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Overview of Neurocognitive Disorders

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Abstract

Cognitive function is a major determinant of an individual's quality of life. However, the number of individuals developing a neurocognitive disorder (NCD) is increasing as the population ages: the number of individuals with dementia is doubling every 20 years and will reach over 115 million worldwide by 2050. There is a need to identify vulnerable individuals early, understand the trajectory of their NCD, and intervene with effective treatments. The *DSM-5* outlines criteria to identify patients with mild NCD and distinguish them from patients with major NCD. Identifying patients early in the course of a dementing disorder can improve the opportunity to develop effective interventions to change the course of the NCD. Research is needed to identify biomarkers and risk factors that indicate an individual's potential for developing an NCD.

Keywords: Dementia, Cognitive Disorders, Diagnosis and Classification in Neuropsychiatry, Geriatric Neuropsychiatry, Neuropsychiatry/neurobiology

Normal Aging

Cognitive functioning is a major health concern that affects an individual's ability to live independently (1, 2) and is a key determinant of quality of life (3). Among older adults, cognitive function varies widely with aging. Generally, some cognitive functions are relatively stable with aging, including vocabulary and knowledge of world events (4), whereas other cognitive functions, particularly those that rely on mental processing speed and attention, working memory, executive function, and verbal recall, decline with age (5–8). These decrements in cognitive functioning with aging have been related to changes in underlying neuroanatomic structures, such as decreases in white matter integrity and decreased volumes of the caudate, cerebellum, hippocampus, prefrontal cortex, and medial temporal lobes (9–11).

Conversely, improved cognitive functioning with aging has been correlated with intact neuroanatomic structures, most notably in the hippocampus and the frontal lobes (12). However, intact neuroanatomic structures may be only one component of improved cognitive aging. Studies linking the size of neuroanatomic structures to functioning have had mixed results (12). The model of the relationship of neuroanatomic structures to cognitive functioning should account for neural connectivity and functional measures such as the response to mental challenges, which can be assessed by modern neuroimaging techniques, including positron emission tomography (PET) and functional magnetic resonance imaging.

The integrity of white matter tracts decreases with age, affecting the connectivity between neural networks and changes in the pattern of response to mental challenges (7, 9, 11). Older adults with improved cognitive performance had greater activation of their frontal lobes and parietal and temporal cortices (5). Increased prefrontal activation in response to mental tasks has been shown to occur in healthy older adults, as well as in individuals with mild cognitive impairment and early dementia (7, 13–15). The increased responsivity in the prefrontal cortex and improved performance on a range of cognitive tasks has also been related to underactivity in posterior regions (7, 16). The greater brain responsivity may therefore be associated with higher cognitive functioning in one anatomic area, that compensates for potential underperformance of another area. Overall, this pattern of responsivity demonstrates the plasticity of the brain in response to the aging process, and the potential for interventions such as cognitive retraining to improve cognition with aging (2).

The concept of brain plasticity and the development of cognitive reserve (17) are important in understanding the aging process. *Cognitive reserve* implies that there is a compensatory mechanism in the form of functional neurons within the same anatomic structure, or the larger neural network, being recruited to compensate for neuronal structures that are not functioning optimally (7). Cognitive training has been demonstrated to improve executive functioning and working memory by strengthening prefrontal networks (18). Aerobic exercise can also improve cognitive reserve by maintaining the integrity of underlying neuroanatomic structures (19–21). Future research, including randomized clinical trials, is needed to determine the public health benefits of nonpharmacologic interventions such as aerobic exercise programs and structured mental exercises (e.g., through the use of video games [22]) in maintaining cognitive health. Developing strategies to improve cognitive performance with aging could provide significant public health benefits.

Neurocognitive Disorders

Understanding normal aging may aid in developing compensatory strategies to maximize function; however, the neurodegenerative dementias show an acceleration of the neuropathological process. The prevalence of Alzheimer's disease (AD), the most common neurodegenerative dementia, increases with age from less than 1% of people who are younger than 60 years to over 40% of those older than 85 years (23). It is estimated that by the year 2050, people over the age of 59 will be approximately 22% of the world's population (24). Stated another way, that is approximately 1.25 billion people, who will disproportionately represent countries with lower socioeconomic status (24). The worldwide estimate of persons with dementia was 35.5 million in 2010, with the number of patients with dementia almost doubling every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 (24). Identifying and treating patients with neurocognitive disorders should therefore be a public health priority.

The *DSM-IV* (25) had four categories for cognitive disorders (delirium, dementia, amnestic disorders, and other cognitive disorders) that were replaced with three categories in the *DSM-5* (26): delirium, mild neurocognitive disorder (NCD), and major NCD. The diagnosis of delirium is an exclusion criterion for patients with other NCDs. Whereas the *DSM-IV* used the areas of cognitive dysfunction to define dementias (e.g., memory impairment, aphasia, apraxia, agnosia, and executive dysfunction), the *DSM-5* substitutes specific cognitive domains: complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition. The criteria in the *DSM-5* are also more inclusive of a range of potential cognitive disorders and do not, for example, restrict the disorders to NCDs that occur primarily in older adults (i.e., AD). The definition for a major NCD in the *DSM-5* also includes NCDs that occur in younger patients, such as those with traumatic brain injury and human immunodeficiency virus (HIV).

The *DSM-5* criteria for the mild and major NCDs are outlined in Box 1. The diagnosis of mild NCD is reserved for individuals with cognitive difficulties that go beyond what would be expected for normal aging, but not to the point of limiting the ability of the person to live independently. These difficulties may

be noticed by coworkers, spouses, or friends and require the individual to use compensatory strategies and accommodations. Mild NCD distinguishes individuals who are living independently and have normal cognitive functioning from those who are having difficulty, but do not have dementia (27). The distinction between mild and major NCDs is operationalized with psychometric tests. Patients with mild NCDs should not be more than one to two standard deviations below the normative scores that are adjusted for age and education, whereas patients with major NCDs fall more than two standard deviations below the norm, or in about the third percentile or lower.

Box 1: *DSM-5* CRITERIA FOR MILD AND MAJOR NEUROCOGNITIVE DISORDERS[a]

A. Evidence of 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. Impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. (Major) 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).

B. (Minor) 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).

Specifiers

1. 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, other medical condition, multiple etiologies, or unspecified.
2. Accompanied by a clinically significant behavioral disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms)
3. Current severity: **Mild:** Difficulties with instrumental activities of daily living (e.g., housework, managing money). **Moderate:** Difficulties with basic activities of daily living (e.g., feeding, dressing). **Severe:** Fully dependent.

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[a]The main distinction between a mild and a major NCD is that people with major NCDs have impairment on neuropsychological testing more than two standard deviations below the norm and a decrease in their ability to live independently. Criteria reprinted from American Psychiatric

Association: *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. Washington, DC, American Psychiatric Association, 2013. Copyright 2013, American Psychiatric Association. Used with permission.

Mild NCDs include diagnoses such as mild cognitive impairment (28–30) as well as older terms, such as *age-associated cognitive decline* (31) and *questionable dementia* (32). The internationally accepted definition of mild cognitive impairment (28) is very similar to the *DSM-5* definition of mild NCD (27). The distinction in these diagnoses may be subtle. Mild cognitive impairment primarily applies to older adults, whereas mild NCD includes all age groups (27).

The prevalence of mild cognitive impairment has been estimated to be 14% to 18% for individuals age 70 years and older (33). Patients with mild cognitive impairment are at significant risk of developing dementia, particularly AD (34). The annual rates of progression from mild cognitive impairment to AD were estimated to range from 5% to 10%, with higher estimates in clinical versus community samples (34, 35). However, it is important to note that most patients with mild cognitive impairment or mild NCD do not necessarily progress to dementia, even after 10 years of follow-up (34). Primary goals in the treatment of neurodegenerative dementias should be to identify the disorders early and develop effective interventions to change the course of the disease.

One strategy to identify patients at risk of progressing from mild to major NCD is to stratify patients with mild cognitive impairment on the basis of a known marker for AD. With AD, several biomarkers can be identified in mild NCD to track the level of cognitive decline relative to disease progression. These biomarkers have been incorporated into the diagnostic criteria for AD and include cerebrospinal fluid (CSF) beta-amyloid, tau and phosphorylated tau, and PET imaging tracers that have high affinity for beta-amyloid (36–41).

Bertens et al. divided patients with mild cognitive impairment into two groups: those with amyloid beta 1–42 ($A\beta_{42}$) in CSF that was below 192 pg/ml (mild cognitive impairment with AD pathology) and patients with mild cognitive impairment and CSF $A\beta_{42}$ levels above 192 pg/ml (mild cognitive impairment–other [42]). Compared with the mild cognitive impairment–other group, the group with mild cognitive impairment with AD pathology showed significant differences on a variety of genetic markers (higher rates of apoplipoprotein ε4 allele carriers), neuroanatomic changes (lower hippocampal volumes, larger ventricles), and clinical variables (lower scores on tests of memory and executive function). These variables, as well as other common markers for determining risk for mild cognitive impairment and mild NCD progressing to AD, are outlined in Box 2.

Box 2: RISK FACTORS ASSOCIATED WITH MINOR NEUROCOGNITIVE DISORDERS[a]

Factors associated with developing minor neurocognitive disorders

- Lower scores on cognitive testing than controls including MMSE, ADAS-cog, and tests assessing memory and executive functioning (42)
- APOE ε4 genotype intermediate between controls and patients with AD (42, 43)
- CSF tau levels intermediate between controls and patients with AD (42)
- Hippocampal volumes approximately one standard deviation smaller than controls (43)
- Larger ventricular volumes than controls (42)
- Decreased FDG-PET uptake in bilateral angular gyrus, posterior cingular, and bilateral inferior temporal gyrus compared with controls (42)
- Major depression (44)

Risk factors for progression from minor neurocognitive disorders to AD

- Amnestic subtype of mild cognitive impairment (33)
- Smaller hippocampal volumes than controls (43, 45, 46)
- More APOE ε4 allele carriers; higher CSF tau levels; decreased FDG-PET uptake as above; smaller hippocampal volumes; larger ventricular volume; lower ADAS-cog, memory, and executive function scores than patients with mild cognitive impairment at lower risk of developing AD (42)
- Major depression (37, 47, 48)

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[a]Risk for developing AD was stratified in the Bertens et al. study by comparing patients with mild cognitive impairment who were classified as having AD pathology if their CSF Aβ1–42 level was below 192 pg/ml and higher risk to develop AD and mild cognitive impairment with lower risk of developing AD if their CSF Aβ1–42 level was below 192 pg/ml (see text [42]). Abbreviations: MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale–Cognitive; APOE ε4, apoliprotein E genotype and ε4 allele; CSF, cerebrospinal fluid; AD, Alzheimer's disease; FDG-PET uptake, fluoro-D-glucose positron emission tomography uptake normalized.

The wide variation in the rate at which patients with neurocognitive disorders progress, as discussed above, is due in part to risk factors that can be divided into two groups: nonmodifiable and modifiable. Nonmodifiable risk factors cannot be mitigated by diet or lifestyle changes and are part of an individual's potential for developing a neurocognitive disorder. For example, the rate of AD is in part determined by nonmodifiable risk factors such as older age, female gender, and apoliprotein E genotype and ε4 allele. Just as important, epidemiological studies have shown that some modifiable factors can increase or decrease the risk of developing dementia. In a recent review, Cheng described physical activity—specifically, aerobic exercise—as a modifiable behavior associated with a decreased the risk of developing dementia (7). Cheng pointed to the advantages of aerobic exercise in improving cerebrovascular and respiratory function; stimulating growth factors, particularly brain-derived neurotrophic factor; and decreasing oxidative stress and the inflammatory response (7). In fact, a number of longitudinal studies support an association of physical exercise with increased hippocampal (49), prefrontal, and cingulate cortex volumes (50); a decreased risk of dementia for older adults (51–54); and a decrease in gray matter volume of patients with mild cognitive impairment or dementia (55, 56).

Other modifiable behaviors and risk factors include lower socioeconomic (24) and educational attainment (57, 58), smoking, and higher homocysteine levels as a proxy for antioxidant status (higher homocysteine levels are an independent risk factor for cerebrovascular disease [23]). In the analysis by Beydoun et al., the most important modifiable factors associated with an increased risk of dementia were elevated plasma homocysteine levels and lower educational attainment (23). A modifiable behavior associated with a lower risk of dementia is increasing mental stimulation (59, 60), although mental stimulation has not been conclusively linked to changes in neuroanatomic structures and can be difficult to quantify (7). Understanding the modifiable behaviors and risk factors can inform policymakers as to where to allocate resources and guide research in treatments that may delay the onset of AD and other dementias from mild NCDs to major NCDs.

A *major NCD* is defined as a significant decline in cognitive abilities that is severe enough to interfere with the individual's everyday activities, such as paying bills, dressing, or preparing meals. The major NCDs are further defined as being probable or possible, classified on the basis of whether there is a behavioral disturbance, and rated for severity (mild, moderate, or severe).

The major NCDs are classified by diagnoses, including AD, frontotemporal lobar degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance or medication use, HIV infection, prion disease, Parkinson's disease, Huntington's disease, another medical condition, multiple etiologies, and

unspecified. The most common major NCDs are AD, vascular dementia (VaD), dementia with Lewy body (DLB), and frontotemporal lobar degeneration. There can be overlap in all of these dementias. For example, vascular disease is common in people over the age of 75 years (61) and therefore is often found in older patients with other NCDs. Determining the contribution of cerebrovascular disease to the dementia symptoms of older patients with other NCDs can be difficult (62). The diagnostic criteria for the major NCDs are outlined in Table 1.

AD is the most common neurodegenerative dementia, and criteria have been established by the National Institute on Aging–Alzheimer's Association work group on diagnostic guidelines for Alzheimer's disease (63). The diagnosis of AD is made with patients who have cognitive difficulties that (a) interfere with usual activities; (b) represent a decline from a previous level of functioning; (c) are not due to delirium; and (d) demonstrate impairment documented by bedside testing or neuropsychological testing in two of the following areas: memory, reasoning, visuospatial ability, language, personality, and behavior.

The work group outlines two types of presentations. The amnestic presentation is the most common and features deficiencies primarily in learning and recall of recently learned information. This should be accompanied by deficiencies in at least one other cognitive domain (impaired reasoning and handling of complex tasks, impaired language functions, or impaired visuospatial ability). Patients diagnosed as having the nonamnestic presentation do not have prominent memory problems but do have one of the following as the primary cognitive deficit: language (word finding), visuospatial ability (inability to recognize faces or common objects), or executive dysfunction (impaired reasoning, judgment, and problem solving).

AD is further categorized as either possible or probable. *Possible* is reserved for patients who have an atypical course (e.g., meets core criteria but experiences a sudden onset of symptoms) or who have a mixed presentation (e.g., evidence of significant cerebrovascular disease). Although the biomarkers discussed above are not included in the core diagnostic criteria, they can be considered further evidence of the pathophysiological process of AD and help confirm the diagnosis. The identification of genetic mutations, including presenilin 1 and 2 and amyloid beta protein, can also be used to increase the certainty of the diagnosis.

Vascular disease causes approximately 15% of the cases of dementia, although, as stated above, many dementias have vascular components, particularly in older patients (62). In fact, pure VaD is relatively rare. In an autopsy study of over 1,100 patients, only 10.8% of patients had a diagnosis of only VaD, and these patients had multiple vascular risk factors (e.g., 85%–95% had histories of diabetes or morphologic signs of hypertension, 65% had myocardial infarction or cardiac decompensation, and 75% had a history of stroke [67). The incidence of pure VaD decreased for older patients (age 60 to 90), in that older patients were more likely to have concomitant age-related neurodegenerative disorders such as AD.

The widely accepted VaD criteria set forth by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (64) have been described as having high specificity, albeit low sensitivity (62). These criteria require that (a) the patient demonstrate a cognitive decline from a previously higher level of functioning manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis); (b) deficits be severe enough to interfere with activities of daily living and not be due to physical effects of stroke alone; (c) there be evidence of cerebrovascular disease, including the presence of focal signs on neurologic examination (e.g., hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria) and neuroimaging consistent with stroke or significant cerebrovascular disease; and (d) onset occur within three months of a stroke or with abrupt deterioration or stepwise progression of cognitive deficits (64, 68).

The risk factors for developing dementia after a stroke include low education attainment, female gender, vascular risk factors (e.g., hypertension, diabetes, smoking, and obesity), stroke location, and global and medial temporal atrophy on neuroimaging (69). Some genes are related to cardiovascular disease, such as

the cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy gene (70), but individuals with this gene represent a rare genotype that does not provide much insight into the nature of VaD (62). Generally, genetic studies have not identified specific mutations that could help with diagnosis or treatment of VaD (62).

The distinction between definite, probable, and possible VaD is primarily clinical. A probable VaD diagnosis is given to patients with neurological signs of cerebrovascular disease, including early gait disturbance, falls, urinary symptoms, and pseudobulbar palsy. For the VaD to be classified as definite, there should be temporal evidence of cerebrovascular disease in relation to the dementia, with the absence of neurofibrillary tangles and neuritic plaques exceeding those expected for the person's age.

If combined with Parkinson's disease dementia, DLB is the second most common degenerative dementia for patients over the age of 65 years (65). Some have argued that given their common pathology and clinical presentations, these two dementias should be viewed along a continuum rather than as discrete disorders (65). In neurological disorders such as Parkinson's disease, dementia is common (71), and early detection of cognitive disorders can provide clinicians with a more complete picture of the challenges affecting the individual.

The core diagnostic criteria for DLB are (a) a progressive decline in cognitive function that interferes with normal functioning, causing prominent memory impairment and deficits in tests of attention, executive function, and visuospatial ability, and (b) fluctuating attention, visual hallucinations that are typically well formed and detailed, and parkinsonian motor features (two criteria for probable and one for possible DLB [72).

In addition, McKeith et al. (72) cited "suggestive features" that can support the diagnosis of probable DLB if core diagnostic criteria are present: rapid eye movement sleep behavior disorder, severe neuroleptic sensitivity, and low dopamine transporter uptake in basal ganglia demonstrated by single-photon emission computed tomography (SPECT) or PET imaging. Finally, some features do not have any diagnostic specificity but can support the diagnosis: repeated falls and syncope; transient, unexplained loss of consciousness; severe autonomic dysfunction; hallucinations in other modalities; systematized delusions; depression; relative preservation of medial temporal lobe structures on a computed tomography or magnetic resonance imaging scan; generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity; abnormal (low uptake) on myocardial scintigraphy; and prominent slow-wave activity on electroencephalogram with temporal lobe transient sharp waves (72).

In movement disorders such as Parkinson's disease, cognitive testing is complicated by the fact that the motor symptoms of some diseases (e.g., bradykinesia in Parkinson's disease) may impair a patient's ability to complete paper-and-pencil cognitive tests. For some movement disorders, specific cognitive tests have been developed with this limitation in mind, such as the Parkinson's Disease–Cognitive Functional Rating Scale (73). This brief 12-item scale assesses functional abnormalities associated with cognitive impairment as well as demonstrated impairments in instrumental activities of daily living of patients with Parkinson's disease who do not have dementia. Note that instrumental activities of daily living are not considered necessary for basic functioning but do allow an individual to live independently. Examples of such activities include managing a checkbook, taking medication as prescribed, and doing daily housework. They can be contrasted with the six basic activities of daily living: eating, bathing, dressing, toileting, transferring (walking), and grooming.

Burn et al. described a wish list for a neuropsychological battery in Parkinson's disease that includes tests sensitive to early cognitive decline, tests that could determine mild cognitive impairment, tests with sensitivity to worsening cognitive impairment over time, and a demonstration of the relationship of cognitive tests for Parkinson's disease biomarkers (37). They pointed out that further research linking the

quantification of biomarkers such as CSF α-synuclein (74) to cognitive status in Parkinson's disease is needed. PET tau and α-synuclein can potentially serve to inform clinicians of disease progression and determine the association of disease progression and cognitive status in Parkinson's disease (37, 74, 75).

Other markers are more sensitive to cognitive decline. In one study, dopamine transporter uptake and perfusion SPECT were used in de novo, drug-naive Parkinson's disease patients to predict cognitive decline over four years (76). Ravina et al. followed Parkinson's disease patients over five and one-half years and found that baseline striatal dopamine transporter binding was predictive of cognitive decline as well as motor-related disability, falling, postural instability, psychosis, and depression (77).

Frontotemporal dementia (FTD) represents a group of disorders characterized by selective degeneration of the frontal and temporal cortices and progressive deficits in behavior, executive dysfunction, or language (66). FTD is the fourth leading type of dementia (behind AD, VaD, and DLB) and is distinguished by the fact that it is the most common dementia among patients with early-onset disease, with 70% of patients experiencing onset before the age of 65 years (66). FTD is also associated with behavioral changes that can make it difficult to distinguish from psychiatric disorders.

There are three clinical variants of FTD. The *behavioral* variant is associated with early behavioral (personality changes, disinhibition, and apathy) and executive deficits. The *nonfluent* variant is associated with primary progressive aphasia and deficits in language production, object naming, syntax, or word comprehension. Finally, the *semantic* variant is characterized by primary progressive aphasia with progressive deficits in knowledge and naming (66). As noted in Bang et al. (66), primary progressive aphasia can be associated with AD, and reconsideration of a diagnosis of FTD should occur if prominent visuospatial impairment or episodic or visual memory impairments are present. Also, patients with significant behavioral disturbances early in the disease process may be more appropriately diagnosed as having a DLB behavioral variant.

Neuroimaging shows atrophy of the frontal and temporal lobes. Evidence on computed tomography or magnetic resonance imaging scans of atrophy of the gray matter in the orbital frontal, insular, and anterior cingulate is even more specific for FTD (78). Approximately 40% of patients with FTD have a family history of dementia (79). Mutations in the *C9orf72*, *MAPT,* and *GRN* genes account for about 60% of all cases of inherited FTD (80).

Cognition and Psychiatric Disorders

Much of the dementia research has focused on identifying AD and neurodegenerative disorders early in the disease process, yet other researchers have pointed out the importance of identifying cognitive disorders early in the course of psychiatric disorders. Cognitive dysfunction may be part of a psychiatric disorder and can be a major contributor to disability. For example, in patients with schizophrenia, cognitive impairment can predict the course of the disorder and be independent of the psychotic symptoms (81). Others argue that cognitive impairment is not a core symptom of schizophrenia, although it could be used as specifier of the disorder (82).

However, Keefe and Fenton argued that cognitive deficits in schizophrenia determine functional outcome more than do core diagnostic criteria, such as positive and negative symptoms, and that these deficits distinguish patients with schizophrenia from those with affective disorders (81). The investigators also asserted that the diagnostic criteria for schizophrenia should include a specific criterion of "a level of cognitive functioning suggesting a consistent severe impairment and/or a significant decline from premorbid levels considering the patient's educational, familial, and socioeconomic background" (81). Identifying and targeting the cognitive symptoms early in the course of schizophrenia may therefore have an impact on an individual's long-term course.

Major depression is also associated with a number of cognitive deficits during the depressive episode, including deficits in attention, memory, psychomotor speed, processing speed, and executive function. These deficits are particularly noted among patients with an earlier onset to their depression and a longer duration of the depressive episode (83) and in tests of executive function, processing speed, attention, and category fluency (84). In many (84–87) but not all (88) longitudinal studies of patients with mood disorders, cognitive deficits (i.e., attention and processing speed) do not normalize even after sustained remission. Residual cognitive symptoms have also been associated with a failure to respond to pharmacotherapy (89).

Neuroanatomic changes that could help explain these deficits have been demonstrated in both unipolar and bipolar patients. These changes are to structures important in both mood and cognitive functioning, including the orbitofrontal cortex, amygdala, and hippocampus (90–93). Other research has pointed to the overlap in symptoms found in depressed patients and patients with neurodegenerative disorders such as reduced neurogenesis, increased apoptosis, and immune-inflammatory responses (94, 95). Major depression may also affect the progression of cognitive dysfunction to dementia. Depression may significantly increase the likelihood of a person progressing from no cognitive dysfunction to mild cognitive impairment (44) and from mild cognitive impairment to AD (47, 48).

Conclusions

Understanding the role of neuroanatomic structures and neural networks with normal aging is essential to developing strategies to optimize cognitive function with aging. These strategies could include nonpharmacological interventions (i.e., diet, exercise, and mental training) as well as public health policies to improve socioeconomic status and educational attainment. Longitudinal studies support the role of interventions in preserving structures important in cognition, such as the hippocampus and prefrontal cortex. Future research, particularly randomized clinical trials, are needed to further refine and develop these interventions.

Neurodegenerative disorders are an important global health concern, with approximately 115 million people worldwide expected to receive a diagnosis of dementia by the year 2050. The *DSM-5* has provided a framework for understanding the continuum of mild cognitive impairment to AD. The *DSM-5* criteria eliminate the requirement of a memory impairment in the diagnosis of a mild or major NCD and introduce new elements of cognitive function, including complex attention and social cognition (27). This approach allows for a broader understanding of cognitive decline and focuses on identifying individuals early in the dementing process, potentially allowing for the provision of effective early interventions that could alter the course of the disorder. Identifying patients early in the course of mild NCD will also facilitate research into strategies that may alter the trajectory of the cognitive decline. Biomarkers will increasingly be used to target vulnerable populations, and research should focus on developing appropriate interventions and strategies to improve long-term outcomes for vulnerable individuals.

Recognizing cognitive disorders in patients with psychiatric disorders is also important in developing an accurate assessment of the patient's functional level and long-term prognosis. This is also the first step toward developing pharmacological and nonpharmacological treatments targeting cognitive dysfunction.

Footnotes

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Figures and Tables

TABLE 1.

Diagnostic Criteria for the Most Common Major Neurocognitive Disorders[a]

Characteristic	Probable Alzheimer's dementia (63)	Vascular dementia (62, 64)	Dementia with Lewy body (43, 65)	Frontotemporal dementia (66)
Clinical				
Onset	Insidious	May be abrupt onset and have a stepwise decline	Progressive cognitive decline and dementia occurs before or concurrently with parkinsonism	Insidious and gradual, often before age 65 years
Impairment	With amnestic presentation, impairment in learning and recall and at least one other cognitive domain; with nonamnestic presentation, impairment in language and visuospatial or executive function with deficits in at least one other cognitive domain[b]	Impairment in memory and two other cognitive domains;[c] deficits severe enough to interfere with ADLs and not due simply to the effects of a stroke or CVA	Fluctuations in alertness and attention; visual hallucinations; parkinsonian motor symptoms[d]	Early behavioral and executive deficits[e] (behavioral variant); primary progressive aphasia, with deficits in speech, grammar, and word output (nonfluent variant) or with deficits in knowledge and naming (semantic variant)
Supporting data or biomarkers[f]	Low CSF $A\beta_{42}$; positive PET amyloid imaging; elevated CSF tau; decreased FDG uptake in the temporoparietal cortex; atrophy of the medial, basal, and lateral temporal lobes and medial parietal cortex on MRI	Evidence of CVA on neuroimaging in temporal proximity to the memory loss (within three months); presence of focal signs on neurologic examination consistent with a	REM sleep behavior disorder; severe neuroleptic sensitivity; low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET	Neuroimaging with predominant frontal or temporal atrophy; atrophy in the frontoinsular region with hypoperfusion and hypometabolism of these regions on FDG-PET

[a]The core criteria for all disorders require a clear change in cognition from baseline. The exclusionary criteria are also similar, requiring that the cognitive changes are not better accounted for by another medical disorder, such as delirium, psychosis, primary aphasia, or another neurocognitive disorder (e.g., AD is unlikely to be diagnosed in the context of severe cerebrovascular disease). Abbreviations used in the table are as follows: CSF, cerebrospinal fluid; $A\beta_{42}$, amyloid-beta 42; PET, positron emission tomography; FDG, fluorodeoxyglucose; ADLs, activities of daily living; CVA, cerebrovascular accident; MRI, magnetic resonance imaging; REM, rapid eye movement; SPECT, single-photon emission computed tomography.

[b]Cognitive domains include impaired ability to acquire and remember new information, impaired reasoning and handling of complex tasks, impaired visuospatial abilities, and impaired language functions.
[c]Cognitive domains include orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis.
[d]Parkinsonian symptoms include bradykinesia, difficulty walking, and rigidity.
[e]Executive deficits include personality changes, disinhibition, and apathy.
[f]Biomarkers are generally not considered in the diagnosis but can increase the certainty of a diagnosis if the clinical criteria are met.
[g]Focal neurological signs could include hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria