HHS Public Access

Author manuscript

Am J Geriatr Psychiatry. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

Am J Geriatr Psychiatry. 2021 April ; 29(4): 375–383. doi:10.1016/j.jagp.2020.07.011.

The Role of Neuropsychiatric Symptoms in Research Diagnostic Criteria for Neurodegenerative Diseases

Jeffrey Cummings, MD, ScD

Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas; Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada

Abstract

Neuropsychiatric syndromes and symptoms play increasingly important roles in research diagnostic criteria for neurodegenerative disorders. Diagnostic criteria were reviewed including those for: dementia, Alzheimer's disease, mild cognitive impairment, mild behavioral impairment, prodromal Alzheimer's disease, dementia with Lewy bodies, prodromal dementia with Lewy bodies, Parkinson's disease, multiple system atrophy, frontotemporal dementia, primary progressive aphasia, progressive supranuclear palsy, corticobasal degeneration, traumatic encephalopathy syndrome, Huntington' disease, amyotrophic lateral sclerorsis. All contemporary research diagnostic criteria for neurodegenerative disorders expect those for Parkinson's disease, primary progressive aphasia, and multisystem atrophy include neuropsychiatric phenomena as core diagnostic criteria. There are no disease-specific neuropsychiatric symptoms; apathy and disinhibition are common in tauopathies, and rapid-eye-movement sleep behavioral disorder occurs almost exclusively in synucleinopathies. Neuropsychiatric symptoms and syndromes are increasingly integrated into research diagnostic criteria for neurodegenerative disorders; they require clinician skills for recognition; their biology is better understood as their relationships to cognitive, motor, and autonomic symptoms of neurodegenerative disorders are studied.

Keywords

Neurodegenerative disorders; neuropsychiatric syndromes; Alzheimer's disease; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; frontotemporal dementia; dementia

Address correspondence to: Jeffrey Cummings, MD, ScD, Cleveland Clinic Lou Ruvo Center for Brain Health, 888 W Bonneville Ave, Las Vegas, NV 89106, T: 702.701.7926, F: 702.722.6584, cumminj@ccf.org.

Author Contributions

JC is responsible for the entire manuscript.

Conflicts of Interest and Source of Funding

JC has provided consultation to Acadia, Actinogen, Alkahest, Allergan, Alzheon, Annovis, Avanir, Axsome, BiOasis, Biogen, Cassava, Cerecin, Cerevel, Cortexyme, Cytox, EIP Pharma, Eisai, Foresight, GemVax, Genentech, Green Valley, Grifols, Merck, Novo Nordisk, Otsuka, Resverlogix, Roche, Samumed, Samus, Signant Health, Third Rock and United Neuroscience pharmaceutical and assessment companies. JC owns the copyright of the Neuropsychiatric Inventory. JC is supported by KMA; NIGMS grant P20GM109025; NINDS grant U01NS093334; and NIA grant R01AG053798.

with Lewy bodies; progressive supranuclear palsy; corticobasal degeneration; traumatic encephalopathy syndrome; multiple system atrophy. depression; psychosis; apathy; agitation

Introduction

Research diagnostic criteria for neurodegenerative disorders (NDD) allow more precise patient diagnosis and management and facilitate research. Research diagnostic criteria lead to the identification of relatively homogenous patient populations that can be enrolled in pharmacologic and nonpharmacologic interventional research as well as in natural history studies. Research diagnostic criteria rapidly transcend research applications and are incorporated into clinical practice. They are periodically updated to reflect advances in scientific understanding of the diagnosis, differential diagnosis, management, and underlying biology of NDD.

NDD affect multiple brain regions and are characterized clinically by combinations of cognitive, neuropsychiatric, motoric, and autonomic changes that comprise the phenotype of the disorders and are integrated in diagnostic criteria. In some cases, such as in the criteria for dementia with Lewy bodies (DLB), biomarkers may be included (1).

Characteristic neuropsychiatric manifestations of NDD contribute importantly to many of the diagnostic criteria, facilitate accurate diagnosis, represent key symptoms that must be managed in the course of the illness, and contribute to an evolving understanding of the biological underpinnings of neuropsychiatric symptoms and syndromes. There has been progress in defining neuropsychiatric syndromes occurring in NDD and these more rigorous definitions contribute to the implementation of the diagnostic criteria. For example, the definition of apathy (2, 3) assists in defining the apathetic syndrome that comprises part of the diagnostic criteria for frontotemporal dementia (FTD) (4).

This review addresses the role of neuropsychiatric symptoms and syndromes in diagnosis of NDD as reflected in current research diagnostic criteria. A key implication of this discussion is that diagnosticians and investigators working with NDD must be knowledgeable about the behavioral aspects of NDD as well as about the cognitive, motoric, and autonomic features. The review draws attention to the shared biology of cognition and behavior and to the evolving understanding of the biology of behavior facilitated by NDD criteria.

Review Methodology

This review is based on a PubMed search for research diagnostic criteria for NDD including dementia, AD, DLB, Parkinson’s disease (PD), FTD, primary progressive aphasia (PPA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), traumatic encephalopathy syndrome (TES), multiple system atrophy (MSA), Huntington’s disease (HD), and amyotrophic lateral sclerosis (ALS). Current diagnostic criteria were identified, and the presence of behavioral features in the criteria was reviewed. Corresponding definitions of the neuropsychiatric symptoms and syndromes including disinhibition, apathy, delusions, hallucinations, psychosis, and depression noted in the criteria were identified and are discussed. Derivative references were reviewed to determine if the neuropsychiatric components of the definitions were assessed in follow-up studies of the criteria.

Research Diagnostic Criteria for Neurodegenerative Disorders

Dementia—The Diagnostic and Statistical Manual, 5th ed.(5) uses the terms Major Neurocognitive Disorder and Mild Neurocognitive Disorder for the clinical syndromes labeled dementia and mild cognitive impairment (MCI) in other approaches. Major Neurocognitive Disorder is defined as exhibiting decline from past cognitive ability manifested by memory impairment, language abnormalities, visuospatial disturbance, executive dysfunction, attention impairment, and abnormal social cognition. The functional changes must be sufficient to interfere with activities of daily living and not exclusively explained by a delirium or some other mental disorder. Decline in social cognition is recognized as lack of empathy and sympathy, reduced insight, poor social judgment, impaired recognition of social cues, and inappropriate social behavior (6, 7). With these criteria, Major Neurocognitive Disorder can be diagnosed on the basis of the presence of one cognitive deficit plus changes in social cognition.

The Diagnostic and Statistical Manual, 5th ed.(5) does not include changes in behavior as part of the definition of Mild Neurocognitive Disorder.

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) advanced criteria for dementia and MCI as well as preclinical AD, MCI due to AD, and AD dementia (8). The NIA-AA approach defines all-cause dementia as having at least two of the following features: memory impairment; impaired reasoning and complex thinking; impaired visuospatial abilities; impaired language; or changes in personality, behavior, or comportment (9). Examples of the latter include uncharacteristic mood fluctuations such as agitation, impaired motivation, reduced initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, and socially unacceptable behaviors. This approach to dementia allows "changes in personality, behavior, or comportment" plus change in one cognitive domain to be the basis of identifying a dementia syndrome. The changes must be sufficiently severe to interfere with work or activities, represent a decline from the individual's previous level of function, and are not better explained by delirium or a psychiatric disorder. The NIA-AA syndrome of dementia is similar to the Diagnostic and Statistical Manual(5) in recognizing behavioral changes to be as important as cognitive changes in defining the dementia syndrome, allowing identification based on change in one aspect of cognition plus change in personality, behavior, or comportment.

NIA-AA criteria for MCI do not include reference to behavioral or neuropsychiatric changes (10).

Alzheimer's Disease: After providing criteria for Major Neurocognitive Disorder, the Diagnostic and Statistical Manual advances more specific criteria for the diagnosis of Major Neurocognitive Disorder due to AD(5). This diagnosis requires the gradually progressive decline of memory impairment plus at least one of: language abnormalities, visuospatial disturbance, executive dysfunction, attention impairment, or social cognition. Gradually compromised social cognition plus memory impairment with appropriate exclusions of delirium and major psychiatric disorders would allow fulfillment of the clinical criteria for

Major Neurocognitive Disorder due to AD. As in the criteria for dementia, behavioral changes are as important as cognitive abnormalities in diagnosis.

The NIA-AA criteria define AD dementia by the presence of a dementia syndrome as previously defined presenting with insidious onset and gradual worsening. The disorder may have either an amnestic or a non-amnestic presentation. Building on the NIA-AA criteria for dementia allows behavior to be one of two key elements sufficient for a diagnosis of AD dementia (9).

NIA-AA criteria for MCI due to AD do not include reference to behavioral or neuropsychiatric changes(10).

The International Society to Advance Alzheimer's Research and Treatment (ISTAART) associated with the AA, has proposed criteria for Mild Behavioral Impairment (MBI) that can occur with or without MCI and is the harbinger of a progressive dementia syndrome(11, 12). MBI identification requires at least one of the following: decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, or abnormal perception or thought content.

The International Work Group (IWG) is devoted to developing a clinical-biological definition of AD. Their approach to AD allows a typical or an atypical phenotype along with biological evidence of AD based on amyloid imaging, cerebrospinal fluid amyloid/tau protein measures, or presence of a mutation known to be associated with autosomal dominant AD (13). The typical phenotype of AD features an episodic type memory impairment. Several atypical presentations are described including a frontal variant that is defined by the presence of early, predominant and progressive behavioral changes featuring apathy or behavioral disinhibition. Neuropsychological assessment of patients with the frontal variant reveals marked executive dysfunction. In this approach, a frontal-type behavioral syndrome plus biological evidence of AD is sufficient for a diagnosis of AD. If functional changes are minor, prodromal AD is the appropriate diagnosis; if functional changes are prominent, AD dementia is the appropriate diagnosis.

Criteria for neuropsychiatric syndromes occurring in AD and other neurocognitive disorders have been developed including psychosis in AD (14, 15), depression in AD (16), agitation in AD and cognitive disorders (17), and apathy in AD and other dementias (2). These criteria were typically developed to apply to AD as the most common late-life dementia; they state that the syndromic criteria can be applied to other dementias as they are not uniquely associated with AD.

Frontotemporal Dementia—FTD includes the behavioral variant (bvFTD), nonfluent primary progressive aphasia (nfPPA), and semantic variant primary progressive aphasia (svPPA) (4). Behavioral variant FTD is the only NDD that requires the presence of behavioral changes to establish the diagnosis(4). The patient must have at least two of the following behavioral symptoms: early behavioral disinhibition; early apathy or inertia; early loss of sympathy or empathy; early perseverative, stereotyped or compulsive/ritualistic behavior; or hyperorality and dietary changes. If neuropsychological abnormalities

(especially executive function deficits) are not present, the patient must have three of the categories of behavioral changes to support a diagnosis. The behavioral changes of bvFTD represent the core diagnostic features. The publication describing the criteria includes a glossary with definitions of disinhibition, apathy or inertia, loss of sympathy or empathy, compulsive behavior, and hyperorality/dietary changes (4). These definitions can apply to the behavioral changes seen in other NDD.

Nonfluent primary progressive aphasia and svPPA do not include specific reference to behavioral features that contribute to meeting the diagnostic criteria (18). Many patients with svPPA develop behavioral changes similar to those of bvFTD including disinhibition, irritability, lack of empathy, mental inflexibility, compulsions, and food taste changes (e.g., preference for sweet foods) (19). In some cases, nfPPA progresses to PSP (see below) with the behavioral features of PSP and depression(20).

Dementia with Lewy Bodies—In addition to the presence of progressive dementia, DLB has four core clinical features: fluctuating cognition, recurrent visual hallucinations, rapid eye movement (REM) sleep behavior disorder, and parkinsonism (1). Probable DLB is diagnosed if two core features are present; alternatively, one core and one indicative biomarker (reduced dopamine transporter signal in the basal ganglia demonstrated by single photon emission tomography or positron emission tomography; abnormally low uptake on ^{123}idoine- metaiodobenzylguanidine (MIBG) myocardial scintigraphy; polysomnographic confirmation of REM sleep without atonia) are sufficient for a diagnosis of probable DLB. Visual hallucinations are present in a majority (62–77%) of patients meeting criteria for DLB (21, 22). REM sleep behavior disorder occurs in 40–50% of patients with DLB(23). Neuropsychiatric features are a prominent component of the criteria for DLB, accounting for two of the four core criteria.

Possible DLB can be identified in a patient with dementia and 1 core clinical feature such as visual hallucinations (1).

Criteria for prodromal DLB focus on patients with MCI. The presence of MCI plus 2 of 4 core features of DLB or 1 core feature plus 1 of the biomarkers leads to the diagnosis of prodromal DLB (24). Visual hallucinations or REM sleep behavior disorder occurring a patient with MCI allow the diagnosis of prodromal DLB.

The prodromal DLB criteria provide provisional guidelines for identification of psychiatric-onset DLB describing neuropsychiatric symptoms that may prior to cognitive manifestations. Late onset visual hallucinations, hallucinations in other sensory modalities, systematized delusions including Capgras syndrome, apathy, anxiety, and depression are suggested as possible presenting features of psychiatric-onset DLB.

Parkinson's Disease Dementia—Parkinson's disease dementia is characterized by impairment in attention, memory, executive and visuo-spatial functions (25). The criteria identify behavioral symptoms (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) as supportive of the diagnosis. Behavioral changes are not identified as core diagnostic criteria.

Criteria for PD MCI do not explicitly identify a role for neuropsychiatric symptoms or behavioral changes in diagnosis (26).

Although neuropsychiatric symptoms do not play a role in the diagnosis of PD, behavioral changes are common among PD patients and criteria for depression in PD (27) and psychosis in PD have been developed (28).

Multiple System Atrophy—Multiple system atrophy (MSA) is characterized by parkinsonian features, cerebellar ataxia, autonomic failure, urogenital dysfunction, and corticospinal abnormalities. The presenting motor disorder most commonly consists of parkinsonism with bradykinesia, rigidity, and gait instability; cerebellar ataxia is the initial motor disorder in a substantial minority of patients. MSA diagnostic criteria do not identify behavioral features useful in diagnosis (29). REM sleep behavioral disorder is common in MSA and is the most common presenting manifestation of the disorder(30). Cognitive impairment including abnormalities of attention, working memory, information retrieval, and visuospatial deficits commonly occur with disease progression (31).

Corticobasal Degeneration—Core diagnostic criteria for CBD include asymmetric limb rigidity or bradykinesia, asymmetric limb dystonia, asymmetric limb myoclonus, orobuccal or limb apraxia, cortical sensory deficit, and alien limb phenomenon(32). Diagnosis is supported by two features of the core CBD syndrome or by a frontobehavioral disorder plus at least one corticobasal feature. The criteria require that the individual be 50 years of age or older with insidious onset and gradual progression of the behavioral and cognitive changes. Symptoms must be present for a minimum of one year. With this approach, a behavioral-type of frontobehavioral syndrome plus one corticobasal syndrome feature is sufficient for a diagnosis of CBD. Apathy or a bvFTD-type disinhibition syndrome are the behavioral features identified as manifestations of the frontobehavioral syndrome (33).

Progressive Supranuclear Palsy—Three levels of certainty have been identified in current PSP criteria (34). Behavioral abnormalities do not meet criteria for Level 1 certainty, but the criteria do allow behavioral abnormalities (frontal cognitive/behavioral presentation) to achieve a Level 2 diagnostic certainty. Apathy is present in 60% of those with PSP and disinhibition is present in 50%; these symptoms comprise the principal elements of the frontal-behavioral presentation (35).

Traumatic Encephalopathy Syndrome—The relationship of TES to the neuropathologic diagnosis of chronic traumatic encephalopathy (CTE) is under investigation and most studies suggest that current TES criteria have good sensitivity and low specificity. CTE is a progressive neurodegenerative disorder characterized by aberrant deposits of phosphorylated tau protein identified at autopsy(36). The current clinical criteria for TES require progressive cognitive impairment with delayed onset following repetitive head trauma (37, 38). Emotional dysregulation, behavioral, and motor disturbance are included as core features(38) or supportive features(37).

Huntington's Disease—The Movement Disorder Society reviewed the criteria for diagnosis of HD and concluded that application of Diagnostic and Statistical Manual, 5th ed.

(5) terms Major Neurocognitive Disorder and Mild Neurocognitive Disorder was appropriate for characterizing the cognitive and behavioral changes o HD provided the individual has confirmatory genetic testing(39).

Amyotrophic Lateral Sclerosis

The diagnostic criteria for ALS depend on electromyographic documentation of motor neuron disease and do not include behavior or psychological criteria(40, 41).

Discussion

Neuropsychiatric syndromes and symptoms contribute importantly to the diagnosis of NDD and are incorporated into the diagnostic criteria of most (Table 1).

There are no neuropsychiatric symptoms or syndromes that are unique to a specific NDD. Apathy, psychosis, depression, agitation, and sleep disturbances occur across NDD albeit at different frequencies. The role of neuropsychiatric syndromes in diagnosis is as a part of a constellation of signs and symptoms that comprise the phenotype characteristic of each NDD and its unique molecular signature and neuro-geographic distribution (42).

The important role played by neuropsychiatric syndromes in NDD diagnosis has several implications. First, assessment and recognition of the neuropsychiatric symptoms and syndromes is essential to accurate diagnosis. Improved interview approaches and rating scales may assist clinicians in detection, characterization, and diagnosis of NDD. Criteria for psychosis, agitation, depression, and apathy occurring in NDD are helpful in recognizing these disorders accurately (2, 14–17). Second, the increasing recognition of behavioral changes in the course of NDD informs understanding of the biology of these syndromes and symptoms. For example, the very high prevalence of neuropsychiatric disorders in DLB implies that the specific molecular, pathological, and circuit changes of this disease create a cerebral ecology uniquely provocative of these symptoms. Apathy and impulsivity are common in bvFTD but also occur in other frontotemporal lobar degeneration syndromes including PSP, CBD, CTE, and some patients with PPA(43). This group of disorders shares a common underlying biology, with tauopathy as the key pathological change. REM sleep behavior disorder occurs almost exclusively in disorders characterized pathologically by alpha-synuclein aggregation including PD, DLB and MSA (44). The criteria for NDD and the inclusion of neuropsychiatric phenomena is facilitating study of the neurobiology of these behaviors.

This review addresses the role of neuropsychiatric syndromes in diagnosing NDD. Similar approaches to incorporating neuropsychiatric syndromes into diagnostic frameworks are seen with other dementias. Criteria for vascular cognitive impairment (VCI) require onset of the clinical syndrome following a cerebrovascular event and evidence of decline in frontal executive functioning, plus one of the following: gait disturbance, urinary symptoms, or personality and mood changes. There must also be evidence on computerized tomography or magnetic resonance imaging of cerebrovascular disease. With this approach, personality and mood changes contribute to meeting the criteria for diagnosis of VCI (45).

An important trend in diagnostic criteria is facilitation of early diagnosis based on behavioral changes. This is evident in the criteria for MBI that may occur with or without MCI and represent the initial manifestations of a progressive disorder (11, 12) and the criteria for prodromal DLB(24).

Review of the literature on neuropsychiatric syndromes in NDD demonstrates that the criteria are typically based on expert opinion experienced with the specific NDD. The criteria are periodically revised and updated as new knowledge accrues. In some cases, sensitivity, specificity, and positive and negative predictive value are examined in follow-up studies. It is rare for the specific contribution of the behavioral changes to these parameters or inter-rater reliability of the assessments to be studied. Similarly, there are few clinicopathologic studies of the behavioral changes in patients who succumb to their illness and come to autopsy. An assessment of the criteria for depression in AD conducted after publication of the criteria, found them to perform effectively in detection of important mood changes in AD (46, 47). A re-examination of the criteria for psychosis in AD encouraged allowing diagnosis of the syndrome in prodromal and preclinical AD as the presenting manifestation of the disorder (15). There were few changes in the core criteria.

Biomarkers play an increasingly important role in diagnosis of NDD and are being integrated into some sets of diagnostic criteria (1, 24, 48). Identifying biomarkers associated with specific behavioral symptoms and syndromes would further strengthen diagnostic criteria and the role of neuropsychiatric symptoms in support of diagnosis (49, 50).

An important role for diagnostic criteria is their application in clinical trials and regulatory interactions. For clinical trials of disease-modifying therapies, criteria allow the construction of trial populations that have greater diagnostic homogeneity. Reduction of neuropsychiatric symptoms or reduction in the emergence of new symptoms will be key aspects of the success of disease modifying treatments of NDD. When neuropsychiatric symptoms and syndromes occurring as part of NDD are the focus of trials, criteria facilitate recruitment of trial populations with homogeneous behavioral changes. There are currently several trials for agitation in AD using research diagnostic criteria for AD and for agitation (51). Some trials recruit across NDD using a common neuropsychiatric endophenotype such as the trial of pimavansarin for dementia-related psychosis (52). These trials are based on the assumption that the test agent influences circuits affected across multiple NDDs.

In summary, neuropsychiatric phenomena play an increasingly important role in diagnostic criteria for NDD. Accurate recognition of neuropsychiatric phenomena improves detection and recognition of NDD. NDD criteria have facilitated studying the neurobiology of behavioral changes in NDD. The criteria and the integrated neuropsychiatric phenomena facilitate clinical trials and the development of new therapies for NDD and their behavioral manifestations. Neuropsychiatric aspects of NDD criteria support nonpharmacologic research and assist clinicians in diagnosis and management of NDD.

Acknowledgements

JC is supported by Keep Memory Alive (KMA); NIGMS grant P20GM109025; NINDS grant U01NS093334; and NIA grant R01AG053798.

References

1. McKeith IG, Boeve BF, Dickson DW, et al.: Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology 2017; 89:88–100 [PubMed: 28592453]
2. Robert P, Onyike CU, Leentjens AF, et al.: Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. Eur Psychiatry 2009; 24:98–104 [PubMed: 19201579]
3. Robert P, Lanctot KL, Aguera-Ortiz L, et al.: Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. Eur Psychiatry 2018; 54:71–76 [PubMed: 30125783]
4. Rascovsky K, Hodges JR, Knopman D, et al.: Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011; 134:2456–2477 [PubMed: 21810890]
5. American Psychiatric Association: Diagnostic and statistical manual, 5th ed., Washington, D.C., American Psychiatric Association Publishing, 2013
6. Henry JD, von Hippel W, Molenberghs P, et al.: Clinical assessment of social cognitive function in neurological disorders. Nat Rev Neurol 2016; 12:28–39 [PubMed: 26670297]
7. Fortier J, Besnard J,Allain P: Theory of mind, empathy and emotion perception in cortical and subcortical neurodegenerative diseases. Rev Neurol (Paris) 2018; 174:237–246 [PubMed: 29622366]
8. Jack CR Jr., Albert MS, Knopman DS, et al.: Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7:257–262 [PubMed: 21514247]
9. McKhann GM, Knopman DS, Chertkow H, et al.: The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7:263–269 [PubMed: 21514250]
10. Albert MS, DeKosky ST, Dickson D, et al.: The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7:270–279 [PubMed: 21514249]
11. Ismail Z, Smith EE, Geda Y, et al.: Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement 2016; 12:195–202 [PubMed: 26096665]
12. Ismail Z, Aguera-Ortiz L, Brodaty H, et al.: The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. J Alzheimers Dis 2017; 56:929–938 [PubMed: 28059789]
13. Dubois B, Feldman HH, Jacova C, et al.: Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014; 13:614–629 [PubMed: 24849862]
14. Jeste DV,Finkel SI: Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. Am J Geriatr Psychiatry 2000; 8:29–34 [PubMed: 10648292]
15. Fischer CE, Ismail Z, Youakim JM, et al.: Revisiting criteria for psychosis in Alzheimer's disease and related dementias: toward better phenotypic classification and biomarker research. J Alzheimers Dis 2020; 73:1143–1156 [PubMed: 31884469]
16. Olin JT, Schneider LS, Katz IR, et al.: Provisional diagnostic criteria for depression of Alzheimer's disease: description and review. Expert Rev Neurother 2003; 3:99–106 [PubMed: 19810852]
17. Cummings J, Mintzer J, Brodaty H, et al.: Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. Int Psychogeriatr 2015; 27:7–17 [PubMed: 25311499]
18. Gorno-Tempini ML, Hillis AE, Weintraub S, et al.: Classification of primary progressive aphasia and its variants. Neurology 2011; 76:1006–1014 [PubMed: 21325651]
19. Montembeault M, Brambati SM, Gorno-Tempini ML, et al.: Clinical, anatomical, and pathological features in the three variants of primary progressive aphasia: a review. Front Neurol 2018; 9:692 [PubMed: 30186225]

20. Santos-Santos MA, Mandelli ML, Binney RJ, et al.: Features of Patients With Nonfluent/Agrammatic Primary Progressive Aphasia With Underlying Progressive Supranuclear Palsy Pathology or Corticobasal Degeneration. JAMA Neurol 2016; 73:733–742 [PubMed: 27111692]
21. Del Ser T, McKeith I, Anand R, et al.: Dementia with lewy bodies: findings from an international multicentre study. Int J Geriatr Psychiatry 2000; 15:1034–1045 [PubMed: 11113984]
22. Eversfield CL,Orton LD: Auditory and visual hallucination prevalence in Parkinson's disease and dementia with Lewy bodies: a systematic review and meta-analysis. Psychol Med 2019; 49:2342–2353 [PubMed: 30474581]
23. Chan PC, Lee HH, Hong CT, et al.: REM Sleep Behavior Disorder (RBD) in Dementia with Lewy Bodies (DLB). Behav Neurol 2018; 2018:9421098 [PubMed: 30018672]
24. McKeith IG, Ferman TJ, Thomas AJ, et al.: Research criteria for the diagnosis of prodromal dementia with Lewy bodies. Neurology 2020; 94:743–745 [PubMed: 32241955]
25. Emre M, Aarsland D, Brown R, et al.: Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007; 22:1689–1707; quiz 1837 [PubMed: 17542011]
26. Litvan I, Goldman JG, Troster AI, et al.: Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord M2012; 27:349–356
27. Marsh L, McDonald WM, Cummings J, et al.: Provisional diagnostic criteria for depression in Parkinson's disease: report of an NINDS/NIMH Work Group. Mov Disord 2006; 21:148–158 [PubMed: 16211591]
28. Ravina B, Marder K, Fernandez HH, et al.: Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Mov Disord 2007; 22:1061–1068 [PubMed: 17266092]
29. Gilman S, Wenning GK, Low PA, et al.: Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008; 71:670–676 [PubMed: 18725592]
30. Giannini G, Mastrangelo V, Provini F, et al.: Progression and prognosis in multiple system atrophy presenting with REM behavior disorder. Neurology 2020; 94:e1828–e1834 [PubMed: 32234825]
31. Stankovic I, Krismer F, Jesic A, et al.: Cognitive impairment in multiple system atrophy: a position statement by the Neuropsychology Task Force of the MDS Multiple System Atrophy (MODIMSA) study group. Mov Disord 2014; 29:857–867 [PubMed: 24753321]
32. Armstrong MJ, Litvan I, Lang AE, et al.: Criteria for the diagnosis of corticobasal degeneration. Neurology 2013; 80:496–503 [PubMed: 23359374]
33. Kertesz A,McMonagle P: Behavior and cognition in corticobasal degeneration and progressive supranuclear palsy. J Neurol Sci 2010; 289:138–143 [PubMed: 19733862]
34. Hoglinger GU, Respondek G, Stamelou M, et al.: Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Mov Disord 2017; 32:853–864 [PubMed: 28467028]
35. Gerstenecker A, Duff K, Mast B, et al.: Behavioral abnormalities in progressive supranuclear palsy. Psychiatry Res 2013; 210:1205–1210 [PubMed: 24035530]
36. Mez J, Daneshvar DH, Kiernan PT, et al.: Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football. JAMA 2017; 318:360–370 [PubMed: 28742910]
37. Reams N, Eckner JT, Almeida AA, et al.: A Clinical Approach to the Diagnosis of Traumatic Encephalopathy Syndrome: A Review. JAMA Neurol 2016; 73:743–749 [PubMed: 27111824]
38. Montenigro PH, Baugh CM, Daneshvar DH, et al.: Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. Alzheimers Res Ther 2014; 6:68 [PubMed: 25580160]
39. Ross CA, Reilmann R, Cardoso F, et al.: Movement Disorder Society Task Force Viewpoint: Huntington's Disease Diagnostic Categories. Mov Disord Clin Pract 2019; 6:541–546 [PubMed: 31538087]
40. Brooks BR, Miller RG, Swash M, et al.: El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000; 1:293–299 [PubMed: 11464847]
41. Costa J, Swash M,de Carvalho M: Awaji criteria for the diagnosis of amyotrophic lateral sclerosis:a systematic review. Arch Neurol 2012; 69:1410–1416 [PubMed: 22892641]

42. Cummings JL: Toward a molecular neuropsychiatry of neurodegenerative diseases. Ann Neurol 2003; 54:147–154 [PubMed: 12891666]
43. Lansdall CJ, Coyle-Gilchrist ITS, Jones PS, et al.: Apathy and impulsivity in frontotemporal lobar degeneration syndromes. Brain 2017; 140:1792–1807 [PubMed: 28486594]
44. Barone DA,Henchcliffe C: Rapid eye movement sleep behavior disorder and the link to alpha-synucleinopathies. Clin Neurophysiol 2018; 129:1551–1564 [PubMed: 29883833]
45. Sachdev P, Kalaria R, O'Brien J, et al.: Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer Dis Assoc Disord 2014; 28:206–218 [PubMed: 24632990]
46. Sepehry AA, Lee PE, Hsiung GR, et al.: The 2002 NIMH Provisional Diagnostic Criteria for Depression of Alzheimer's Disease (PDC-dAD): gauging their validity over a decade later. J Alzheimers Dis 2017; 58:449–462 [PubMed: 28453472]
47. Teng E, Ringman JM, Ross LK, et al.: Diagnosing depression in Alzheimer disease with the national institute of mental health provisional criteria. Am J Geriatr Psychiatry 2008; 16:469–477 [PubMed: 18515691]
48. Jack CR Jr., Bennett DA, Blennow K, et al.: NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018; 14:535–562 [PubMed: 29653606]
49. Ruthirakuhan M, Lanctot KL, Di Scipio M, et al.: Biomarkers of agitation and aggression in Alzheimer's disease: A systematic review. Alzheimers Dement 2018; 14:1344–1376 [PubMed: 29940162]
50. Ruthirakuhan M, Herrmann N, Andreazza AC, et al.: Agitation, oxidative stress, and cytokines in Alzheimer disease: biomarker analyses from a clinical trial with nabilone for agitation. J Geriatr Psychiatry Neurol 2019; 891988719874118
51. Liu CS, Ruthirakuhan M, Chau SA, et al.: Pharmacological management of agitation and aggression in Alzheimer's disease: a review of current and novel treatments. Curr Alzheimer Res 2016; 13:1134–1144 [PubMed: 27137221]
52. Cummings J, Ballard C, Tariot P, et al.: Pimavanserin: potential treatment for dementia-related psychosis. J Prev Alzheimers Dis 2018; 5:253–258 [PubMed: 30298184]

Highlights

Review questions: What is the role of neuropsychiatric symptoms and syndromes in research diagnostic criteria for neurodegenerative disorders?

Main finding: Neuropsychiatric symptoms and syndromes are included in research diagnostic criteria for dementia, Alzheimer's disease, prodromal Alzheimer's disease, dementia with Lewy bodies, prodromal dementia with Lewy bodies, frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy.

Key meaning of the finding: Awareness of behavioral changes is essential to accurate diagnosis of neurodegenerative disorders. Inclusion of neuropsychiatric symptoms and syndromes in research diagnostic criteria facilitates study of the neurobiology of these disorders.

Table 1.

Neuropsychiatric syndromes and symptoms included in diagnostic criteria for NDD.

Neurodegenerative Disorder	Neuropsychiatric Symptoms and Syndromes Included in Diagnostic Criteria
Major neurocognitive disorder (DSM)	Social cognition including recognition of emotions, theory of mind, and insight
Dementia (NIA-AA)	Changes in personality, behavior, or comportment
Mild neurocognitive disorder (DSM)	None
Mild cognitive impairment (NIA-AA)	None
Major neurocognitive disorder due to Alzheimer's disease (DSM)	Social cognition including recognition of emotions, theory of mind, and insight
Alzheimer's disease dementia (NIA-AA)	Changes in personality, behavior, or comportment
Mild cognitive impairment due to Alzheimer's disease (NIA-AA)	None
Mild Behavioral Impairment (MBI)	Decreased motivation; affective dysregulation; impulse dyscontrol; social inappropriateness; abnormal perception or thought content
IWG AD dementia; frontal variant	Apathy, disinhibition
IWG prodromal AD; frontal variant	Apathy, disinhibition
Dementia with Lewy bodies	Recurrent visual hallucinations
Prodromal dementia with Lewy bodies	Recurrent visual hallucinations
Psychiatric onset dementia with Lewy bodies	Visual hallucinations, hallucinations in other sensory modalities, systematized delusions including Capgras syndrome, apathy, anxiety, and depression
Parkinson's disease dementia	None
Parkinson's disease mild cognitive impairment	None
Behavioral variant frontotemporal dementia	Behavior disinhibition; apathy/inertia; loss of sympathy or empathy; perseverative, stereotyped, or compulsive/ritualistic behavior; hyperorality and dietary changes
Nonfluent primary progressive aphasia	None
Semantic variant primary progressive aphasia	None
Progressive supranuclear palsy	Frontal cognitive/behavioral syndrome
Corticobasal degeneration	Frontotemporal syndrome
Traumataic encelphalopathy syndrome	Behavioral dysregulation; mood changes
Huntington's disease	Social cognition including recognition of emotions, theory of mind, and insight (from DSM)
Amyotrophic lateral sclerosis	None

DSM – Diagnostic and Statistical Manual of Mental Disorders, 5th edition; IWG – International Work Group; NIA-AA – National Institute on Aging – Alzheimer's Association