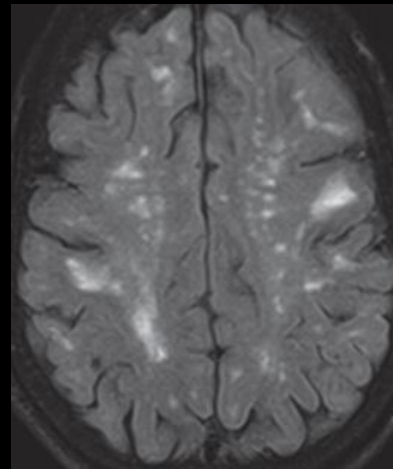
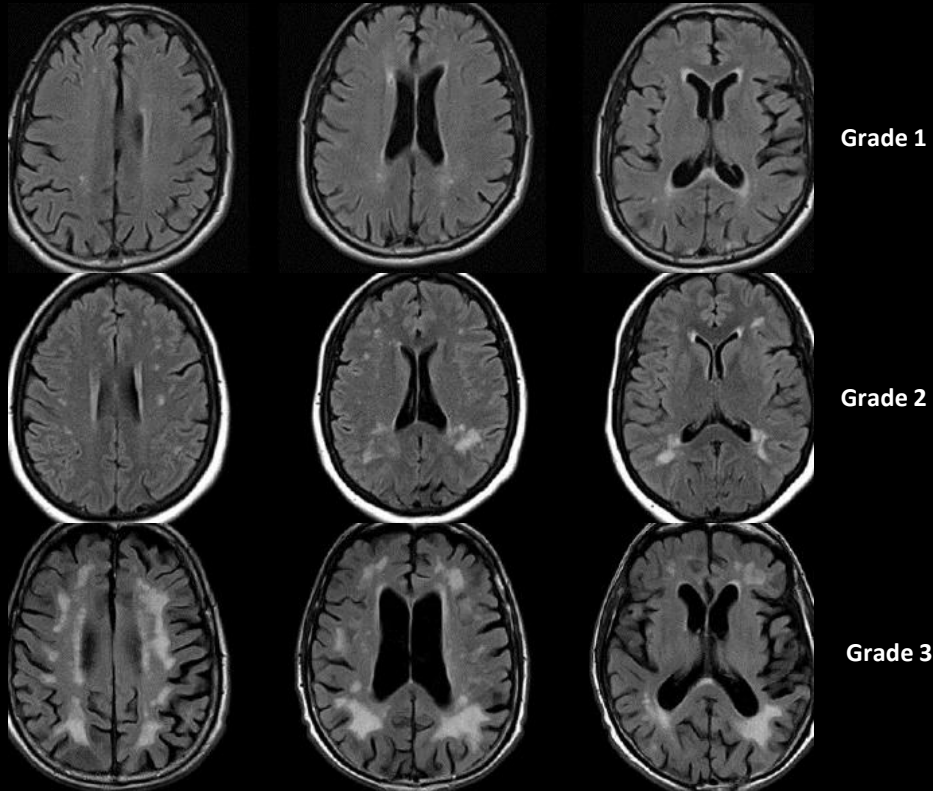


Test hypotheses generated from the history and cognitive examination

Standard Imaging: Vascular Disease

T2/FLAIR hyperintensities

- Location:
 - Small vessel ischemic disease: periventricular (ependymal loss, ischemic demyelination), subcortical (lipohyalinosis), juxtacortical (arteriole atherosclerosis)
 - Cerebral amyloid angiopathy: centrum semiovale
- Severity (Fazekas Scale):

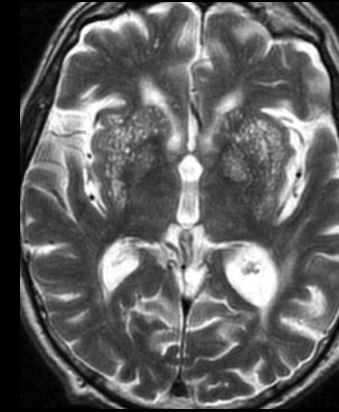


Cerebral amyloid angiopathy

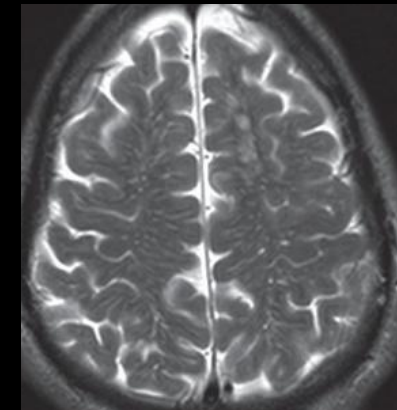
Charidimou *Lancet Neurol* 2022

Dilated perivascular spaces

- Hypertensive vasculopathy: basal ganglia
- Cerebral amyloid angiopathy: centrum semiovale



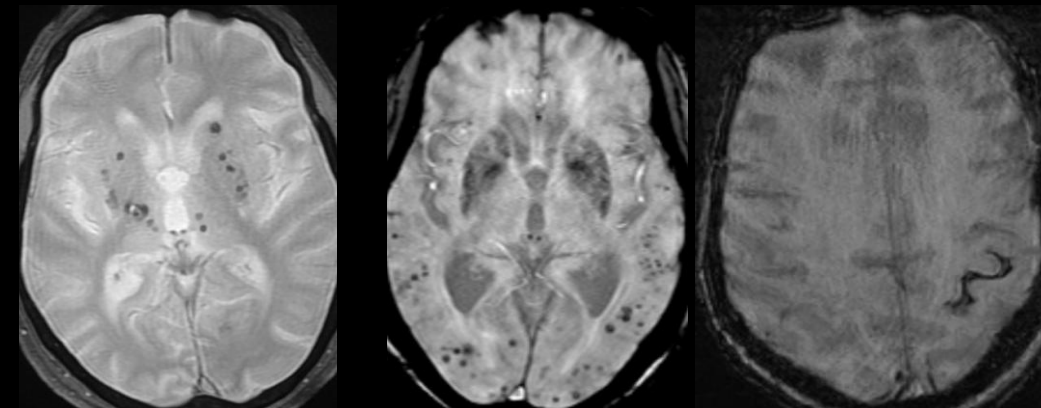
Fergus *Stroke* 2010



Charidimou *Lancet Neurol* 2022

Susceptibility

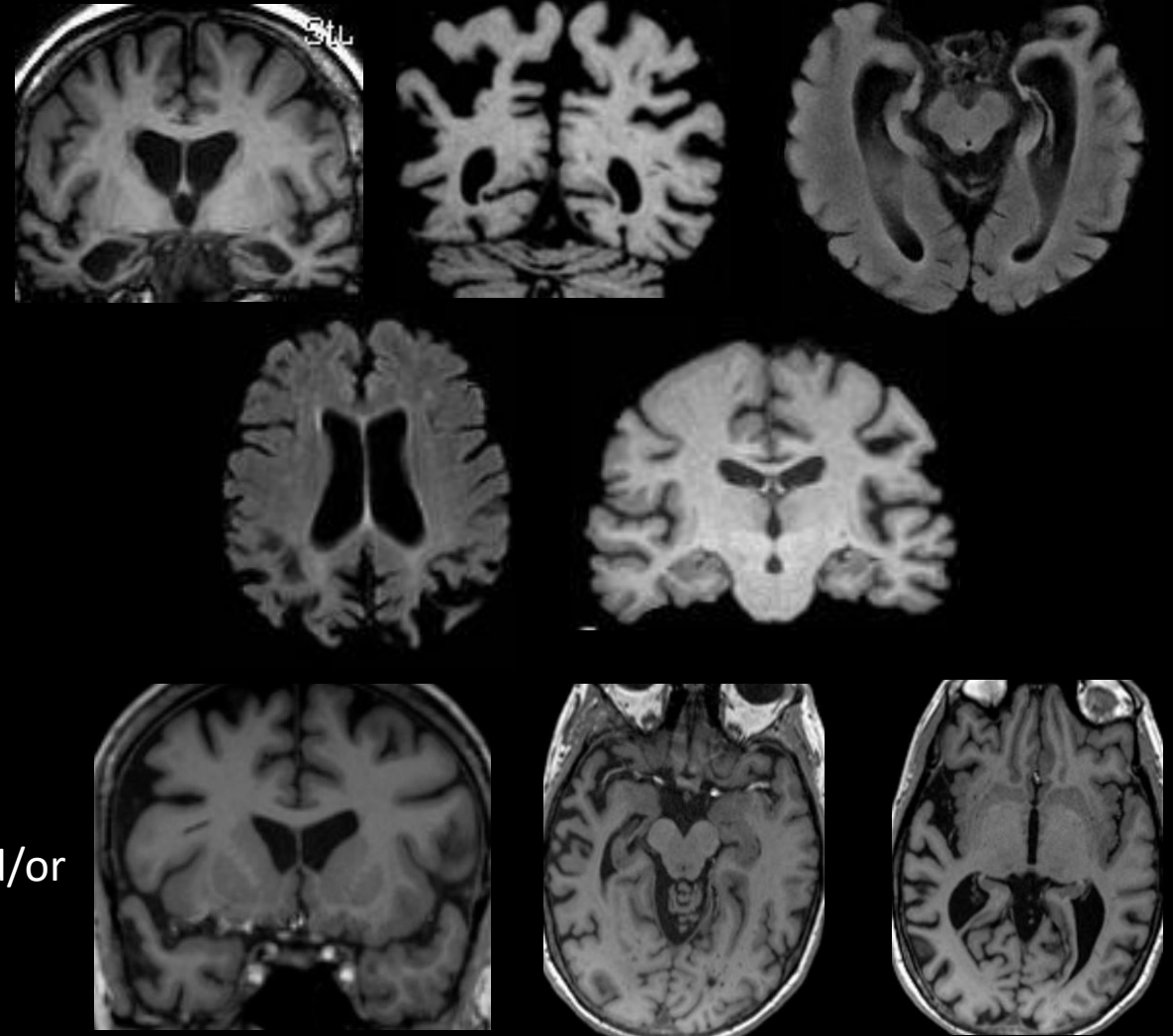
- HTN: subcortical > cortical microhemorrhages
- CAA: cortical microhemorrhages, superficial siderosis



Standard Imaging: Atrophy

High resolution T1 imaging (e.g., SPGR, MPRAGE); 3d reconstruction

- Typical (amnesic) AD: early atrophy in medial temporal, posterolateral temporal, parietal cortices.
- Atypical (non-amnesic) AD: early atrophy in posterolateral temporal, parietal $\pm$ dorsal frontal, occipital cortices
- Atypical, non-AD: early asymmetrical atrophy in frontal and/or temporal lobes



Labs: Non-molecular biomarker

Labs	Utilities/Comments
Standard: Comprehensive metabolic panel, TSH, B12, CBC	Abnormalities are rarely the principal cause of cognitive dysfunction, but may contribute; note eGFR
Also pertinent: Hgb A1c, lipid profile, homocysteine, 25-OH vitamin D, PT, PTT	Consider ordering if recent results not available
Situation-specific (blood): thiamine; treponemal Abs; HIV 1/2 Ab/Ag; rheumatologic labs; autoimmune encephalopathy panel; neurofilament light chain (NfL), GFAP	Informed by social history, general medical illness, time course
Situation-specific (CSF): protein, glucose, cell counts; IgG index, oligoclonal bands; autoimmune encephalopathy panel; cytology, flow cytometry,, IL-10; VDRL, viral PCRs/cultures, bacterial, mycobacterial, fungal stains/cultures, BioFire array; 14-3-3	Informed by history, time course, associated symptoms/signs; usually conducted inpatient

Labs: Molecular Biomarker and Genetic

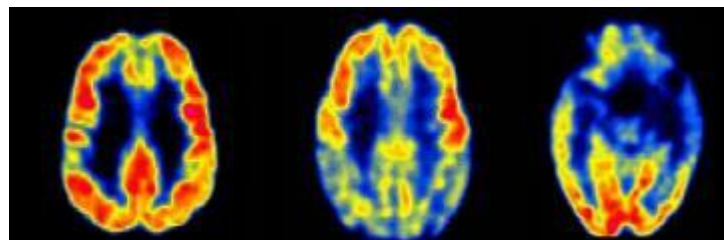
Labs	Utilities/Comments
CSF: Abeta42, total tau, p-tau181*; alpha-synuclein sAA; IgH gene arrangement, MYD88 analysis	Standard of care; CSF amyloid and tau has comparable diagnostic accuracy to amyloid PET
Plasma p-tau217*, Abeta 42/40*	Recommended for use by subspecialists, in context of comprehensive evaluation
Skin biopsy: alpha-synuclein	Useful in Parkinson disease, dementia with Lewy bodies, multiple system atrophy
Apolipoprotein E (APOE) genotype	Used for risk stratification for candidates to receive amyloid-lowering immunotherapies; not sensitive or specific for AD
Genetic: Amyloid Precursor Protein (APP), Presenilin 1 (PSEN1), Presenilin 2 (PSEN2) mutations*	Useful when family history suggests an autosomal dominant pattern of inheritance
Genetic: Progranulin (GRN), Microtubule-associated protein tau (MAPT) mutations; C9orf72 repeat expansion*	Most common autosomal dominant gene mutations associated with FTLD

* FDA approved

Extended Imaging: Neurodegeneration

Modalities	Utilities	Limitations
^{18}F-fluorodeoxyglucose (FDG) PET	- Discriminate syndromic FTD, AD, DLB with some predictive value for underlying neuropathology - Discriminate degenerative from non-degenerative cognitive impairment (negative predictive value)	- Lack of molecular specificity - Potential for false-positive results (e.g., asymptomatic <i>APOE4</i> carriers) - Variable insurance coverage for non-Medicare patients and indications other than discriminating FTD from AD
^{18}F-fluorodopa PET dopamine transporter (DaT) imaging	- Discriminate degenerative from non-degenerative (e.g., vascular, medication-induced) parkinsonism	- Lack of molecular specificity - Does not discriminate between neurodegenerative conditions causing parkinsonism

FDG-PET

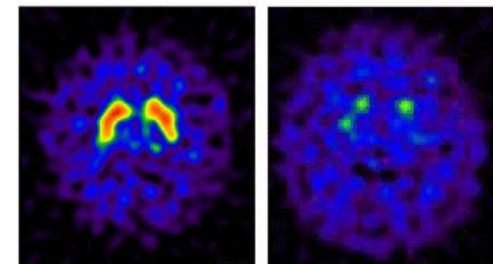


Normal

AD
syndromes

FTD
syndromes

Dopamine transporter imaging

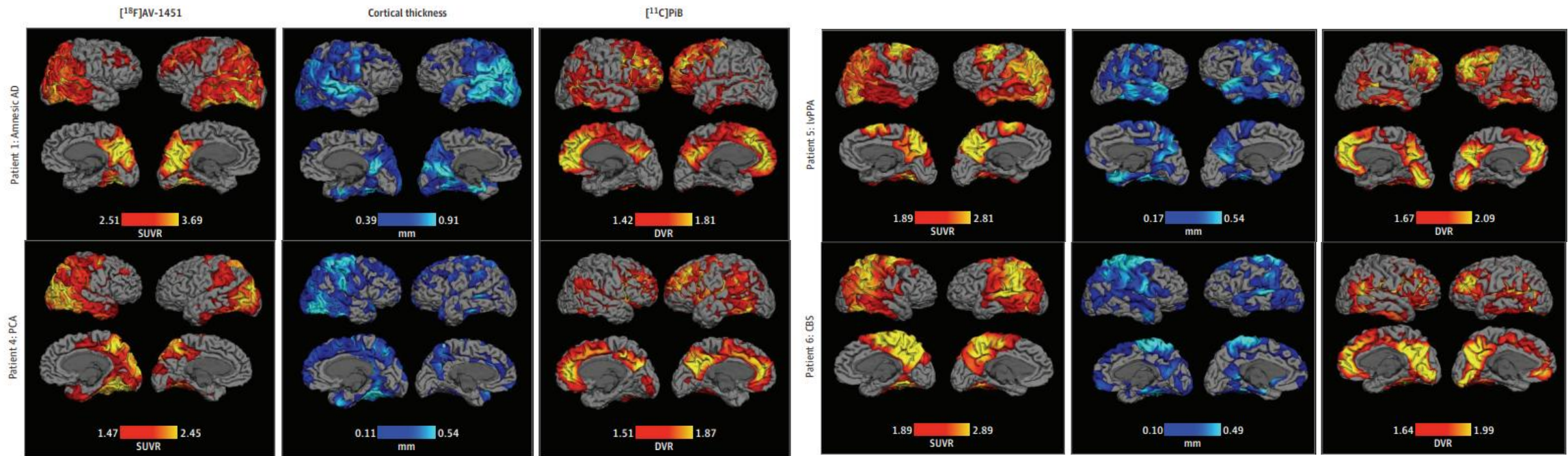


Normal

Degenerative

Extended Imaging: Molecular Pathology

Modalities	Utilities	Limitations
^{18}F-Amyloid PET (florbetapir, florbetaben, flutemetamol)	- Detect fibrillar beta-amyloid with high sensitivity and specificity against neuropathological gold standard). - FDA-approved and covered by Medicare	- Elevated fibrillar beta-amyloid does not equate to a diagnosis of AD (necessary but not sufficient)
^{18}F-Tau PET (Flortaucipir)	- Provides information about not only molecular pathology but also topography, pertinent to disease stage and phenotype. - Substantially elevated uptake in neocortical regions is highly predictive of elevated beta-amyloid.	- FDA-approved, increasingly covered by insurance



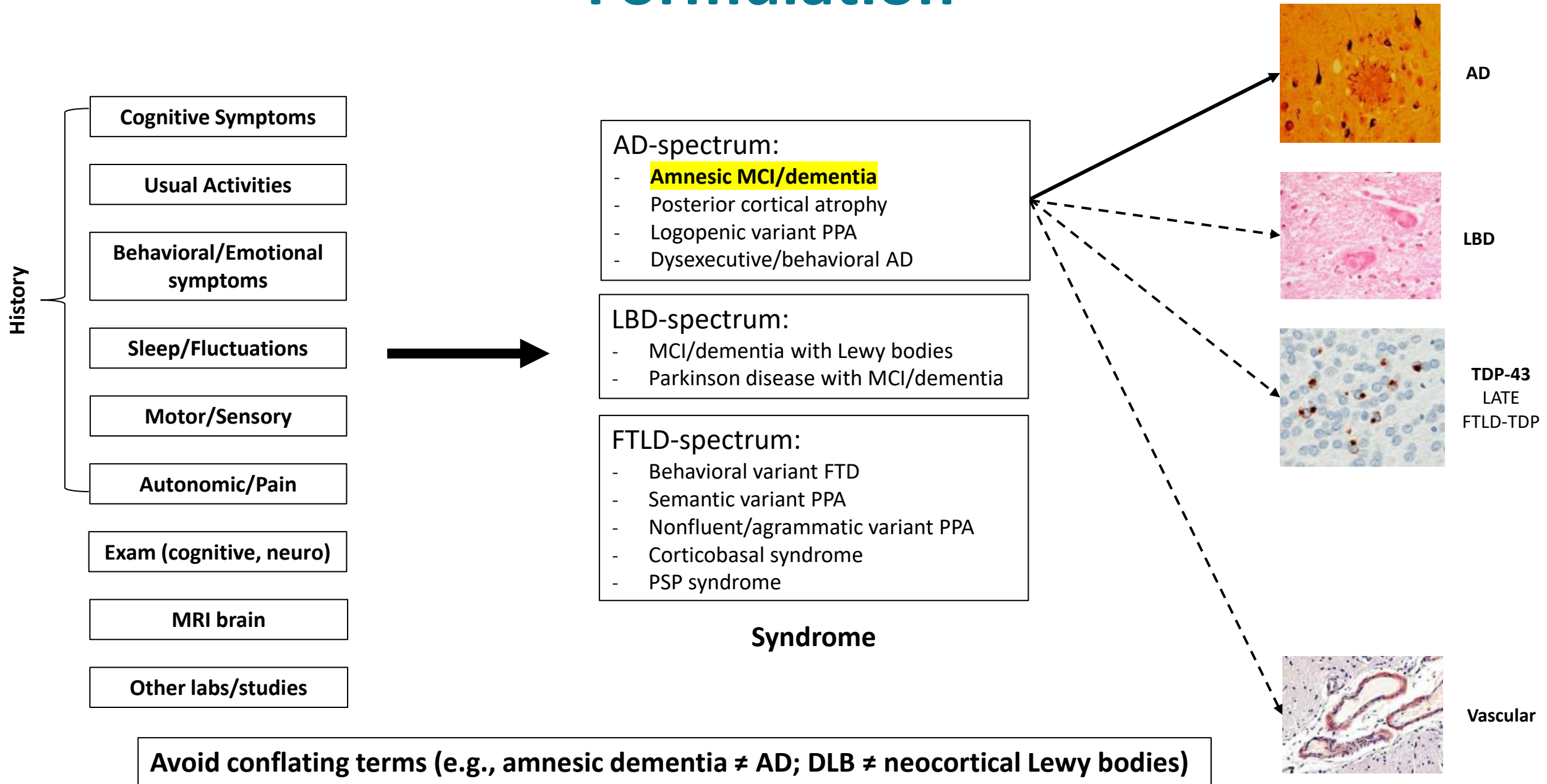
Additional Studies, Referrals

Studies, Referrals	Utilities/Comments
Neuropsychology	Establish, clarify cognitive profile; longitudinal time course; time to wait for evaluation is frequently long
Audiology	Hearing correction liberates attention, working memory resources
Ophthalmology, Neuro-ophthalmology	Evaluate basic vision in cases of visual hallucinations, higher visual deficits
Electroencephalogram (EEG): routine, long-term ambulatory	Evaluate paroxysmal symptoms; AD increases risk of focal seizures; useful in Lewy body disorders d/t fluctuations and inattention
Polysomnogram ± Sleep Medicine referral	Evaluate for obstructive sleep apnea; RBD
Electromyogram, nerve conduction studies (EMG/NCV) ± Neuromuscular referral	Evaluate for motor neuron disease
Autonomic testing (Autonomic neurology referral)	Evaluate for dysautonomia
Direct admission to inpatient neurology service	Expedite workup for rapidly progressive dementia

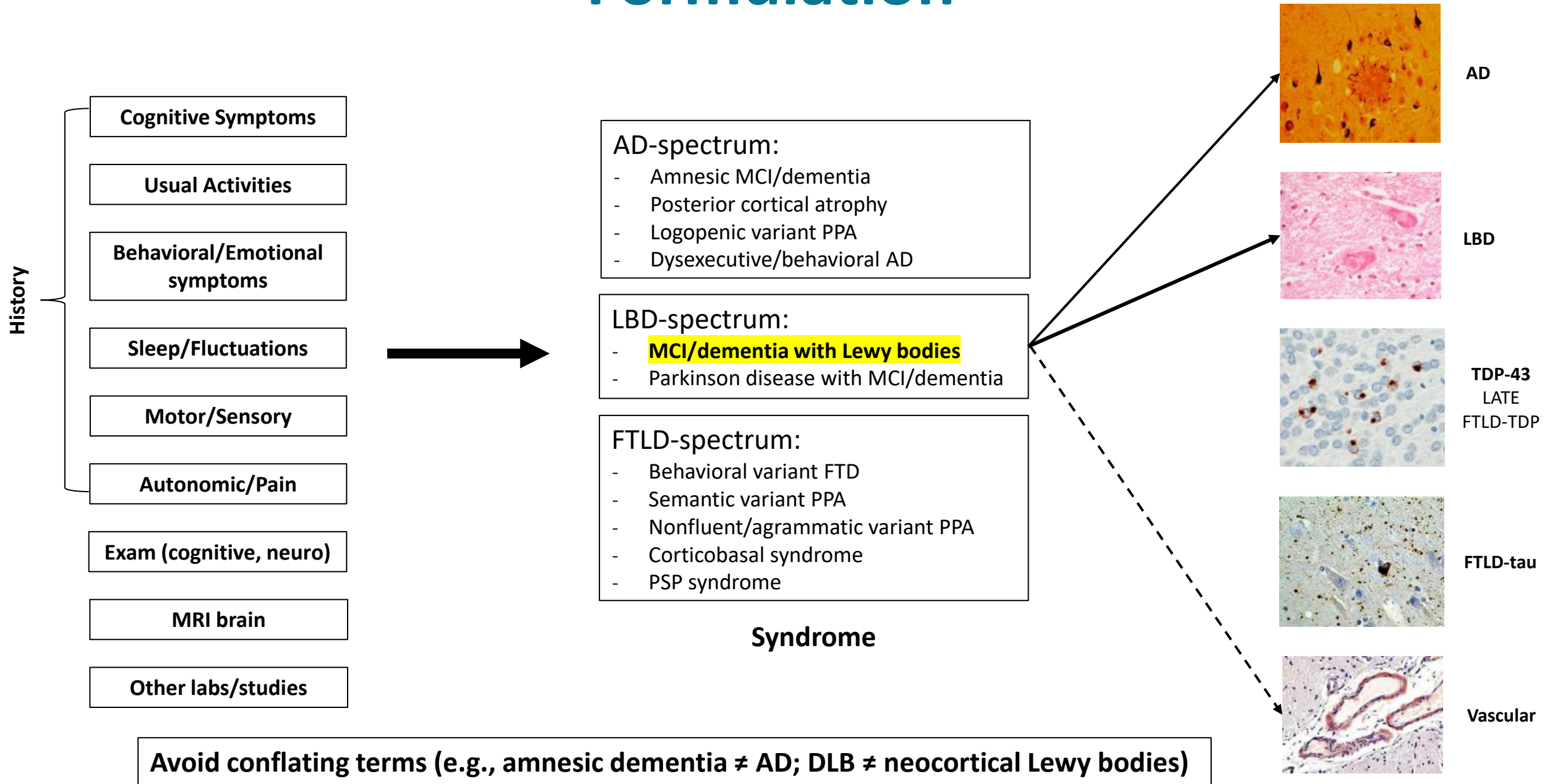
Extended Biomarkers: When to Obtain

- 1. When indicated to determine eligibility for treatment with a disease-modifying therapy (e.g., lecanemab or donanemab).**
- 2. Additional situations when having the information would be helpful to guide management considerations.**
- 3. To increase diagnostic confidence in atypical presentations (e.g., non-amnestic MCI/dementia, early-onset illness).**
- 4. When the patient and/or their family values the potential higher diagnostic confidence provided by the information.**

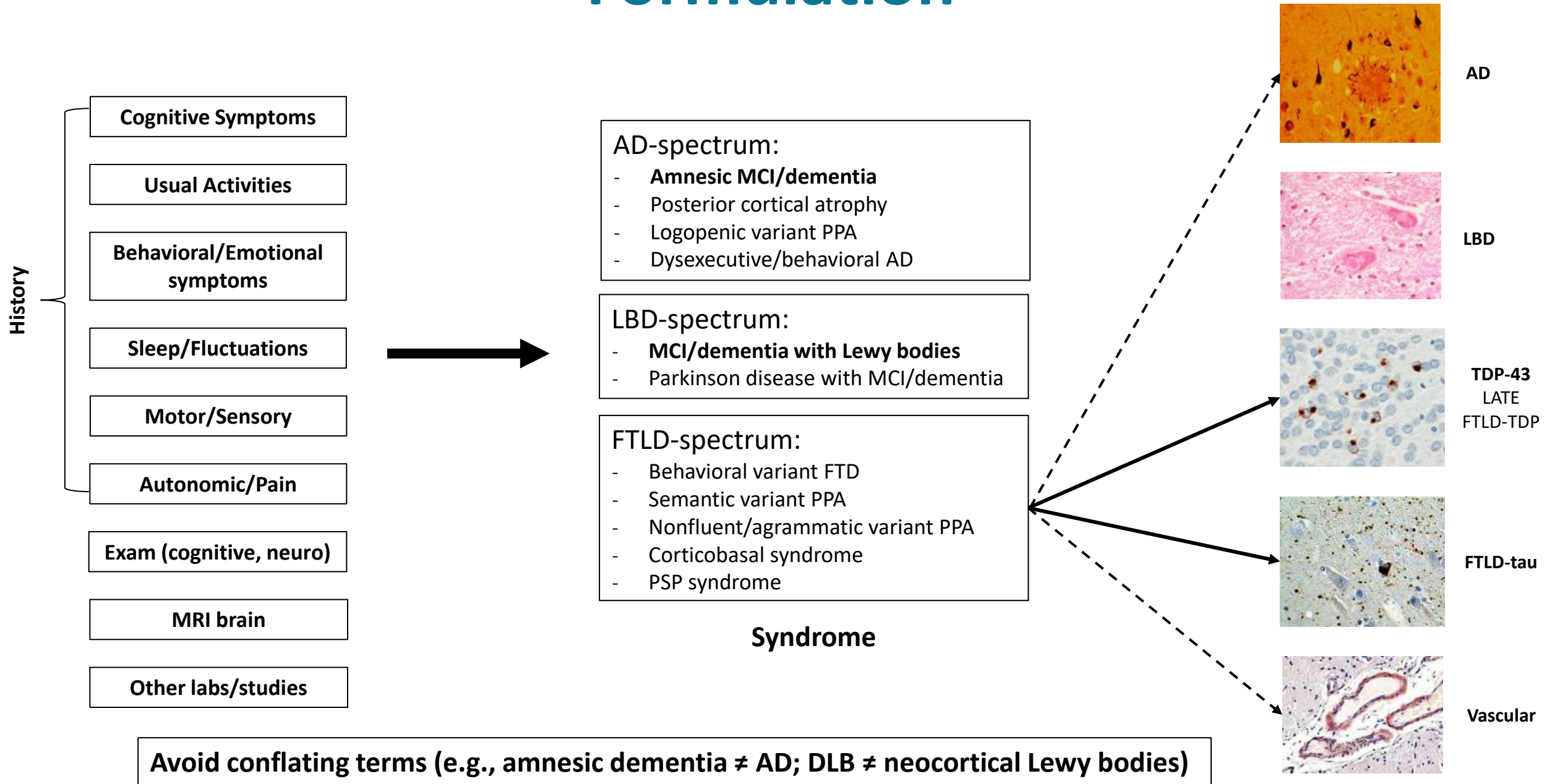
Formulation



Formulation



Formulation



Neuropsychiatric features of common conditions

Alzheimer disease

- Irritability
- Anxiety
- Apathy
- Depression
- Paranoia
- Poor insight

Lewy body disease

- Recurrent formed visual hallucinations[‡]
- Anxiety*
- Depression*
- Apathy*
- Systematized delusions*
- Hallucinations in non-visual modalities*

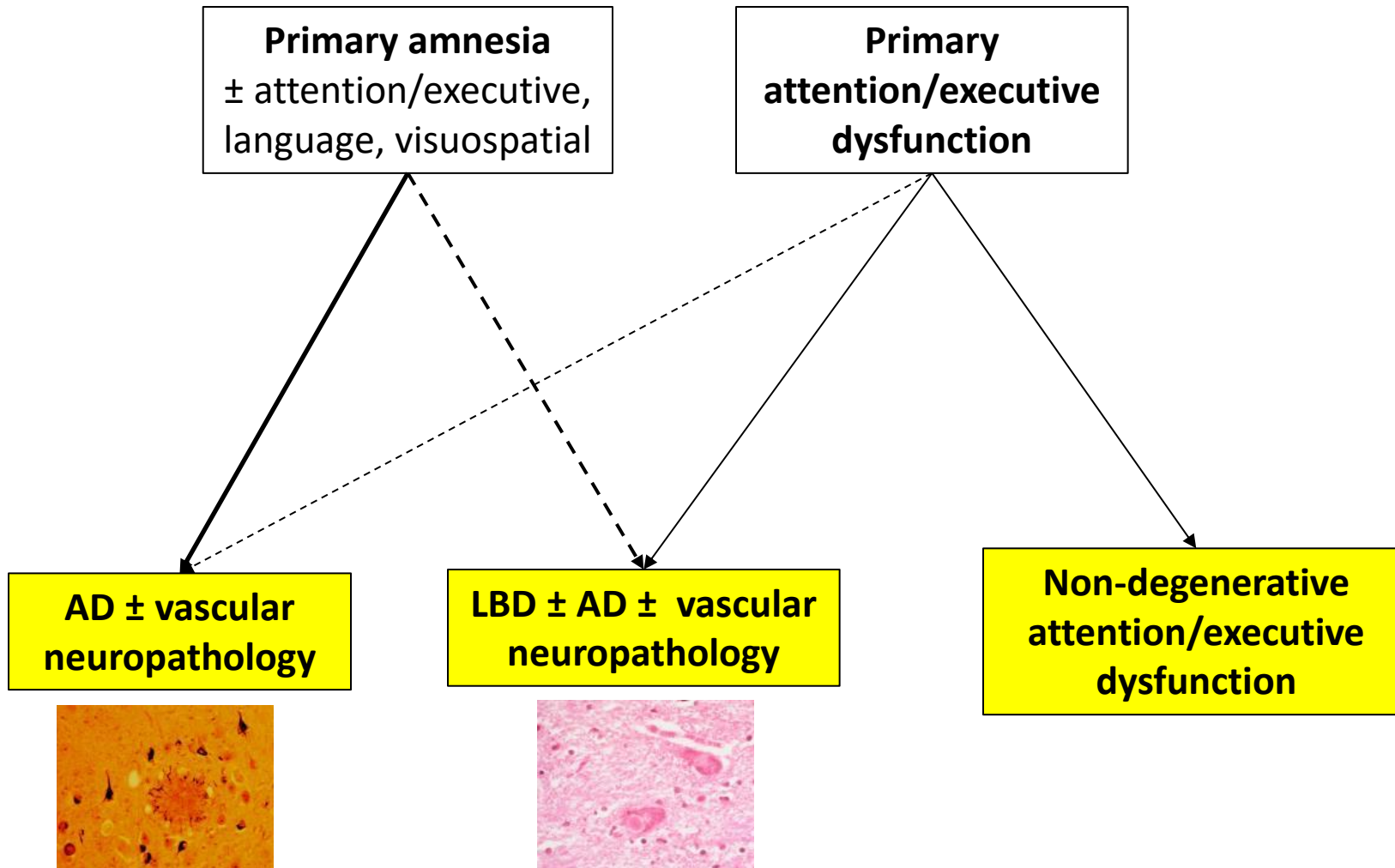
[‡] Core clinical feature

* Supportive clinical feature

Non-progressive disorders of attention and executive functioning



Challenges: Common Conditions

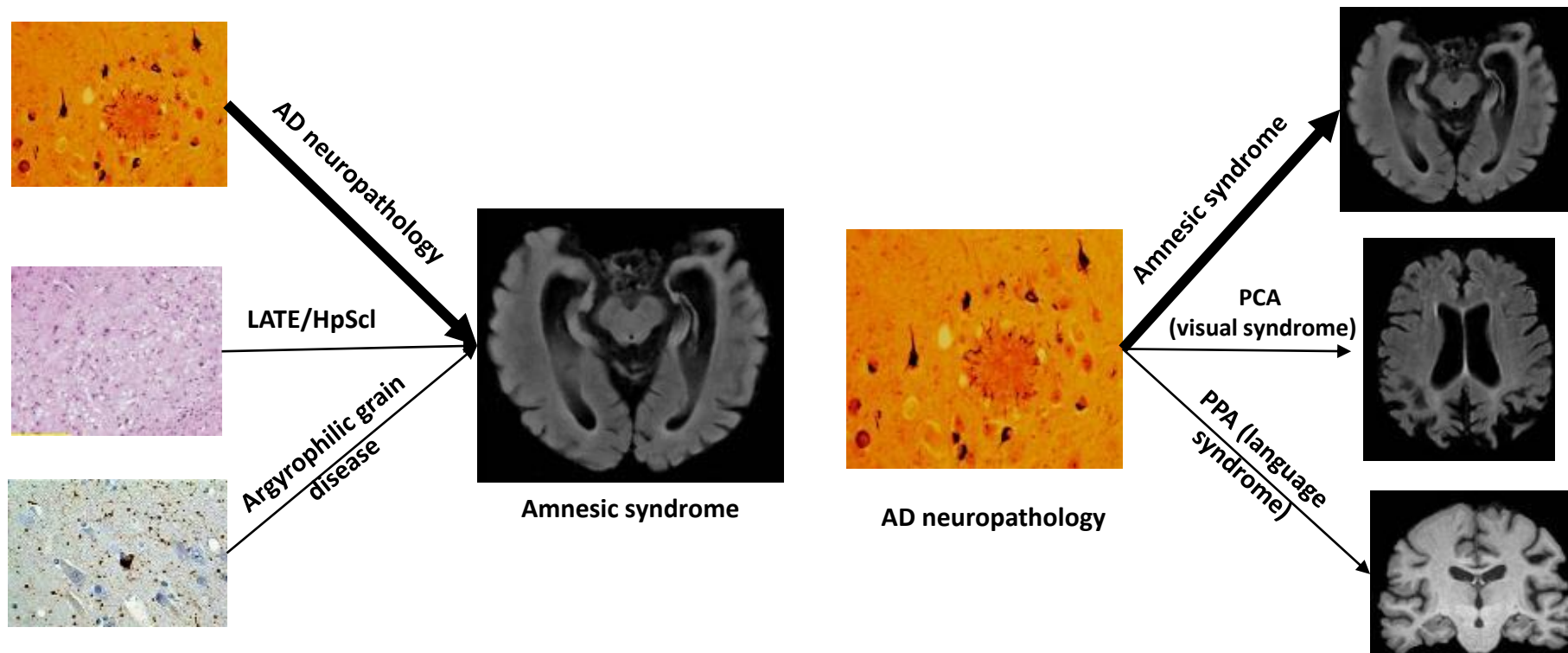


1. Discriminating amnesia from attention/executive dysfunction
2. Discriminating between static and progressive time course
3. Variable penetrance of secondary cognitive and associated features
4. Non-specificity of associated features
5. Occam's razor vs Hickam's dictum

Common pitfall: Conflating syndrome and neuropathology

- **Consequences:**

- Under-recognition of non-canonical neuropathologies underlying specific syndromes.
- Under-recognition of non-canonical syndromes associated with specific neuropathologies.



Common pitfall: Assuming a single underlying neuropathology

- **Examples:**

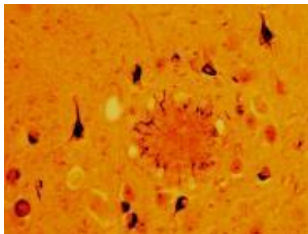
- Diagnosing “vascular dementia” in a patient with high T2/FLAIR burden or primary dysexecutive cognitive profile
- Diagnosing “AD” or “LBD” in a patient with mixed AD/LBD neuropathology.

- **Basis:**

- Historical under-recognition of mixed neuropathological diagnoses.

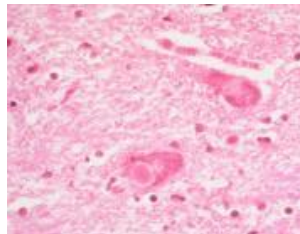
- **Consequences:**

- Potentially missing prognostic value and/or potential therapeutic implications.



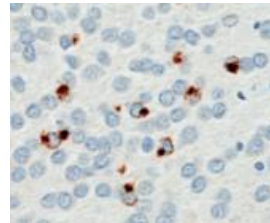
AD

Abeta42, PHF tau

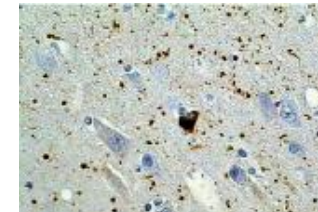


LBD

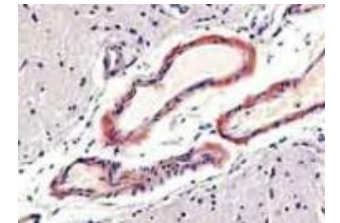
Alpha-synuclein



TDP-43



FTLD-tau



Vascular disease

Accurate diagnosis provides the foundation for longitudinal care

	SCD/ Preclinical	MCI	Mild dementia	Mod. dementia	Sev. dementia
Symptomatic pharmacotherapy (cognition)	-	+/- (off-label)	+	+	+/-
Disease modifying pharmacotherapy	?	+++	++	-	-
Cognitive rehabilitation therapy	-	++	+	-	-
Compensatory strategies, brain health habits, vascular risk factors	+++	++	+	-	-
Safety	-	+	+++	+++	+
Advance directives/planning	+	+++	+++	++	++
Care arrangements/Caregiver support	-	+	++	+++	+++
Clinical therapeutic research (if interested)	+++	+++	++	-	-

Thank you

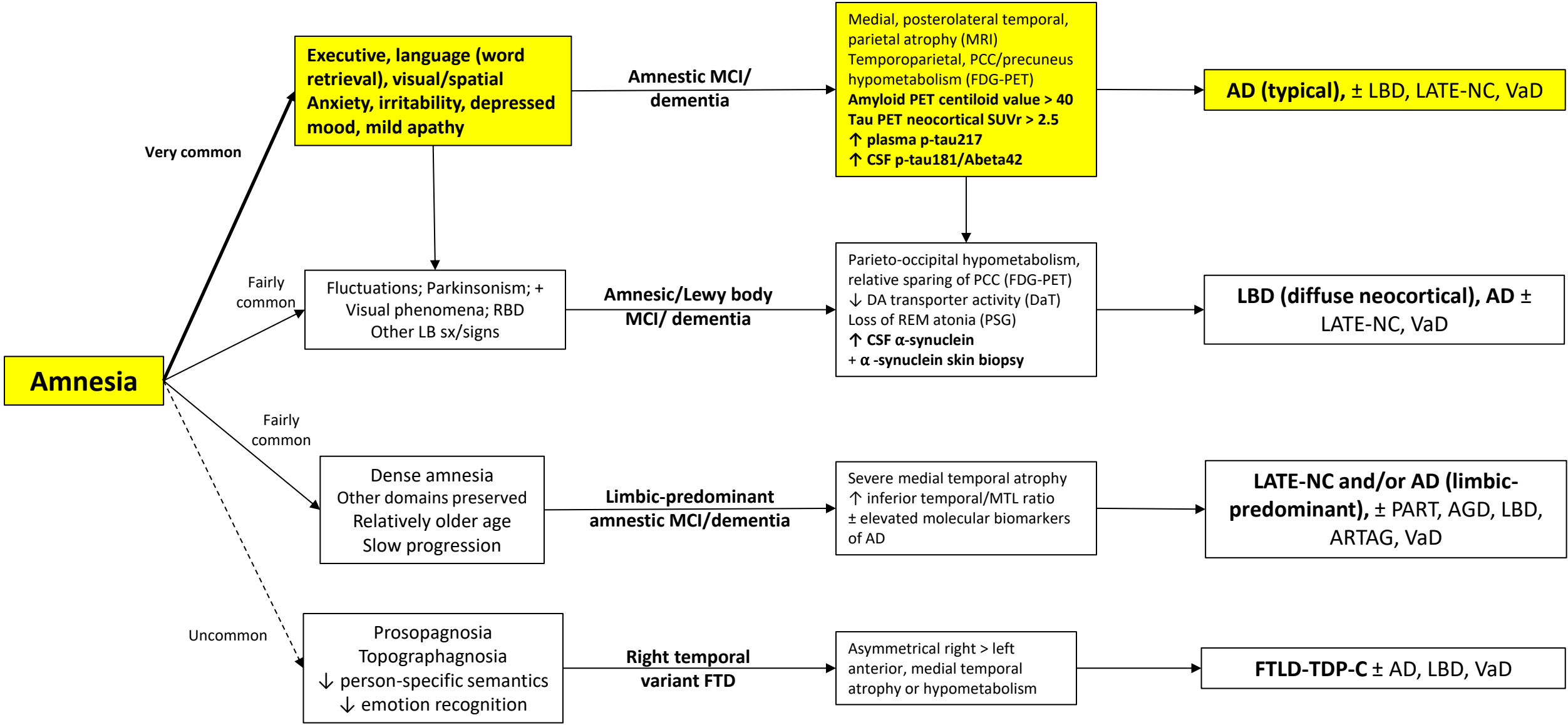


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617-732-8085; BWHmemory@partners.org
- MGH FTD Unit: 617-726-5571; MGHFTDunit@partners.org



Reference: Diagnostic Criteria

- **Formulation:**
 - Dickerson et al. *CNS Spectrums* 2017;22:439-49.
- **NIA-Alzheimer's Association Diagnostic criteria:**
 - Dementia due to AD: McKhann et al. *Alzheimers Dement* 2011;7:263-9.
 - MCI due to AD: Albert et al. *Alzheimers Dement* 2011;7:270-9.
- **DLB consortium criteria:** McKeith *Neurology* 2017;89:1-13.
- **Other clinical diagnostic criteria:**
 - PPA: Gorno-Tempini et al. *Neurology* 2011;76:1006-14.
 - PCA: Crutch et al. *Alzheimers Dement* 2017;13:870-84.
 - bvFTD: Rascovsky et al. *Brain* 2011;134:2456-77.
 - Sporadic CJD: Hermann et al. *Lancet Neurol* 2021;20:235-46.
- **Network degeneration:**
 - Seeley et al. *Neuron* 2009;62:42-52.



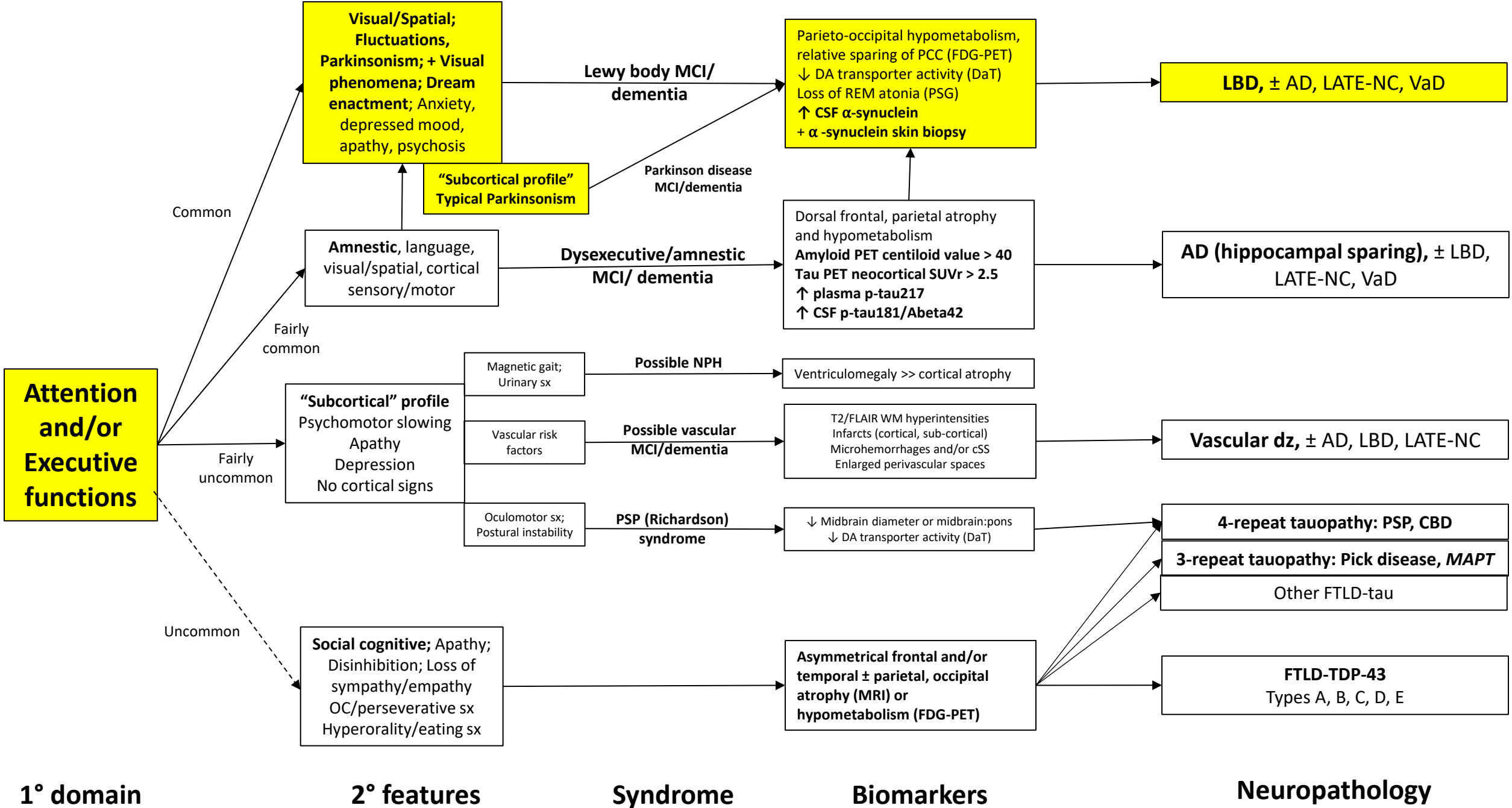
1° domain

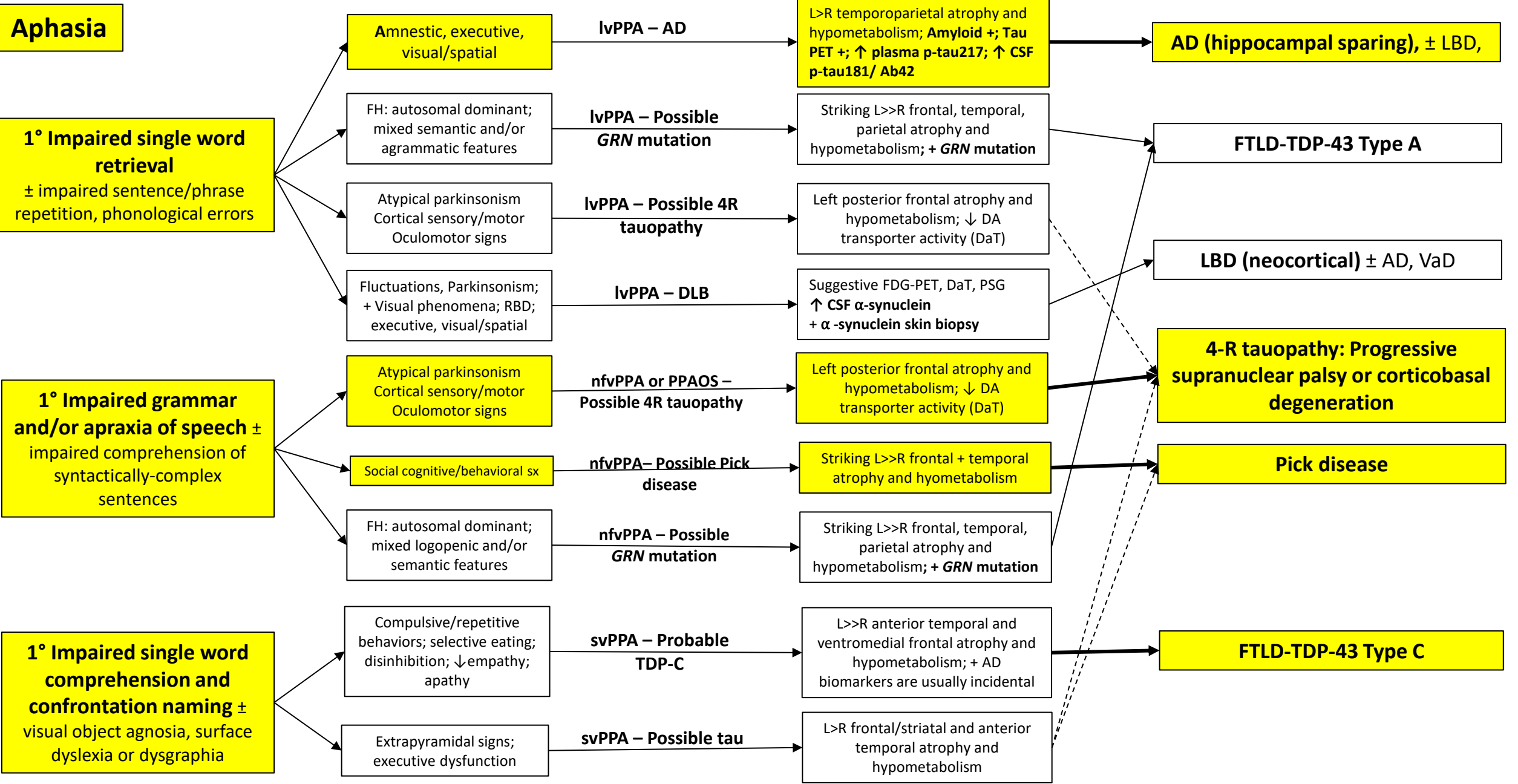
2° features

Syndrome

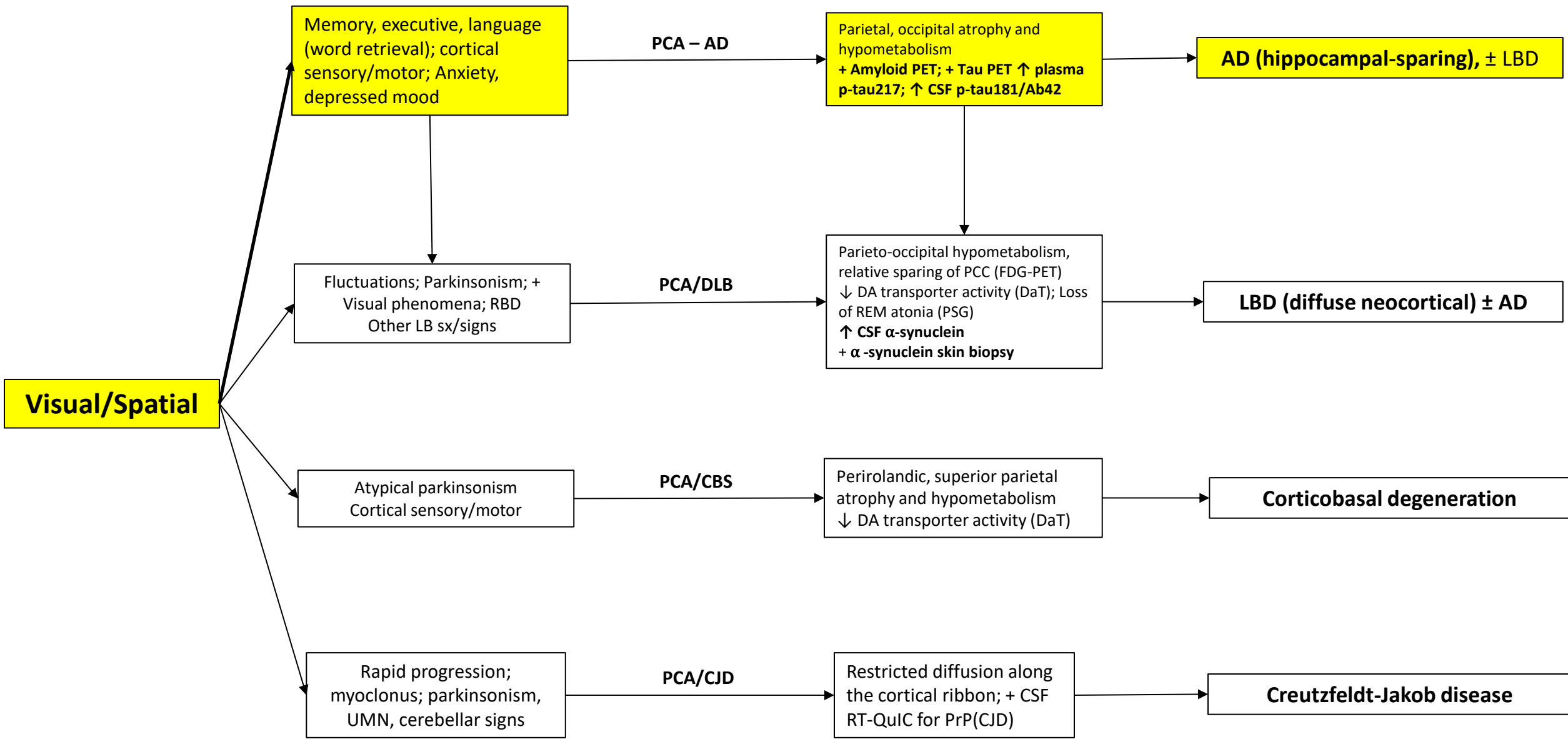
Biomarkers

Neuropathology





1° domain **2° features** **Syndrome** **Biomarkers** **Neuropathology**



1° domain

2° features

Syndrome

Biomarkers

Neuropathology