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felix platter

Diagnostic Manual

Memory Clinic

Universitäre Altersmedizin

FELIX PLATTER

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Vorwort

Das Diagnostic Manual der Memory Clinic Basel entstand aus dem Wunsch heraus, eine Übersicht über die aktuellsten Konsensus-Kriterien für klinische Syndrome zur Verfügung zu haben, die vor allem bei Menschen mit Hirnleistungsstörungen im höheren Lebensalter auftreten können.

Während für die medizinische Dokumentation derzeit in erster Linie auf das Klassifikations-Modell von ICD-10 Bezug genommen wird, orientieren wir uns in der Memory Clinic bei der Einstufung des Schweregrades von Hirnleistungsstörungen am «Diagnostic and Statistical Manual of Mental Disorders» (DSM-5) der American Psychiatric Association (APA, 2013). Die Übersicht des Kapitels «Mental Disorders» ist daher am Beginn des Manuals zusammenfassend dargestellt.

Die Basis für eine sorgfältige Differentialdiagnostik stellen dann die sehr viel differenzierteren Diagnosekriterien wichtiger klinischer Syndrome dar, welche von Expertengruppen formuliert wurden und in der hier vorliegenden zweiten Version unseres Diagnostic Manual zusammengestellt sind. Nicht für alle im DSM-5 aufgeführten möglichen Ursachen neurokognitiver Störungen existieren solche Kriterien, sodass auch wir keine vollständige Übersicht zu allen Ätiologien präsentieren können. Wir sind jedoch überzeugt, dass diese hier zusammengestellte Übersicht im klinischen Alltag eine wertvolle Hilfe bei der Klärung differentialdiagnostischer Fragestellungen sein kann.

Die Wissenschaft ist im Fluss, es wird weitere Erkenntnisse geben, die zu Verfeinerungen der Kriterien führen werden. Wir werden «am Ball» bleiben und das Manual auch in Zukunft aktualisieren. Über Anregungen für weitere Auflagen freuen wir uns.

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I. Classification of Neurocognitive Disorders

Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

Mild neurocognitive disorder

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
   2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

For mild NCD, performance typically lies in the 1–2 or more standard deviation range (between the 3rd and 16th percentiles).

Major neurocognitive disorder

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
   2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

For major NCD, performance is typically 2 or more standard deviations below appropriate norms (3rd percentile or below).

Specify current severity

a. Leicht (mild): Difficulties with instrumental activities of daily living (e.g., housework, managing money).

b. Mittel (moderate): Difficulties with basic activities of daily living (e.g., feeding, dressing).

c. Schwer (severe): Fully dependent.

Specify:

- Without behavioral disturbance: If the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.
- With behavioral disturbance (specify disturbance): If the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g. psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms).

Specify whether due to:

- Alzheimer's disease
- Frontotemporal Lobar Degeneration
- Lewy body disease
- Vascular disease
- Traumatic brain injury
- Substance/medication use
- HIV infection
- Prion disease
- Parkinson's disease
- Huntington's disease
- Another medical condition
    - Structural lesions (e.g. primary or secondary brain tumors, subdural hematoma, slowly progressive or normal-pressure hydrocephalus)
    - Hypoxia related to hypoperfusion from heart failure, endocrine conditions (e.g., hypothyroidism, hypercalcemia, hypoglycemia)
    - Nutritional conditions (e.g., deficiencies of thiamine or niacin)
    - Other infectious conditions (e.g., neurosyphilis, cryptococcosis)
    - Immune disorders (e.g., temporal arteritis, systemic lupus erythematosus)
    - Hepatic or renal failure
    - Metabolic conditions (e.g., Kuf's disease, adrenoleukodystrophy, metachromatic leukodystrophy, other storage diseases of adulthood and childhood)
    - Other neurological conditions (e.g., epilepsy, multiple sclerosis)
    - Unusual causes of central nervous system injury, such as electrical shock or intracranial radiation, are generally evident from the history
- Multiple etiologies
- Unspecified

II. Diagnostic Criteria

1. Subjective Cognitive Decline (SCD)

Jessen et al., 2014

A conceptual framework for clinical research on SCD

Key points on SCD in preclinical AD

1. There is evidence that SCD occurs at the preclinical stage of AD and may serve as a symptomatic indicator of preclinical AD because
    a. longitudinal data support SCD as a risk factor for future cognitive decline as well as for MCI and AD dementia
    b. there is cross-sectional biomarker evidence for an increased prevalence of preclinical AD in those with SCD
    c. individuals with SCD and biomarker evidence for AD are at increased risk of future cognitive decline and progression to MCI and AD dementia
2. Current knowledge is insufficient to comprehensively define specific features of SCD in preclinical AD. The characteristics of SCD in preclinical AD are probably variable and are expressed heterogeneously.
3. Preclinical AD is, by definition, a biomarker diagnosis, and SCD is neither required for the diagnosis of preclinical AD nor is it necessarily present in all cases of preclinical AD. SCD by itself may never be sufficient to diagnose preclinical AD.
4. Numerous causes of SCD other than preclinical AD exist. These include, but are not limited to, SCD in MCI due to AD/prodromal AD, dementia, normal aging, psychiatric and neurologic disorders other than AD, or related to effects of medication and substance use.

Research criteria for pre-MCI subjective cognitive decline (SCD)

1. Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.
2. Normal age-, gender-, and education-adjusted performance on standardized cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal Alzheimer's disease (AD).

1 and 2 must be present

Exclusion criteria

- Mild cognitive impairment, prodromal AD, or dementia
- Can be explained by a psychiatric* or neurologic disease (apart from AD), medical disorder, medication, or substance use

** Individual symptoms of depression or anxiety, which do not reach the threshold of a disorder, are not considered exclusion criteria.*

SCD plus (preclinical AD)

= Features that increase the likelihood of preclinical AD in individuals with SCD according to current data:

- Subjective decline in memory, rather than other domains of cognition
- Onset of SCD within the last 5 years
- Age at onset of SCD >60 years
- Concerns (worries) associated with SCD
- Feeling of worse performance than others of the same age group

If available or possible to obtain in the respective study:

- Confirmation of cognitive decline by an informant
- Presence of the APOE ε4 genotype
- Biomarker evidence for AD (defines preclinical AD)

2. Alzheimer's Disease

2.1. MCI due to AD

Albert et al., 2011

- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time).
- Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains).
- Preservation of independence in functional abilities.
- Not demented.

Etiology of MCI consistent with AD pathophysiological process.

- Rule out vascular, traumatic, medical causes of cognitive decline, where possible.
- Provide evidence of longitudinal decline in cognition, when feasible.
- Report history consistent with AD genetic factors, where relevant.

2.2. AD Dementia

McKhann et al., 2011

Distinguish between: probable AD dementia and possible AD dementia.

Probable AD dementia: core clinical criteria

Meets criteria for dementia described earlier in the text and, in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

B. Clear-cut history of worsening of cognition by report or observation; and

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

a) *Amnestic presentation:* It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.

b) Nonamnestic presentations:

- Language presentation: The most prominent deficits are in word finding, but deficits in other cognitive domains should be present.
- Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
- Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD dementia should not be applied when there is evidence of

(a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden;

or (b) core features of dementia with Lewy bodies other than dementia itself;

or (c) prominent features of behavioral variant frontotemporal dementia;

or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia;

or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Possible AD dementia: core clinical criteria

A diagnosis of possible AD dementia should be made in either of the circumstances mentioned in the following paragraphs.

Atypical course

Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline;

or

Etiologically mixed presentation

Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden;

or (b) features of dementia with Lewy bodies other than the dementia itself;

or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.

2.3. National Institute on Aging-Alzheimer's Association (NIA-AA) Research Framework

Jack et al., 2018

Unlike the 2011 NIA-AA criteria for MCI or AD dementia based on clinical criteria (i.e., without biomarkers), the 2018 research framework is **not intended for general clinical practice**. It is called a "research framework" because it needs to be thoroughly examined and modified if needed before being adopted into general clinical practice.

General information:

The NIA-AA research framework defines AD biologically, by neuropathologic change or biomarkers, and treats cognitive impairment as a symptom/sign of the disease rather than the definition of the disease. Thus, the term "Alzheimer's disease" refers to an aggregate of neuropathologic changes and is defined in vivo by biomarkers and by postmortem examination, not by clinical symptoms.

Syndrome vs. disease:

We approached the definition of AD with the distinction between a syndrome and a disease in mind. Some will argue that a specific syndrome, that is, a multidomain amnestic dementia (after other potential etiologies have been excluded), should define AD in living people. Our position, however, is that dementia is not a "disease" but rather a syndrome composed of signs and symptoms that can be caused by multiple diseases, one of which is AD. As we elaborate in the following paragraph, there are two major problems with using a syndrome to define AD; it is neither sensitive nor specific for the neuropathologic changes that define the disease, and it cannot identify individuals who have biological evidence of the disease but do not (yet) manifest signs or symptoms.

Definition of Alzheimer's disease

Biomarker profiles and categories

AT(N) profiles	**Biomarker category**	
A–T–(N)–	Normal AD biomarkers	
A+T–(N)–	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)–	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T–(N)+	Alzheimer's and concomitant suspected non-Alzheimer's pathological change	
A–T+(N)–	Non-AD pathologic change	
A–T–(N)+	Non-AD pathologic change	
A–T+(N)+	Non-AD pathologic change	

NOTE. Binarizing the three AT(N) biomarker types leads to eight different biomarker "profiles". Every individual can be placed into one of the three general biomarker "categories" based on biomarker profiles: those with normal AD biomarkers (no color), those with non-AD pathologic change (dark

grey), and those who are in the Alzheimer's continuum (light grey). The term "Alzheimer's continuum" is an umbrella term that denotes either Alzheimer's pathologic change or AD.
NOTE. If an individual has an abnormal amyloid biomarker study, but a biomarker for tau is not available, then the individual is placed into the "Alzheimer's continuum". A missing biomarker group can be labeled with an asterisk (*). For example, A+(N)+ without a T biomarker would be A+T(N)+.*

Missing biomarkers

A missing biomarker group is denoted *; missing T would therefore be T*. Participants in these studies may be categorized on the basis of information that is available, that is, A+T* places the participant in the "Alzheimer's continuum," and A–T*(N)+ is suspected non-AD pathologic change.

Another common situation will be studies with MRI but without either PET or CSF molecular biomarkers for amyloid and tau. In this situation, while MRI cannot be used as a biomarker of the Alzheimer's continuum, it is useful as a measure of cerebrovascular disease and of nonspecific neurodegeneration, which in turn is a predictor of future clinical decline.

AT(N) biomarker grouping

A:	Aggregated Aβ or associated pathologic state CSF $A\beta_{42}$, or $A\beta_{42}$/ $A\beta_{40}$ ratio Amyloid PET
T:	Aggregated tau (neurofibrillary tangles) or associated pathologic state CSF phosphorylated tau Tau PET
(N):	Neurodegeneration or neuronal injury Anatomic MRI FDG PET CSF total tau

Staging and severity

Two types of categorical clinical staging schemes are proposed:

1. Syndromal categorical cognitive staging that uses traditional syndromal categories and is applicable to all members of a recruited cohort (i.e., includes all biomarker profiles).
2. Numeric clinical staging scheme that is applicable only to those in the Alzheimer's continuum, which the committee felt might be particularly useful in clinical trials.

Syndromal staging of cognitive continuum: applicable to all members of a research cohort independent from biomarker profiles

Cognitively unimpaired

- Cognitive performance within expected range for that individual based on all available information. This may be based on clinical judgment and/or on cognitive test performance (which may or may not be based on comparison to normative data, with or without adjustments for age, education, occupation, sex, etc.).
- Cognitive performance may be in the impaired/abnormal range based on population norms, but performance is within the range expected for that individual.
- A subset of cognitively unimpaired individuals may report subjective cognitive decline and/or demonstrate subtle decline on serial cognitive testing.

Mild cognitive impairment

- Cognitive performance below expected range for that individual based on all available information. This may be based on clinical judgment and/or on cognitive test performance (which may or may not be based on comparison to normative data with or without adjustments for age, education, occupation, sex, etc.).
- Cognitive performance is usually in the impaired/abnormal range based on population norms, but this is not required as long as the performance is below the range expected for that individual.
- In addition to evidence of cognitive impairment, evidence of decline in cognitive performance from baseline must also be present. This may be reported by the individual or by an observer (e.g., study partner) or observed by change on longitudinal cognitive testing/behavioral assessments or by a combination of these.
- May be characterized by cognitive presentations that are not primarily amnestic.[1]
- Although cognitive impairment is the core clinical criteria, neurobehavioral disturbance may be a prominent feature of the clinical presentation.[2]
- Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, either self-reported or corroborated by a study partner.

Dementia

- Substantial progressive cognitive impairment that affects several domains and/or neurobehavioral symptoms. May be reported by the individual or by an observer (e.g., study partner) or observed by change on longitudinal cognitive testing.
- Cognitive impairment and/or neurobehavioral symptoms result in clearly evident functional impact on daily life. No longer fully independent / requires assistance with daily life activities. This is the primary feature differentiating dementia from MCI.
- May be subdivided into mild, moderate, and severe.

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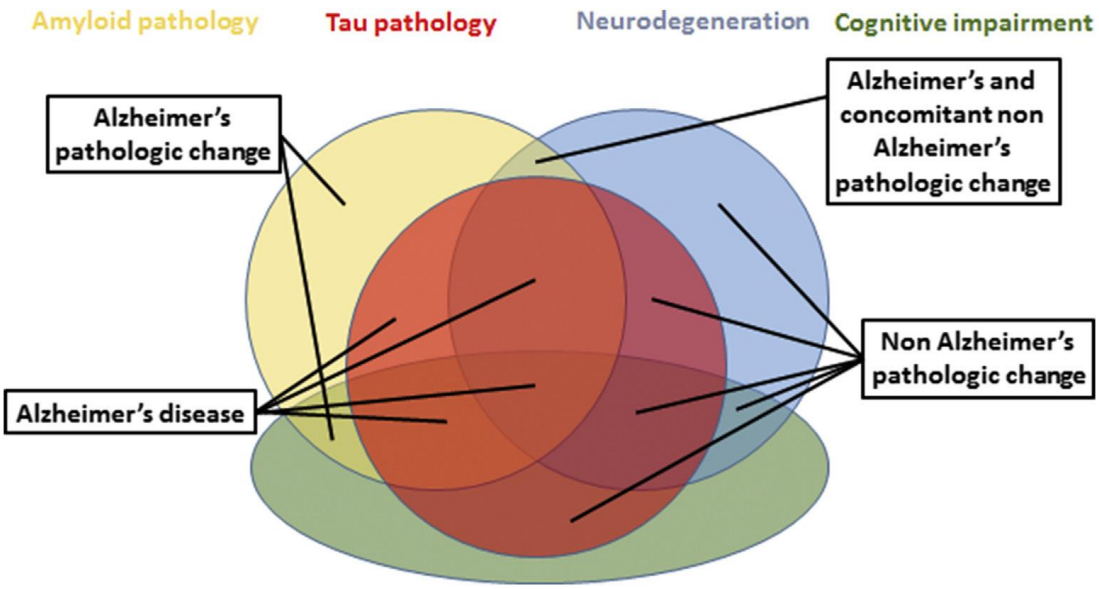
[1] *For MCI and dementia: Cognitive impairment may be characterized by presentations that are not primarily amnestic.*

[2] *For MCI and dementia: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—commonly coexist and may be a prominent part of the presentation.*

Descriptive nomenclature: syndromal cognitive staging combined with biomarkers

		Cognitive Stage		
		Cognitively Unimpaired	**Mild Cognitive Impairment**	**Dementia**
Biomarker Profile	A–T–(N)–	Normal AD biomarkers, cognitively unimpaired	Normal AD biomarkers with MCI	Normal AD biomarkers with dementia
	A+T–(N)–	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	A+T+(N)–	Preclinical Alzheimer's disease	Alzheimer's disease with MCI (prodromal AD)	Alzheimer's disease with dementia
	A+T+(N)+			
	A+T–(N)+	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change with dementia
	A–T+(N)–	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia
	A–T–(N)+			
	A–T+(N)+			

NOTE. Formatting denotes three general biomarker "categories" based on biomarker profiles: those with normal AD biomarkers (no color), those with non-AD pathologic change (dark grey), and those who are in the Alzheimer's continuum (light grey).



Descriptive nomenclature Venn diagram. We illustrate how AT(N) biomarker grouping and cognitive status interact for classification of research participants in this Venn diagram. For simplicity, MCI and dementia are combined into a single (cognitively impaired) category and the A–T–(N)– groups are not shown. Also "Alzheimer's and concomitant non-Alzheimer's pathologic change" [A+T–(N)+] in cognitively impaired is not shown in this figure.

Numeric clinical staging—applicable only to individuals in the Alzheimer's continuum

Stage 1

Performance within expected range on objective cognitive tests.

- Cognitive test performance may be compared to normative data of the investigators' choice, with or without adjustment (the choice of the investigators) for age, sex, education, etc.[1]
- Does not report recent decline in cognition or new onset of neurobehavioral symptoms of concern.
- No evidence of recent cognitive decline or new neurobehavioral symptoms by report of an observer (e.g., study partner) or by longitudinal cognitive testing if available.

Stage 2

- Normal performance within expected range on objective cognitive tests.
- Transitional cognitive decline: decline in previous level of cognitive function, which may involve any cognitive domain(s) (i.e., not exclusively memory).
- May be documented through subjective report of cognitive decline that is of concern to the participant.
    - Represents a change from individual baseline within past 1–3 years, and persistent for at least 6 months.
    - May be corroborated by informant but not required.
- Or may be documented by evidence of subtle decline on longitudinal cognitive testing but not required.
- Or may be documented by both subjective report of decline and objective evidence on longitudinal testing.
- Although cognition is the core feature, mild neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist. In some individuals, the primary compliant may be neurobehavioral rather than cognitive. Neurobehavioral symptoms should have a clearly defined recent onset, which persists and cannot be explained by life events.[2]
- No functional impact on daily life activities.

Stage 3

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

- Evidence of decline from baseline, documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral assessments.
- May be characterized by cognitive presentations that are not primarily amnestic.[3]
- Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, that is, may take more time or be less efficient but still can complete, either self-reported or corroborated by a study partner.

Stage 4

Mild dementia

- Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing.
- Clearly evident functional impact on daily life, affecting mainly instrumental activities.
- No longer fully independent / requires occasional assistance with daily life activities.

Stage 5

Moderate dementia

- Progressive cognitive impairment or neurobehavioral changes. Extensive functional impact on daily life with impairment in basic activities.
- No longer independent and requires frequent assistance with daily life activities.

Stage 6

Severe dementia

- Progressive cognitive impairment or neurobehavioral changes. Clinical interview may not be possible.
- Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

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[1]For stages 1–6: Cognitive test performance may be compared to normative data of the investigators' choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.

[2]For stages 2–6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.

[3]For stages 3–6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.

Alzheimer's clinical syndrome

For clinical research without biomarkers or with incomplete biomarker information.

While the main thesis of this research framework focuses on a biological definition of AD, we stress that for some types of studies incorporation of biomarkers is not necessary.

We strongly recommend that a clinically ascertained syndrome consistent with what has historically been labeled "probable or possible AD" be referred to as **Alzheimer's clinical syndrome**, but not as AD or some modified form of AD (e.g., "possible or probable AD"). This terminology applies to both mildly impaired and demented individuals and is consistent with our position that a syndrome is not a disease, while at the same time recognizing the deeply engrained use of the term Alzheimer.

3. Vascular Cognitive Disorder

Sachdev et al., 2014; Smith, 2016

Diagnostic criteria for vascular cognitive disorders (VCD): a VASCOG statement

There are two aspects to the diagnosis of a VCD:

a) The establishment of the presence of a cognitive disorder.
b) The determination that vascular disease is the dominant if not exclusive pathology that accounts for the cognitive deficits.

Evidence for predominantly vascular etiology of cognitive impairment

A. One of the following clinical features:

1. The onset of the cognitive deficits is temporally related to one or more cerebrovascular events (CVE).
   [Onset is often abrupt with a stepwise or fluctuating course owing to multiple such events, with cognitive deficits persisting beyond 3 months after the event. However, subcortical ischemic pathology may produce a picture of gradual onset and slowly progressive course, in which case A2 applies.]

   The evidence of CVEs is one of the following:
   a) Documented history of a stroke, with cognitive decline temporally associated with the event.
   b) Physical signs consistent with stroke (e.g., hemiparesis, lower facial weakness, Babinski sign, sensory deficit including visual field defect, pseudobulbar syndrome—supranuclear weakness of muscles of face, tongue and pharynx, spastic dysarthria, swallowing difficulties and emotional incontinence).

2. Evidence for decline is prominent in speed of information processing, complex attention and/or frontal-executive functioning in the absence of history of a stroke or transient ischemic attack. One of the following features is additionally present:

   a) Early presence of a gait disturbance (small step gait or marche petits pas, or magnetic, apraxic-ataxic or parkinsonian gait); this may also manifest as unsteadiness and frequent, unprovoked falls.
   b) Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease.
   c) Personality and mood changes: abulia, depression, or emotional incontinence.

B. Presence of significant neuroimaging (MRI or CT) evidence of cerebrovascular disease (one of the following):

1. One large vessel infarct is sufficient for mild VCD, and two or more large vessel infarcts are generally necessary for VaD (or major VCD).
2. An extensive or strategically placed single infarct, typically in the thalamus or basal ganglia may be sufficient for VaD (or major VCD).
3. Multiple lacunar infarcts (> two) outside the brainstem; 1–2 lacunes may be sufficient if strategically placed or in combination with extensive white matter lesions.
4. Extensive and confluent white matter lesions.
5. Strategically placed intracerebral hemorrhage, or two or more intracerebral hemorrhages.
6. Combination of the above.

Exclusion criteria (for mild and major VCD)

1. History
   a) Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging or history of vascular events.
   b) Early and prominent parkinsonian features suggestive of Lewy body disease.
   c) History strongly suggestive of another primary neurological disorder such as multiple sclerosis, encephalitis, toxic or metabolic disorder, etc., sufficient to explain the cognitive impairment.

2. Neuroimaging
   a) Absent or minimal cerebrovascular lesions on CT or MRI.

3. Other medical disorders severe enough to account for memory deficit and related symptoms
   a) Other disease of sufficient severity to cause cognitive impairment, e.g., brain tumor, multiple sclerosis, encephalitis.
   b) Major depression, with a temporal association between cognitive impairment and the likely onset of depression.
   c) Toxic and metabolic abnormalities, all of which may require specific investigations.

4. Other medical disorders severe enough to account for memory deficit and related symptoms
   a) Other disease of sufficient severity to cause cognitive impairment, e.g., brain tumor, multiple sclerosis, encephalitis.
   b) Major depression, with a temporal association between cognitive impairment and the likely onset of depression.
   c) Toxic and metabolic abnormalities, all of which may require specific investigations.

5. *[For research]* The presence of biomarkers for Alzheimer's disease (cerebrospinal Aβ and pTau levels or amyloid imaging at accepted thresholds) excludes the diagnosis of probable VCD and indicates AD with cerebrovascular disease.

Criteria for vascular cognitive disorder: miscellaneous aspects

Level of certainty

1. **Probable:**
   a) Clinical criteria for VCD are supported by neuroimaging.
   b) Both clinical and genetic evidence of cerebrovascular disease (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL; cerebral autosomal recessive arteriopathy with subcortical autosomal recessive leukoencephalopathy, CARASIL; hereditary endotheliopathy, retinopathy, nephropathy, and stroke, HERNS; pontine autosomal dominant microangiopathy and leukoencephalopathy, PADMAL; retinal vasculopathy with cerebral leukodystrophy, RVCL; collagen, type IV, alpha1 (COL4A1) related disorders).

[*For research:* The presence of biomarkers for Alzheimer's disease (cerebrospinal Aβ and pTau levels or amyloid imaging at accepted thresholds) excludes the diagnosis of probable VCD.]

2. **Possible:**
   Clinical criteria for VCD are met, but neuroimaging is not available (if appropriate neuroimaging is available and not supportive of VCD, the diagnosis of possible VCD should not be made).

Subtypes of VCD

1. **Hemorrhagic or ischemic**
2. **Cortical-subcortical or subcortical ischemic**

Multiple causation

1. **VCD with concomitant AD** (major or mild)
   a) Meets criteria for VCD (except for exclusion criteria)
   b) Meets criteria for AD (possible)
   State which etiology is clinically more salient: vascular or Alzheimer's

2. **VCD with additional pathology**; e.g., Lewy body disease

3. **VCD with contribution from depression**
   Associated behavioral or psychiatric symptoms: with psychotic symptoms, depression, agitation, apathy, etc.

Vascular pathology of vascular cognitive impairment

(Smith et al., 2016; modified with permission from Sachdev et al., 2014)

Parenchymal lesions of vascular etiology

- Large vessel atherothromboembolic disease
- Multiple infarcts
- Single strategically placed infarct
- Small vessel disease
- Multiple lacunar infarcts
- Ischemic white matter damage
- Dilated perivascular spaces
- Microinfarcts
- Microhemorrhages
- Hemorrhage
- Intracerebral hemorrhage
- Multiple microbleeds
- Subarachnoid hemorrhage

- Hypoperfusion
- Hippocampal sclerosis
- Laminar cortical necrosis

Types of vascular pathologies

- Atherosclerosis
- Cardiac, atherosclerotic, and systemic emboli
- Arteriolosclerosis
- Lipohyalinosis
- Cerebral amyloid angiopathy
- Vasculitis
- Venous collagenosis
- Arteriovenous fistulae
  Hereditary angiopathies (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL])
- Berry aneurysms
- Miscellaneous vasculopathies (e.g., moyamoya disease)
- Cerebral venous thrombosis

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4. Behavioral Variant FTD

Rascovsky et al., 2011

International consensus criteria for behavioral variant FTD (FTDC)

***** *As a general guideline "early" refers to symptom presentation within the first 3 years.*

Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD.

A. Shows progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant).

Possible bvFTD

Three of the following behavioral/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioral disinhibition [one of the following symptoms (A.1–A.3) must be present]:
   - A.1. Socially inappropriate behavior
   - A.2. Loss of manners or decorum
   - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
   - C.1. Diminished response to other people's needs and feelings
   - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behavior [one of the following symptoms (D.1–D.3) must be present]:
   - D.1. Simple repetitive movements
   - D.2. Complex, compulsive or ritualistic behaviors
   - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
   - E.1. Altered food preferences
   - E.2. Binge eating, increased consumption of alcohol or cigarettes
   - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria.

A. Meets criteria for possible bvFTD.

B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores).

C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:

C.1. Frontal and/or anterior temporal atrophy on MRI or CT

C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

Behavioral variant FTD with definite FTLD pathology

Criterion A and either criterion B or C must be present to meet criteria.

A. Meets criteria for possible or probable bvFTD.

B. Histopathological evidence of FTLD on biopsy or postmortem.

C. Presence of a known pathogenic mutation.

Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.

A. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders.

B. Behavioral disturbance is better accounted for by a psychiatric diagnosis.

C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process.

5. Primary Progressive Aphasia

Gorno-Tempini et al., 2011

Inclusion and exclusion criteria for the diagnosis of PPA:

Based on criteria by Mesulam

Inclusion: *Criteria 1–3 must be answered positively*

1. Most prominent clinical feature is difficulty with language
2. These deficits are the principal cause of impaired daily living activities
3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease

Exclusion: *Criteria 1–4 must be answered negatively for a PPA diagnosis*

1. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis
3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments.
4. Prominent, initial behavioral disturbance

5.1. Diagnostic Features for the Nonfluent/Agrammatic Variant PPA

I. Clinical diagnosis of nonfluent/agrammatic variant PPA

At least one of the following core features must be present:

1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)

At least two of three of the following other features must be present:

1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge

II. Imaging-supported nonfluent/agrammatic variant diagnosis

Both of the following criteria must be present:

1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Imaging must show one or more of the following results:
    a) Predominant left posterior fronto-insular atrophy on MRI
    b) Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET

III. Nonfluent/agrammatic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:

1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

5.2. Diagnostic Criteria for the Semantic Variant PPA

I. Clinical diagnosis of semantic variant PPA

Both of the following core features must be present:

1. Impaired confrontation naming
2. Impaired single-word comprehension

At least three of the following other diagnostic features must be present:

1. Impaired object knowledge, particularly for low-frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)

II. Imaging-supported semantic variant PPA diagnosis

Both of the following criteria must be present:

1. Clinical diagnosis of semantic variant PPA
2. Imaging must show one or more of the following results:
   a) Predominant anterior temporal lobe atrophy
   b) Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

III. Semantic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:

1. Clinical diagnosis of semantic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

5.3. Diagnostic Criteria for Logopenic Variant PPA

I. Clinical diagnosis of logopenic variant PPA

Both of the following core features must be present:

1. Impaired single-word retrieval in spontaneous speech and naming
2. Impaired repetition of sentences and phrases

At least three of the following other features must be present:

1. Speech (phonologic) errors in spontaneous speech and naming
2. Spared single-word comprehension and object knowledge
3. Spared motor speech
4. Absence of frank agrammatism

II. Imaging-supported logopenic variant diagnosis

Both criteria must be present:

1. Clinical diagnosis of logopenic variant PPA
2. Imaging must show at least one of the following results:
    a. Predominant left posterior perisylvian or parietal atrophy on MRI
    b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET

III. Logopenic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:

1. Clinical diagnosis of logopenic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g., AD, FTLD-tau, FTLD-TDP, other)
3. Presence of a known pathogenic mutation

5.4. Mixed Variant PPA (Vandenberghe, 2016)

1. Objective word-finding deficit

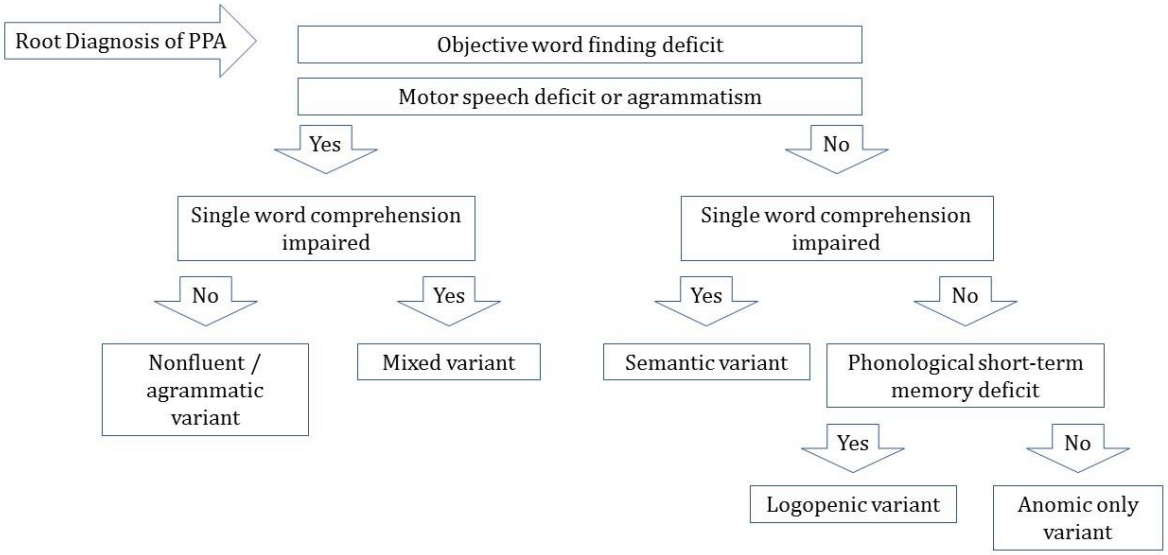
and

2. Motor speech deficit or agrammatism

and

3. Comprehension impaired

PPA overview adapted from Vandenberghe, 2016



6. Posterior Cortical Atrophy

Crutch et al., 2017

Level 1 classification: PCA

Clinical, cognitive, and neuroimaging features are rank ordered in terms of (decreasing) frequency at first assessment as rated by online survey participants.

Clinical features:

- Insidious onset
- Gradual progression
- Prominent early disturbance of visual ± other posterior cognitive functions

Cognitive features:

At least three of the following must be present as early or presenting features ± evidence of their impact on activities of daily living:

- Space perception deficit
- Simultanagnosia
- Object perception deficit
- Constructional dyspraxia
- Environmental agnosia
- Oculomotor apraxia
- Dressing apraxia
- Optic ataxia
- Alexia
- Left/right disorientation
- Acalculia
- Limb apraxia (not limb-kinetic)
- Apperceptive prosopagnosia
- Agraphia
- Homonymous visual field defect
- Finger agnosia

All of the following must be evident:

- Relatively spared anterograde memory function
- Relatively spared speech and nonvisual language functions
- Relatively spared executive functions
- Relatively spared behavior and personality

Neuroimaging:

Predominant occipito-parietal or occipito-temporal atrophy / hypometabolism / hypoperfusion on MRI / FDG-PET / SPECT

Exclusion criteria:

- Evidence of a brain tumor or other mass lesion sufficient to explain the symptoms

- Evidence of significant vascular disease including focal stroke sufficient to explain the symptoms
- Evidence of afferent visual cause (e.g., optic nerve, chiasm, or tract)
- Evidence of other identifiable causes for cognitive impairment (e.g., renal failure)

Level 2 classification: PCA-pure vs. PCA-plus

PCA-pure

Individuals must fulfill the criteria for the core clinico-radiological PCA syndrome (level 1) and not fulfill core clinical criteria for any other neurodegenerative syndrome.

PCA-plus

Individuals must fulfill the criteria for the core clinico-radiological PCA syndrome (level 1) and also fulfill core clinical criteria for at least one other neurodegenerative syndrome, such as

PCA + dementia with Lewy bodies (DLB)

Following the diagnostic criteria proposed by the DLB consortium (McKeith et al., 2005)*, individuals must exhibit two or more core features of DLBs (list A) or one or more core features (list A) and one or more suggestive features (list B):

A. Core features

- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations that are typically well formed and detailed
- Spontaneous features of parkinsonism

B. Suggestive features

- Rapid eye movement (REM) sleep behavior disorder
- Severe neuroleptic sensitivity
- Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

** Please see the most recent criteria for DLB on p. 32, chapter 8.1 (McKeith et al, 2017).*

PCA + corticobasal syndrome (CBS)

Following the modified CBS criteria proposed by Armstrong et al. (2013), a diagnosis of probable CBS requires asymmetric presentation of two of:

A. limb rigidity or akinesia
B. limb dystonia
C. limb myoclonus

plus two of:

D. orobuccal or limb apraxia
E. cortical sensory deficit
F. alien limb phenomena (more than simple levitation)

Possible corticobasal syndrome may be symmetric and requires presentation of one of A–C plus one of D-F.

Level 3 classification: diagnostic criteria for disease-level descriptions

PCA-AD

Following IWG2 (Dubois et al., 2014), the classification of PCA-AD (and, by extension, of IWG2's broader category of "atypical AD") requires fulfillment of the PCA syndrome (classification level 1) plus in vivo evidence of Alzheimer's pathology (at least one of the following):

- Decreased $A\beta_{1-42}$ together with increased T-tau and/or P-tau in CSF
- Increased tracer retention on amyloid PET
- Alzheimer's disease autosomal-dominant mutation present (in PSEN1, PSEN2, or APP)

If autopsy confirmation of AD is available, the term definite PCA-AD would be appropriate.

PCA-LBD

Molecular biomarkers for LBD are currently unavailable; therefore, an in vivo diagnosis of PCA-LBD cannot be assigned at present. For individuals who are both classified as PCA-mixed by virtue of fulfilling DLB clinical criteria and shown to be AD-biomarker negative, the term probable PCA-LBD may be appropriate. If autopsy confirmation of LBD is available, the term definite PCA-LBD would be appropriate. Other disease-level classifications may also be appropriate for individuals with mixed or multiple pathologies (e.g., PCA-AD/LBD).

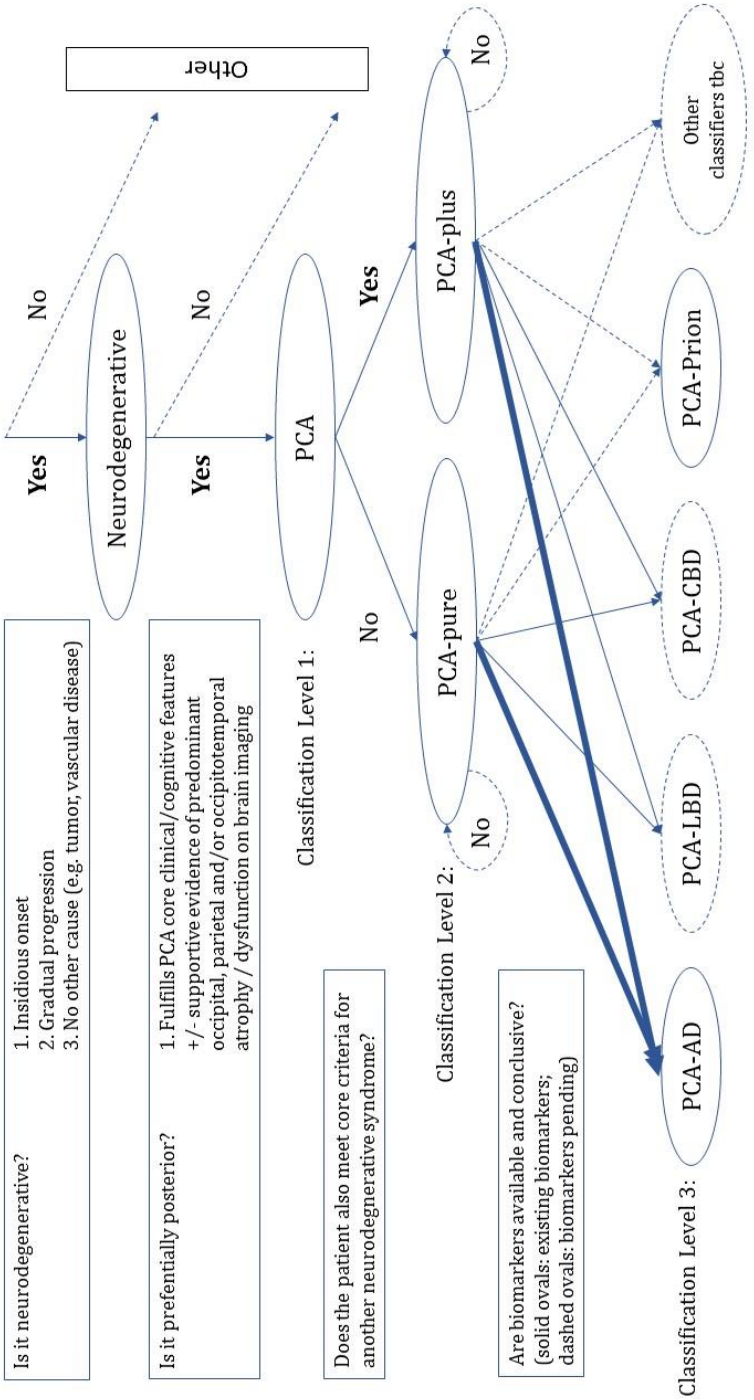
PCA-CBD

Molecular biomarkers for CBD are currently unavailable; therefore, an in vivo diagnosis of PCA-CBD cannot be assigned at present. For individuals who are both classified as PCA-mixed by virtue of fulfilling CBS criteria and shown to be AD-biomarker negative, the term probable PCA-CBD may be appropriate. If autopsy confirmation of CBD is available, the term definite PCA-CBD would be appropriate.

PCA-prion

There are a number of promising biomarkers for prion disease (e.g., Orru et al., 2014; Jackson et al., 2014; McGuire et al., 2012), but these have yet to be incorporated into diagnostic criteria. Pending this process, an in vivo diagnosis of PCA-prion may be feasible. If autopsy confirmation of prion disease is available or a known genetic form of prion disease has been determined, the term definite PCA-prion would be appropriate.

Diagnostic process and PCA classification (adapted from Crutch et al., 2017)



Among the disease-level classifications, PCA-AD and PCA-prion (solid ovals) are distinguished from PCA-LBD and PCA-CBD (dashed ovals) owing to the current availability of in vivo pathophysiological biomarkers. The thickness of lines connecting classification levels 2 and 3 is intended to reflect the status of AD as the most common cause of PCA.

7. Parkinson's Disease Dementia

Emre et al., 2007

Features of dementia associated with Parkinson's disease

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria*
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
   - Impairment in more than one cognitive domain
   - Representing a decline from premorbid level
   - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:
   - Attention: impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
   - Executive functions: impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
   - Visuo-spatial functions: impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
   - Memory: impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
   - Language: core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present

2. Behavioral features:
   - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
   - Changes in personality and mood including depressive features and anxiety
   - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
   - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
   - Excessive daytime sleepiness

** See Supplementary for the Queen Square Brain Bank criteria.*

III. Features which do not exclude PD-D but make the diagnosis uncertain

- Co-existence of any other abnormality which may by itself cause cognitive impairment but judged not to be the cause of dementia, e.g., presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present, make it impossible to reliably diagnose PD-D

- Cognitive and behavioral symptoms appearing solely in the context of other conditions, such as:
  - Acute confusion due to
    a) Systemic diseases or abnormalities
    b) Drug intoxication
  - Major depression according to DSM IV
- Features compatible with "probable vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Criteria for the diagnosis of probable and possible PD-D

Probable PD-D

A. Core features: Both must be present
B. Associated clinical features:
   - Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
   - The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of probable PD-D; lack of behavioral symptoms, however, does not exclude the diagnosis
C. None of the group III features present
D. None of the group IV features present

Possible PD-D

A. Core features: Both must be present
B. Associated clinical features:
   - Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
   - Behavioral symptoms may or may not be present

OR

C. One or more of the group III features present
D. None of the group IV features present

8. Atypical Parkinsonian Syndromes

McFarland, 2016

Primary causes of atypical parkinsonism

(Modified with permission from Jankovic J, Lang AE, Saunders, 2008)

Multisystem disease

- Lewy body disease (see 8.1)
- Progressive supranuclear palsy (see 8.2)
- Multiple system atrophy (see 8.3)
- Corticobasal degeneration (see 8.4)
- Parkinsonism-dementia-amyotrophic lateral sclerosis

Heredodegenerative disorders

- Huntington's disease
- Spinocerebellar ataxias (especially types 2, 3, and 17)
- Wilson's disease
- Hereditary ceruloplasmin deficiency
- Neuronal brain iron accumulation disorders (e.g., PKAN2)
- X-linked dystonia parkinsonism (Lubag disease)
- Gerstmann-Sträussler-Scheinker syndrome
- Neuronal ceroid lipofuscinoses
- Mitochondrial cytopathies

Red flags for differentiating atypical parkinsonism from Parkinson's disease

Features predictive of atypical parkinsonism

- Rapid disease progression
- Early gait instability, falls
- Absence or paucity of tremor
- Irregular jerky tremor, myoclonus
- Poor/absent response to levodopa

Additional features of atypical parkinsonism (and associated disorder)

- Abnormal eye movements (progressive supranuclear palsy)
- Pyramidal tract / cerebellar signs (multiple system atrophy)
- Dysautonomia (multiple system atrophy)
- Severe dysarthria, dysphonia, or stridor (multiple system atrophy)
- Apraxia, alien limb, myoclonus (corticobasal syndrome)
- Early, prominent dementia (dementia with Lewy bodies, progressive supranuclear palsy / corticobasal syndrome)

8.1. Lewy Body Disease

McKeith et al., 2017

Revised criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (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 three 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 behavior 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
    - Rigidity

Supportive clinical features

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

Indicative biomarkers

- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET
- Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy
- Polysomnographic confirmation of REM sleep without atonia

Supportive biomarkers

- Relative preservation of medial temporal lobe structures on CT/MRI scan
- Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging
- Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

Probable DLB can be diagnosed if:

- Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or
- Only one core clinical feature is present, but with one or more indicative biomarkers.

Probable DLB should not be diagnosed on the basis of biomarkers alone.

Possible DLB can be diagnosed if:

- Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or
- One or more indicative biomarkers are present but there are no core clinical features.

DLB is less likely:

- In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or
- If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.

Important:

DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term Parkinson's disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.

8.2. Progressive Supranuclear Palsy

Höglinger et al., 2017

Basic features (B1–B3)

Basic features need to be present in a patient in order to be considered for the diagnosis of progressive supranuclear palsy (PSP) of any phenotype and at any stage. Mandatory inclusion criteria indicate the presence of a sporadic, adult-onset, gradually progressive neurodegenerative disease. Mandatory exclusion criteria rule out PSP and need to be applied in any patient. Context-dependent exclusion criteria also rule out PSP, but should be applied only in patients presenting with suggestive, unusual clinical features justifying further investigation.

B1: Mandatory inclusion criteria

1. Sporadic occurrence*
2. Age 40 or older at onset** of first PSP-related symptom***
3. Gradual progression of PSP-related symptoms***

** MAPT rare variants (mutations) may lead to inherited phenocopies of the sporadic disease with a Mendelian trait pattern.*
*** MAPT rare variants carriers may have earlier disease onset*
**** Consider any new onset of neurological, cognitive, or behavioral deficit that subsequently progresses during the clinical course in absence of another identifiable cause as a PSP-related symptom*

B2: Mandatory exclusion criteria

(Suggestive of other conditions which may mimic aspects of PSP clinically)

Clinical findings

I. Predominant, otherwise unexplained impairment of episodic memory, suggestive of AD
II. Predominant, otherwise unexplained autonomic failure, e.g., orthostatic hypotension (orthostatic reduction in blood pressure after 3 minutes standing ≥30 mm Hg systolic or ≥15 mm Hg diastolic), suggestive of multiple system atrophy or Lewy body disease
III. Predominant, otherwise unexplained visual hallucinations or fluctuations in alertness, suggestive of dementia with Lewy bodies
IV. Predominant, otherwise unexplained multisegmental upper and lower motor neuron signs, suggestive of motor neuron disease (pure upper motor neuron signs are not an exclusion criterion)
V. Sudden onset or stepwise or rapid progression of symptoms, in conjunction with corresponding imaging or laboratory findings, suggestive of vascular etiology, autoimmune encephalitis, metabolic encephalopathies, or prion disease
VI. History of encephalitis
VII. Prominent appendicular ataxia
VIII. Identifiable cause of postural instability, e.g., primary sensory deficit, vestibular dysfunction, severe spasticity, or lower motor neuron syndrome

Imaging findings

1. Severe leukoencephalopathy, evidenced by cerebral imaging

2. Relevant structural abnormality, e.g., normal pressure or obstructive hydrocephalus; basal ganglia, diencephalic, mesencephalic, pontine or medullary infarctions, hemorrhages, hypoxic-ischemic lesions, tumors, or malformations

B3: Context-dependent exclusion criteria

(Suggestive of other conditions which may mimic aspects of PSP clinically; need to be verified only if suggestive clinical findings are present)

Imaging findings

1. In syndromes with sudden onset or stepwise progression, exclude stroke, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or severe cerebral amyloid angiopathy, evidenced by diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery, or T2*-MRI
2. In cases with very rapid progression, exclude cortical and subcortical hyperintensities on DWI-MRI suggestive of prion disease

Laboratory findings

1. In patients with PSP-CBS, exclude primary AD pathology (typical CSF constellation [i.e., both elevated total tau/phospho-tau protein and reduced β-amyloid 42] or pathological β-amyloid PET imaging)
2. In patients aged <45 years, exclude
   a) Wilson's disease (e.g., reduced serum ceruloplasmin, reduced total serum copper, increased copper in 24-hour urine, and Kayser-Fleischer corneal ring)
   b) Niemann-Pick disease, type C (e.g., plasma cholestan-3β,5α,6β-triol level, filipin test on skin fibroblasts)
   c) Hypoparathyroidism
   d) Neuroacanthocytosis (e.g., Bassen-Kornzweig, Levine-Critchley, McLeod disease)
   e) Neurosyphilis
3. In rapidly progressive patients, exclude
   a) Prion disease (e.g., elevated 14-3-3, neuron-specific enolase, very high total tau protein [>1,200 pg/mL], or positive real-time quaking-induced conversion in CSF)
   b) Paraneoplastic encephalitis (e.g., anti-Ma1, anti-Ma2 antibodies)
4. In patients with suggestive features (i.e., gastrointestinal symptoms, arthralgias, fever, younger age, and atypical neurological features such as myorhythmia), exclude Whipple's disease (e.g., *T. whipplei* DNA polymerase chain reaction in CSF)

Genetic findings

1. MAPT rare variants (mutations) are no exclusion criterion, but their presence defines inherited, as opposed to sporadic PSP.
2. MAPT H2 haplotype homozygosity is not an exclusion criterion but renders the diagnosis unlikely.
3. LRRK2 and Parkin rare variants have been observed in patients with autopsy-confirmed PSP, but their causal relationship is unclear so far.
4. Known rare variants in other genes are exclusion criteria, because they may mimic aspects of PSP clinically, but differ neuropathologically; these include

a) Non-MAPT-associated frontotemporal dementia (e.g., C9orf72, GRN, FUS, TARDBP, VCP, CHMP2B)
b) PD (e.g., SYNJ1, GBA)
c) AD (APP, PSEN1, PSEN2)
d) Niemann-Pick disease, type C (NPC1, NPC2)
e) Kufor-Rakeb syndrome (ATP13A2)
f) Perry syndrome (DCTN1)
g) Mitochondrial diseases (POLG, mitochondrial rare variants)
h) Dentatorubral-pallidoluysian atrophy (ATN1)
i) Prion-related diseases (PRNP)
j) Huntington's disease (HTT)
k) Spinocerebellar ataxia (ATXN1, 2, 3, 7, 17)

Core clinical features

	Functional Domain			
Levels of certainty	**Ocular motor dysfunction**	**Postural instability**	**Akinesia**	**Cognitive dysfunction**
Level 1	01: Vertical supranuclear gaze palsy	P1: Repeated unprovoked falls within 3 years	A1: Progressive gait freezing within 3 years	C1: Speech/language disorder, i.e., nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	02: Slow velocity of vertical saccades	P2: Tendency to fall on the pull-test within 3 years	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	C2: Frontal cognitive/behavioral presentation
Level 3	03: Frequent macro square wave jerks or "eyelid opening apraxia"	P3: More than two steps backward on the pull-test within 3 years	A3: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	C3: Corticobasal syndrome

Levels with lower numbers are considered to contribute higher certainty to a diagnosis of PSP than levels with higher numbers. Operationalized definitions of the core clinical features are provided in the table below.

Supportive features

Clinical Clues	Imaging Findings
CC1: Levodopa-resistance	IF1: Predominant midbrain atrophy or hypometabolism
CC2: Hypokinetic, spastic dysarthria	IF2: Postsynaptic striatal dopaminergic degeneration
CC3: Dysphagia	
CC4: Photophobia	

Operationalized definitions of core clinical features, supportive clinical clues, and supportive imaging findings

Domain	Feature	Definition
Ocular motor dysfunction (01–03)		
01	Vertical supranuclear gaze palsy	A clear limitation of the range of voluntary gaze in the vertical more than in the horizontal plane, affecting both up- and downgaze, more than expected for age, which is overcome by activation with the vestibulo-ocular reflex; at later stages, the vestibulo-ocular reflex may be lost, or the maneuver prevented by nuchal rigidity
02	Slow velocity of vertical saccades	Decreased velocity (and amplitude) of vertical greater than horizontal saccadic eye movements This may be established by quantitative measurements of saccades, such as infrared oculography, or by bedside testing. Gaze should be assessed by command (“Look at the flicking finger”) rather than by pursuit (“Follow my finger”), with the target >20 degrees from the position of primary gaze. To be diagnostic, saccadic movements are slow enough for the examiner to see their movement (eye rotation), rather than just initial and final eye positions in normal subjects; a delay in saccade initiation is not considered slowing; findings are supported by slowed or absent fast components of

		vertical optokinetic nystagmus (i.e., only the slow following component may be retained)
03	Frequent macro square wave jerks or “eyelid opening apraxia”	Macro square wave jerks are rapid involuntary saccadic intrusions during fixation, displacing the eye horizontally from the primary position and returning it to the target after 200 to 300 milliseconds; most square wave jerks are <1 degree in amplitude and rare in healthy controls, but up to 3 to 4 degrees and more frequent (>10/min) in PSP. “Eyelid opening apraxia” is an inability to voluntarily initiate eyelid opening after a period of lid closure in the absence of involuntary forced eyelid closure (i.e., blepharospasm); the term is written in quotation marks because the inability to initiate eyelid opening is often attributed to activation of the pretarsal component of the orbicularis oculi (i.e., pretarsal blepharospasm) rather than failure to activate the levator palpebrae
Postural instability (P1–P3)		
P1	Repeated unprovoked falls within 3 years	Spontaneous loss of balance while standing, or history of more than one unprovoked fall, within 3 years after onset of PSP-related features
P2	Tendency to fall on the pull-test within 3 years	Tendency to fall on the pull-test if not caught by examiner, within 3 years after onset of PSP-related features. The test examines the response to a quick, forceful pull on the shoulders with the examiner standing behind the patient and the patient standing erect with eyes open and feet comfortably apart and parallel, as described in the MDS-UPDRS item 3.12
P3	More than two steps backward on the pull-test within 3 years	More than two steps backward, but unaided recovery, on the pull-test, within 3 years after onset of PSP-related features
Akinesia (A1-A3)		
A1	Progressive gait freezing within 3 years	Sudden and transient motor blocks or start hesitation are predominant within 3 years after onset of PSP-related symptoms, progressive and not responsive to levodopa; in the early disease course, akinesia may be

		present, but limb rigidity, tremor, and dementia are absent or mild
A2	Parkinsonism, akinetic-rigid, predominantly axial and levodopa resistant	Bradykinesia and rigidity with axial predominance, and levodopa resistance (see clinical clue CC1 for operationalized definition)
A3	Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	Bradykinesia with rigidity and/or tremor, and/or asymmetric predominance of limbs, and/or levodopa responsiveness (see clinical clue CC1 for operationalized definition)
Cognitive dysfunction (C1–C3)		
C1	Speech/language disorder	Defined as at least one of the following features, which has to be persistent (rather than transient): 1. Nonfluent/agrammatic variant of primary progressive aphasia (nfaPPA): loss of grammar and/or telegraphic speech or writing 2. Progressive apraxia of speech (AOS): effortful, halting speech with inconsistent speech sound errors and distortions or slow, syllabically segmented prosodic speech patterns Both with spared single-word comprehension, object knowledge, and word retrieval during sentence repetition
C2	Frontal cognitive/behavioral presentation	Defined as at least three of the following features, which have to be persistent (rather than transient): 1. Apathy: Reduced level of interest, initiative, and spontaneous activity; clearly apparent to informant or patient 2. Bradyphrenia: Slowed thinking; clearly apparent to informant or patient

		3. Dysexecutive syndrome: E.g., reverse digit span, Trails B or Stroop test, Luria sequence (at least 1.5 SD below mean of age- and education-adjusted norms) 4. Reduced phonemic verbal fluency: E.g., "D, F, A, or S" words per minute (at least 1.5 SD below mean of age- and education-adjusted norms) 5. Impulsivity, disinhibition, or perseveration: E.g., socially inappropriate behaviors, overstuffing the mouth when eating, motor recklessness, applause sign, palilalia, echolalia
C3	CBS	Defined as at least one sign each from the following two groups (may be asymmetric or symmetric): 1. Cortical signs: a) Orobuccal or limb apraxia b) Cortical sensory deficit c) Alien limb phenomena (more than simple levitation) 2. Movement disorder signs: a) Limb rigidity b) Limb akinesia c) Limb myoclonus
Supportive clinical clues (CC1–CC4)		
CC1	Levodopa resistance	Levodopa resistance is defined as improvement of the MDS-UPDRS motor scale by ≤30%; to fulfill this criterion patients should be assessed having been given at least 1,000 mg (if tolerated) for at least 1 month, or once patients have received this treatment, they could be formally assessed following a challenge dose of at least 200 mg

CC2	Hypokinetic, spastic dysarthria	Slow, low volume and pitch, harsh voice
CC3	Dysphagia	Otherwise unexplained difficulty in swallowing, severe enough to request dietary adaptations
CC4	Photophobia	Intolerance to visual perception of light attributed to adaptative dysfunction
Imaging findings		
IF1	Predominant midbrain atrophy or hypometabolism	Atrophy or hypometabolism predominant in midbrain relative to pons, as demonstrated, e.g., by MRI or [^{18}F]DG-PET
IF2	Postsynaptic striatal dopaminergic degeneration	Postsynaptic striatal dopaminergic degeneration, as demonstrated, e.g., by [^{123}I]IBZM-SPECT or [^{18}F]-DMFP-PET

Degrees of diagnostic certainty, obtained by combinations of clinical features and clinical clues

- The basic features B1 + B2 + B3 (see Table 1) apply for all probable, possible, and suggestive criteria.
- Additional presence of imaging findings (IF1 or IF2) qualifies for the label-imaging-supported diagnosis.

Definition	Combinations	Predominance Type	Abbreviation
Suggestive of PSP			
Suggestive of PSP, but not passing the threshold for possible or probable PSP	02 or 03	PSP with predominant ocular motor dysfunction	s. o. PSP-OM
	P1 or P2	PSP with predominant postural instability	s. o. PSP-PI
Suitable for early identification	03 + (P2 or P3)	PSP with Richardson's syndrome	s. o. PSP-RS
	(A2 or A3) + (03, P1, P2, C1, C2, CC1, CC2, CC3, or CC4)	PSP with predominant parkinsonism	s. o. PSP-P

	C1	PSP with predominant speech/language disorder	s. o. PSP-SL
	C2 + (03 or P3)	PSP with predominant frontal presentation	s. o. PSP-F
	C3	PSP with predominant CBS	s. o. PSP-CBS
Possible PSP			
Substantially more sensitive, but less specific for PSP ***Suitable for descriptive epidemiological studies and clinical care***	01	PSP with predominant ocular motor dysfunction	poss. PSP-OM
	02 + P3	PSP with Richardson's syndrome	poss. PSP-RS
	A1	PSP with progressive gait freezing	poss. PSP-PGF
	(01 or 02) + C1	PSP with predominant speech/language disorder	poss. PSP-SL
	(01 or 02) + C3	PSP with predominant CBS	poss. PSP-CBS
Probable PSP			
Highly specific, but not very sensitive for PSP ***Suitable for therapeutic and biological studies***	(01 or 02) + (P1 or P2)	PSP with Richardson's syndrome	prob. PSP-RS
	(01 or 02) + A1	PSP with progressive gait freezing	prob. PSP-PGF
	(01 or 02) + (A2 or A3)	PSP with predominant parkinsonism	prob. PSP-P
	(01 or 02) + C2	PSP with predominant frontal presentation	prob. PSP-F
Definite PSP			
Gold standard defining the disease entity	Neuropathological diagnosis	Any clinical presentation	def. PSP

8.3. Multiple System Atrophy

Palma, Norcliffe-Kaufmann, & Kaufmann, 2018

Current consensus criteria for the diagnosis of multiple system atrophy (MSA)
Adapted from Gilman et al., 2008

Criteria for **definite MSA** include neuropathological findings during postmortem examination of:

a. Widespread and abundant cerebral α-synuclein-positive glial cytoplasmic inclusions
b. Neurodegenerative changes in striatonigral or olivopontocerebellar region

Criteria for **probable MSA** include a sporadic progressive adult (>30 years old)—onset disease characterized by:

a. Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, *and*
b. Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor or postural instability), *or*
c. A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia or cerebellar oculomotor dysfunction)

Criteria for **possible MSA** include a sporadic progressive adult (>30 years old)–onset disease characterized by:

a. Parkinsonism (bradykinesia with rigidity tremor or postural instability), *or*
b. Cerebellar syndrome (gait ataxia with cerebellar dysarthria limb ataxia or cerebellar oculomotor dysfunction), *and*
c. At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency frequency or incomplete bladder emptying erectile dysfunction in males or significant orthostatic BP decline that does not meet the level required in probable MSA), *and*
d. At least one of the following features:

- Babinski sign with hyperreflexia
- Stridor
- Rapidly progressive parkinsonism
- Poor response to levodopa
- Postural instability within 3 years of motor onset
- Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
- Dysphagia within 5 year of motor onset
- Atrophy on MRI of putamen middle cerebellar peduncle, pons, or cerebellum
- Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
- Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

Differentiating multiple system atrophy-parkinsonian type and multiple system atrophy-cerebellar type from idiopathic Parkinson's disease

(McFarland et al., 2016)

Multiple system atrophy-parkinsonian type may be differentiated from Parkinson's disease by its more symmetrical appearance, atypical tremor, dystonia (antecollis), early dysarthria/dysphonia, gait and postural instability, dysautonomia, and rapid progression.

Multiple system atrophy-parkinsonian type (MSA-P)

- Symmetrical onset
- Rapid progression
- Tremor (distal, myoclonic)
- Frequent rigidity, hypokinesia
- Dystonia (axial), anterocollis (dropped head)
- Early falls
- Dysarthria, dysphonia
- Sleep apnea, rapid eye movement (REM) sleep behavior disorder
- Respiratory/laryngeal stridor
- Hyperreflexia, Babinski signs
- Dysautonomia (69% versus 5% in Parkinson's disease)
- Poor/unsustained levodopa response (≈30%)
- Dyskinesia (orofacial common)

Multiple system atrophy-cerebellar type (MSA-C)

- Cerebellar limb and gait ataxia
- Early falls
- Dysarthria (scanning, ataxic)
- Dysphagia
- Gaze impairment (hypokinetic/hyperkinetic saccades)
- Lower and upper motor neuron signs
- Emotionality, depression, anxiety
- Progressive dementia

8.4. Corticobasal Syndrome / Corticobasal Degeneration

Armstrong et al., 2013

Clinicopathologic studies have revealed that the originally described clinical features of CBD, now called corticobasal syndrome (CBS), are often due to other pathologies. Thus, the distinction between corticobasal **syndrome** (i.e., the clinical presentation, chapter 8.4.1) and corticobasal **degeneration** (i.e., the pathological diagnosis, chapter 8.4.2) must be made.

8.4.1. Corticobasal Syndrome (CBS)

Probable corticobasal syndrome

Asymmetric *presentation of* ***two*** *of:*

a) Limb rigidity or akinesia

b) Limb dystonia

c) Limb myoclonus

Plus two *of:*

d) Orobuccal or limb apraxia

e) Cortical sensory deficit

f) Alien limb phenomena (more than simple levitation)

Possible corticobasal syndrome

*May be symmetric—****one*** *of:*

a) Limb rigidity or akinesia

b) Limb dystonia

c) Limb myoclonus

Plus one *of:*

d) Orobuccal or limb apraxia

e) Cortical sensory deficit

f) Alien limb phenomena (more than simple levitation)

8.4.2. Diagnostic Criteria for Corticobasal Degeneration

Clinical CBD phenotypes and features were combined to create two sets of criteria:
more specific clinical research criteria for probable CBD and broader criteria for possible CBD that are more inclusive but have a higher chance to detect other tau-based pathologies.

	Clinical research criteria for probable sporadic CBD	**Clinical criteria for possible CBD**[1]
Presentation	Insidious onset and gradual progression	Insidious onset and gradual progression
Minimum duration of symptoms (years)	1	1
Age at onset (years)	≥50	No minimum
Family history (2 or more relatives)	Exclusion	Permitted
Permitted phenotypes (see table on p. 45 for criteria)	1) Probable CBS or 2) bvFTD or PPA plus at least one CBS feature (a–f)	1) Possible CBS or 2) bvFTD or PPA or 3) PSPS plus at least one CBS feature b–f
Genetic mutation affecting tau (e.g., MAPT)	Exclusion	Permitted

[1] Possible CBD emphasizes clinical presentations consistent with CBD but ones that may also overlap with other tau-based pathologies.

Exclusion criteria for both clinical research criteria for probable sporadic CBD and possible CBD:

1. Evidence of Lewy body disease: classic 4-Hz Parkinson's disease resting tremor, excellent and sustained levodopa response, or hallucinations
2. Evidence of multiple system atrophy: dysautonomia or prominent cerebellar signs
3. Evidence of amyotrophic lateral sclerosis: presence of both upper and lower motor neuron signs
4. Semantic- or logopenic-variant primary progressive aphasia
5. Structural lesion suggestive of focal cause
6. Granulin mutation or reduced plasma progranulin levels; TDP-43 mutations; FUS mutations

7. Evidence of Alzheimer's disease (this will exclude some cases of CBD with coexisting amyloid. Data from one brain bank suggest that excluding cases with evidence of amyloid may result in missing approximately 14% of CBD cases [D. Dickson, personal communication, 2012]): laboratory findings strongly suggestive of AD such as low CSF Ab42 to tau-ratio or positive ^{11}C–Pittsburgh compound B PET; or genetic mutation suggesting AD (e.g., presenilin, amyloid precursor protein)

Clinical phenotypes (syndromes) associated with the pathology of corticobasal degeneration* ***(McFarland et al., 2016)***

(Modified with permission from Armstrong MJ et al., Neurology.34 B, 2013, American Academy of Neurology)

Syndrome	Key Features
Corticobasal syndrome (CBS) (classic corticobasal degeneration)	Asymmetric limb rigidity, akinesia, dystonia, or myoclonus *PLUS* Orobuccal or limb apraxia, cortical sensory deficit, or alien limb phenomenon **Probable CBS** is two features in each of the categories above; **possible CBS** is one feature in each of the categories above and may be symmetric
Frontal behavioral (frontotemporal dementia) variant (bvFTD; see chapter 3)	Executive dysfunction, behavioral or personality changes
Posterior cortical atrophy syndrome (PCA; see chapter 5)	Visuospatial disturbance, apraxia, myoclonus, association with Alzheimer's disease pathology
Progressive nonfluent/agrammatic aphasia (PPA; see chapter 4.1)	Effortful, agrammatic speech; impaired grammar/sentence comprehension or groping, or distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome (PSPS; see chapter 7.2)	Axial or symmetric limb rigidity/akinesia, postural instability, falls, urinary incontinence, behavioral changes, supranuclear vertical gaze palsy

No study conclusively identified clinical features or imaging characteristics distinguishing CBD from other pathologies. Potential differentiating features are described in the supplemental text of the source publication (Armstrong et al., 2013) but require validation with larger sample sizes.

9. HIV-associated neurocognitive disorders (HAND)

Antinori et al., 2007

Revised research criteria for HIV-associated neurocognitive disorders (HAND) (modified from Neurobehavioral Research Center criteria) – ("Frascati criteria")

HIV-associated asymptomatic neurocognitive impairment (ANI)*

1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
2. The cognitive impairment does not interfere with everyday functioning.
3. The cognitive impairment does not meet criteria for delirium or dementia.
4. There is no evidence of another preexisting cause for the ANI.[#]

* If there is a prior diagnosis of ANI, but currently the individual does not meet criteria, the diagnosis of ANI in remission can be made.

[#] If the individual with suspected ANI also satisfies criteria for a major depressive episode or substance dependence, the diagnosis of ANI should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use.

HIV-1-associated mild neurocognitive disorder (MND)*

1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
   Typically, this would correspond to an MSK scale stage of 0.5 to 1.0.
2. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):
   - Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning.
   - Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning.
3. The cognitive impairment does not meet criteria for delirium or dementia.
4. There is no evidence of another preexisting cause for the MND.[#]

* If there is a prior diagnosis of MND, but currently the individual does not meet criteria, the diagnosis of MND in remission can be made.

[#] If the individual with suspected MND also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of MND should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use.

HIV-1-associated dementia (HAD)*

1. Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means. (Note that where neuropsychological testing is not available, standard neurological evaluation and simple bedside testing may be used, but this should be done as indicated in algorithm; see below).
   Typically, this would correspond to an MSK scale stage of 2.0 or greater.
2. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities).
3. The pattern of cognitive impairment does not meet criteria for delirium (e.g., clouding of consciousness is not a prominent feature); or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present.
4. There is no evidence of another, preexisting cause for the dementia (e.g., other CNS infection, CNS neoplasm, cerebrovascular disease, preexisting neurologic disease, or severe substance abuse compatible with CNS disorder).[#]

* If there is a prior diagnosis of HAD, but currently the individual does not meet criteria, the diagnosis of HAD in remission can be made.

[#] If the individual with suspected HAD also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of HAD should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month has elapsed following cessation of substance use. Note that the consensus was that even when major depression and HAD occurred together, there is little evidence that pseudodementia exists and the cognitive deficits do not generally improve with treatment of depression.

Whereas the above mentioned «Frascati criteria» - in the scientific community denoted as gold standard - emphasize sensitivity to deficits associated with HAND, the criteria outlined by Gisslén et al. (2011) emphasize specificity. They set a threshold of 1.5 SD, rather than 1 SD below the normative mean to determine impairment in ANI and MND.

III. Criteria for Determining the Severity of a Neuropsychological Disorder

Frei et al., 2016

Schweregrad der Störung und diagnostische Kriterien[1]	**Funktionsfähigkeit im privaten Alltag und Beruf**	**Orientierende Richtwerte bezüglich der Arbeitsunfähigkeit**[2]
Minimale neuropsychologische Störung: a. Nur unter starker Belastung oder durch neuropsychologische Tests feststellbare leichte Minderleistungen einer oder vereinzelter kognitiver Teilfunktionen (1 bis 2 SD unter dem Mittelwert) *und/oder* b. Keine fassbaren oder nur unter starker Belastung vorhandene Auffälligkeiten in den Bereichen der Affektivität, des Verhaltens oder der Persönlichkeit	Die Person kann sich subjektiv gestört fühlen. Ihre Funktionsfähigkeit ist aber im privaten Alltag nicht eingeschränkt. Und berufliche Leistungen werden praktisch unvermindert vollbracht. Die Person fällt in ihrem sozialen Umfeld nicht auf. Bei Aufgaben und Tätigkeiten mit sehr hohen Anforderungen kann die Funktionsfähigkeit jedoch leicht eingeschränkt sein.	Grad der Arbeitsunfähigkeit von 0 bis 10%
Leichte neuropsychologische Störung: a. Leichte Minderleistungen mehrerer kognitiver Teilfunktionen (1 bis 2 SD unter dem Mittelwert) *und/oder* b. Leichte Auffälligkeiten in den Bereichen der Affektivität, des Verhaltens oder der Persönlichkeit	Die Funktionsfähigkeit ist im Alltag und unter den meisten beruflichen Anforderungen nicht eingeschränkt. Die Person fällt in ihrem sozialen Umfeld auch kaum auf. Bei Aufgaben und Tätigkeiten mit hohen Anforderungen ist die Funktionsfähigkeit aber eingeschränkt.	Grad der Arbeitsunfähigkeit von 10 bis 30%
Leichte bis mittelgradige neuropsychologische Störung: a. Eine oder allenfalls zwei kognitive Teilfunktionen sind deutlich (mehr als 2 SD unter dem Mittelwert) sowie weitere leicht vermindert (1 bis 2 SD unter dem Mittelwert) *und/oder* b. Leichte bis mittelschwere Auffälligkeiten in den Bereichen der Affektivität, des Verhaltens oder der Persönlichkeit	Die Funktionsfähigkeit ist im Alltag und unter den meisten beruflichen Anforderungen leicht eingeschränkt. Die Person fällt in ihrem sozialen Umfeld leicht auf. In Berufen oder bei Aufgaben mit hohen Anforderungen ist die Funktionsfähigkeit aber mittelgradig eingeschränkt.	Grad der Arbeitsunfähigkeit von 30 bis 50%

[1] Eine im Einzelfall davon abweichende Einstufung des Schweregrades sollte eingehend begründet werden.

[2] Bei diesen Richtwerten handelt es sich lediglich um orientierende Angaben. Der Grad der Arbeitsunfähigkeit kann jedoch – in Abhängigkeit der Charakteristika einer Störung sowie des jeweiligen beruflichen Anforderungsprofils – erheblich von diesen Richtwerten abweichen.

Mittelgradige neuropsychologische Störung: a. Mindestens zwei kognitive Teilfunktionen sind deutlich (mehr als 2 SD unter dem Mittelwert) sowie weitere leicht vermindert (1 bis 2 SD unter dem Mittelwert) sowie weitere allenfalls leicht vermindert (1 bis 2 SD unter dem Mittelwert) *und/oder* b. Mittelschwere Auffälligkeiten in den Bereichen der Affektivität, des Verhaltens oder der Persönlichkeit	Die Funktionsfähigkeit ist im Alltag und unter den meisten beruflichen Anforderungen deutlich eingeschränkt. Es können nur noch einfachere Arbeiten ausgeführt werden. Die Person fällt in ihrem sozialen Umfeld auch deutlich auf. In Berufen oder bei Aufgaben mit hohen Anforderungen ist die Funktionsfähigkeit sogar stark eingeschränkt.	Grad der Arbeitsunfähigkeit von 50 bis 70%
Mittelgradige bis schwere neuropsychologische Störung: a. Die Mehrzahl der kognitiven Teilfunktionen ist deutlich (mehr als 2 SD unter dem Mittelwert) sowie weitere leicht vermindert (1 bis 2 SD unter dem Mittelwert) *und/oder* b. Mittelschwere bis schwere Auffälligkeiten in den Bereichen der Affektivität, des Verhaltens oder der Persönlichkeit	Die Funktionsfähigkeit ist im Alltag und unter sämtlichen beruflichen Anforderungen deutlich eingeschränkt. Es können nur noch sehr einfache Arbeiten unter intensiver Supervision ausgeführt werden. Die Person fällt in ihrem sozialen Umfeld auch deutlich auf. Einfache Tätigkeiten sind unter Umständen in einer geschützten Werkstatt oder einer vergleichbaren Umgebung möglich.	Grad der Arbeitsunfähigkeit von 70 bis 90%
Schwere neuropsychologische Störung: a. Beinahe alle der kognitiven Teilfunktionen sind deutlich vermindert (mehr als 2 SD unter dem Mittelwert) und können eventuell testpsychologisch gar nicht mehr erfasst werden *und/oder* b. Schwere Auffälligkeiten in den Bereichen der Affektivität, des Verhaltens oder der Persönlichkeit	Die Funktionsfähigkeit ist im Alltag und unter sämtlichen beruflichen Anforderungen stark eingeschränkt. Weiter fällt die Person in ihrem sozialen Umfeld stark auf. Meist ist der Betroffene voll arbeitsunfähig. Unter Umständen ist eine Tätigkeit in einer geschützten Werkstatt noch möglich.	Grad der Arbeitsunfähigkeit von 100%
Schwerste neuropsychologische Störung: Der Patient reagiert kaum oder häufig nicht angepasst auf Umweltreize. Die kognitiven Funktionen und die übrigen psychischen Bereiche sind schwer gestört. Kognitive Leistungen können testpsychologisch nicht erfasst werden.	Die Funktionsfähigkeit ist im Alltag stark eingeschränkt. Der Betroffene ist beinahe rund um die Uhr auf die Hilfe von Drittpersonen angewiesen. Eine Tätigkeit in einer geschützten Werkstatt ist nicht möglich.	Grad der Arbeitsunfähigkeit von 100%

Das Beurteilungssystem

Kriterium a

Das jeweilige «Kriterium a» bezieht sich auf die kognitiven Funktionen. Diese sind ungeachtet des Nachweises eines organischen Substrats zu bewerten – also unabhängig davon, ob eine «organische» oder «nichtorganische» psychische Störung vorliegt. Die hypothesengeleitete, testpsychologische Abklärung der kognitiven Funktionen stellt die Kernaufgabe der Neuropsychologie dar. Die Interpretation der neuropsychologischen Testergebnisse entspricht dabei der im DSM-5 vorgeschlagenen Vorgehensweise. Testresultate zwischen einer bis zwei Standardabweichungen (SD) unter dem jeweiligen Mittelwert sprechen im Allgemeinen für eine leichte Störung.

Kriterium b

Das jeweilige «Kriterium b» bezieht sich auf weitere psychische Bereiche – wie insbesondere die Affektivität, das Sozialverhalten, die Kritikfähigkeit oder die Persönlichkeit. Die Beurteilung dieser zusätzlichen psychischen Bereiche kann im Rahmen einer klinischen Einschätzung, unter Verwendung von Selbst- und Fremdbeurteilungsfragebögen sowie anhand von strukturierten und standardisierten psychopathologischen Instrumenten erfolgen.

IV. Multidimensional Criteria for neurocognitive, somatic, and psychiatric malingering

Sherman et al., 2020

Malingering is the volitional feigning or exaggeration of neurocognitive, somatic, or psychiatric symptoms for the purpose of obtaining material gain and services or avoiding formal duty, responsibility, or undesirable outcome. It is indicated by clear and compelling evidence based on the four criteria listed as follows (Criteria A–D).

A. Presence of an external incentive

A clearly identifiable and substantial external incentive for feigning or exaggeration of deficits or symptoms is present at the time of examination.

External incentives for malingering include access to a desirable outcome such as financial settlement, disability payment, wage replacement, social assistance; access to services or accommodations in community, academic, or work settings, or access to prescription medication.

External incentives may also include avoidance of an undesirable outcome such as those related to criminal proceedings (e.g., avoiding being deemed competent to stand trial or avoiding criminal sentencing), military service (e.g., avoiding deployment), or work or school settings (e.g., avoiding probation, suspension, expulsion, or termination). Avoidance of an undesirable outcome in the context of malingering may also be adaptive (e.g., feigning illness to be released in a hostage situation or to avoid being returned to an abusive situation). External incentives for malingering may also include avoiding having to fulfill more basic duties and responsibilities such as avoiding work, school, or examinations, or home responsibilities.

The kinds of evaluations associated with external incentives for malingering include those related to personal injury litigation, determination of disability benefits and worker's compensation, social services eligibility, criminal proceedings, military evaluations, and evaluations for specific clinical diagnoses that are associated with external incentives, such as those for brain injury, intellectual disability, chronic pain and related conditions, unexplained medical or neurological symptoms, ADHD, and learning disability, among others.

B. Invalid presentation on examination indicative of feigning or exaggeration

On examination of the examinee, there is either (a) compelling inconsistencies indicative of deliberate exaggeration or feigning of deficits or symptoms or (b) psychometric evidence of exaggeration or feigning of deficits or symptoms on performance validity tests (PVTs) or symptom validity tests (SVTs).

Definitions

Compelling inconsistencies are observations during the examination that indicate definitive evidence of feigning or exaggeration. They are defined as clear and compelling evidence indicative of feigning or exaggeration of neurocognitive, somatic, or psychiatric deficits or symptoms observed during the evaluation (e.g., unequivocal demonstration of disputed capacity when the examinee thinks he or she is unobserved; clear discrepancies between skills observed during the interview or while in the

evaluation setting that are highly implausible and that indicate feigning, dissimulation, or distortion of symptoms). Note that compelling inconsistencies that are documented in written, audio, video, or electronic form such as social media would be included under Criterion C (Marked Discrepancies) because they form part of the records or documentation for the case rather than part of the direct examination of the patient.

Performance validity tests (PVTs) are objective tests designed to detect invalid cognitive performance.

Symptom validity tests (SVTs) are self-report scales that measure over-reporting of self-reported cognitive, somatic, or psychiatric symptoms.

To meet criteria for Invalid Presentation on Examination Indicative of Feigning or Exaggeration, the examinee must present with one or more of the following criteria.

1. Invalid Neurocognitive Presentation. One or more of a, b, or c must be present.

a. One or more compelling inconsistencies pertaining to cognitive deficits or symptoms are observed or documented during the evaluation.
b. Invalid Scores on PVTs.
   Psychometric evidence of invalid cognitive test performance based on (a) using at minimum two or more PVTs that alone or in combination have a low false-positive rate (i.e., 0.10), while (b) taking into account the ratio of failed PVT scores to total number of PVTs administered, (c) minimizing PVT redundancy, and (d) using PVT cutoffs that have been validated in clinical studies. Obtaining one PVT in the significantly below-chance range also would meet this criterion (i.e., significantly below-chance performance on forced-choice tests based on binomial probability theory).
c. Psychometric evidence of exaggerated cognitive symptoms on self-reported SVTs.
   Psychometric evidence of exaggerated symptom reporting using SVTs that alone or in combination have a low false-positive rate (i.e., 0.10). For example, one or more SVT scores measuring primarily feigned or exaggerated cognitive symptoms in the invalid range using (a) tests with an acceptable false-positive rate, (b) tests that provide non-redundant information, and (c) tests that have cutoffs that have been validated in clinical studies would meet this criterion.

2. Invalid Somatic Symptom Presentation. One or both of a or b must be present.

a. One or more compelling inconsistencies pertaining to somatic symptoms are observed or documented during the evaluation.
b. Psychometric evidence of exaggerated somatic symptoms on self-reported SVTs.
   Psychometric evidence of exaggerated symptom reporting using SVTs that alone or in combination have a low falsepositive rate (i.e., 0.10). For example, one or more SVT scores measuring primarily feigned or exaggerated somatic symptoms in the invalid range using (a) SVTs with an acceptable false-positive rate, (b) SVTs that provide nonredundant information, and (c) SVTs that have cutoffs that have been validated in clinical studies would meet this criterion.

3. Invalid Psychiatric Presentation. One or both of a or b must be present.

a. One or more compelling inconsistencies pertaining to psychiatric symptoms are observed or documented during the evaluation.

b. Psychometric evidence of exaggerated psychiatric symptoms on self-reported SVTs.
Psychometric evidence of exaggerated symptom reporting using SVTs that alone or in combination have a low false-positive rate (i.e., 0.10). For example, one or more symptom validity test scores measuring primarily feigned or exaggerated psychiatric symptoms in the invalid range using (a) tests with an acceptable false-positive rate, (b) tests that provide non-redundant information, and (c) tests that have cutoffs that have been validated in clinical studies would meet this criterion.

4. Invalid Mixed Symptom Presentation.

Evidence of compelling inconsistency and/or psychometric evidence of invalid or exaggerated PVT or SVT results across two or more of cognitive, somatic, or cognitive domains.

For example, the following would each satisfy this criterion:

- Two or more compelling inconsistencies across domains (i.e., two or more of B1a, B2a, and B3a).
- Psychometric evidence in more than one domain (i.e., two or more among B1b, B1c, B2b, and B3b).
- One or more compelling inconsistencies combined with psychometric evidence of invalid or exaggerated deficits or symptoms in one or more domains (i.e., one or more compelling inconsistencies with one or more of either of B1b, B1c, B2b, or B3b).

C. Marked discrepancies

One or more marked discrepancies between obtained test data/symptom report and the types of evidence are present, as follows:

1. Natural history and pathogenesis of the condition in question
Information obtained by self-report or through tests or scales is markedly discrepant from currently accepted models of normal and abnormal neurological, medical, or psychiatric functioning in a way that suggests feigning or exaggeration of deficits or symptoms.
2. Records and other media
Information obtained by self-report or through tests or scales is markedly inconsistent with records or other documented history (e.g., audio, video, social media) in a way that suggests feigning or exaggeration of deficits or symptoms.
3. Reliable collateral informant report.
Information obtained by self-report or through tests or scales is markedly discrepant from day-to-day level of function described by at least one reliable collateral informant with minimal stakes in the outcome of the evaluation, in a way that suggests feigning or exaggeration of dysfunction.

D. Behaviors meeting Criteria B are not fully accounted for by another developmental, medical, or psychiatric condition

Behaviors meeting Criteria B are assumed to reflect an informed, rational, and volitional attempt toward acquiring or achieving outcomes as defined in Criterion A and cannot be fully accounted for by significant developmental, medical, or psychiatric conditions that result in significantly diminished capacity to appreciate laws or mores against malingering or inability to conform behavior to such standards. Examples of significant developmental, medical, and psychiatric conditions are listed as follows:

- Moderate to severe dementia.
- Moderate to severe intellectual disability (e.g., IQ < 60).
- Severe psychiatric, neurological, or other medical disorders associated with cognitive impairment sufficient to preclude independence in basic activities of daily living.

Malingering can co-occur in conditions associated with cognitive deficits including mild intellectual disability, mild dementia, or mild cognitive impairment. Similarly, malingering can co-occur in psychiatric or neurological conditions defined by somatoform symptoms (e.g., somatic symptom disorder, conversion disorder/functional neurological symptom disorder, factitious disorder, unexplained medical symptoms) and in the presence of other psychiatric conditions (e.g., depression).

Specifiers

The four specifiers for the clinical presentation of malingering are described as follows.

Malingering of neurocognitive dysfunction

In addition to meeting criteria A, C, and D, the individual meets Criteria B1a, B1b, or B1c for feigned or exaggerated cognitive dysfunction, that is, one or more of the following:

- A compelling inconsistency pertaining to cognitive deficits or symptoms.
- Invalid cognitive performance as demonstrated by performance validity tests.
- Invalid cognitive symptoms as demonstrated by symptom validity tests.

Malingering of somatic symptoms

In addition to meeting Criteria A, C, and D, the individual meets Criteria B2a or B2b for feigned or exaggerated somatic symptoms, that is, either of the following:

- A compelling inconsistency pertaining to somatic symptoms.
- Invalid somatic symptom report as demonstrated by symptom validity tests.

Malingering of psychiatric symptoms

In addition to meeting criteria A, C, and D, the individual meets Criteria B3a or B3b for feigned or exaggerated psychiatric symptoms, that is, either of the following:

- A compelling inconsistency pertaining to psychiatric symptoms.
- Invalid psychiatric symptom report on symptom validity tests.

Malingering with Mixed Presentation

In addition to meeting criteria A, C, and D, the individual meets Criteria B4 for feigned or exaggerated symptoms in more than one domain (i.e., cognitive, somatic, and/or psychiatric).

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VI. Supplementary

1: UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria*

Step 1. Diagnosis of parkinsonian syndrome

- Bradykinesia
- At least one of the following
    - Muscular rigidity
    - 4–6 Hz rest tremor
    - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2. Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumor or communication hydrocephalus on imaging study
- Negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3. Supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

** From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181–184.*

2: Pathologies with distinct neuropathological signatures

SNAP - Suspected non-Alzheimer disease pathophysiology

Jack Jr., C.R., Knopman, D.S., Chételat, G., Dickson, D., Fagan, A.M., Frisoni, G.B., . . . Vos, S.J.B. Nature Rev Neurology, 2016;12: 117-124.

SNAP is a biomarker based concept that applies to individuals with normal levels of amyloid-beta biomarkers in the brain, but in whom biomarkers of neurodegeneration are abnormal. The term SNAP is applicaple to any amyloid-negative, neurodegeneration-positive individual regardless of clinical status, except when the pathology underlying neurodegeneration can be reliably inferred from the clinical presentation. Clinically normal and mildly impaired individuals with SNAP have worse clinical and/or cognitive outcome than individuals with normal levels of neurodegeneration and amyloid-beta biomarkers.

PART – Primary age-related tauopathy

Crary, J.F., Trojanowski, J.Q., Schneider, J.A., Abisambra, J.F., Abner, E.L., . . ., Nelson, P.T. Acta Neuropathol, 2014;128:755–766. DOI:10.1007/s00401-014-1349-0

PART refers to brains with neurofibrillary tangles (NFTs) that are indistinguishable from those of Alzheimer's disease, in the absence of amyloid-beta plaques. For these "NFT+/Abeta-" brains, for which formal criteria for AD neuropathologic changes are not met, the NFTs are mostly restricted to structures in the medial temporal lobe, basal forebrain, brainstem, and olfactory areas. Symptoms in persons with PART usually range from normal to amnestic cognitive changes, with only a minority exhibiting profound impairment. This pathological process cannot be specifically identified pre-mortem at the present time.

LATE – Limbic predominant age-related TDP-43 encephalopathy

Nelson, P. T., Dickson, D. W., Trojanowski, J. Q., Jack, C.R. Jr., Boyle, P. A., Arfanakis, K., . . . Schneider, J. A. Brain 2019;142(6):1503-1527. doi: 10.1093/brain/awz099

LATE neuropathological change (LATE-NC) is defined by a stereotypical TDP-43 proteinopathy in older adults, with or without coexisting hippocampal sclerosis pathology. LATE-NC is a common TDP-43 proteinopathy, associated with an amnestic dementia syndrome that mimicked Alzheimer's-type dementia in retrospective autopsy studies. LATE is distinguished from frontotemporal lobar degeneration with TDP-43 pathology based on its epidemiology (LATE generally affects older subjects), and relatively restricted neuroanatomical distribution of TDP-43 proteinopathy. Many subjects with LATE-NC have comorbid brain pathologies, often including amyloid-b plaques and tauopathy.

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