# Neurobehavioral Assessment

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## ABSTRACT

**Purpose of Review:** This article presents a multidimensional, integrative approach to clinical assessment and management of neurobehavioral disorders.

**Recent Findings:** Behavioral neurology and neuropsychiatry has grown as a subspecialty along with increased recognition of two common brain disorders: dementia and traumatic brain injury. Alzheimer disease is a highly prevalent dementia and a prototypical memory disorder, which has led to a primary focus on *cognitive* screening and assessment. By contrast, recent attention concerning possible long-term sequelae of repetitive traumatic brain injury has emphasized aberrant *behavior* (eg, depression, impulsivity, aggression). Clinical phenotyping across cognitive and behavioral dimensions, in conjunction with advancements in structural and functional neuroimaging, brain electrophysiologic techniques, and molecular genetics, is essential to improve diagnostic precision and therapeutic targeting along the spectrum of CNS disorders.

**Summary:** All neurologists benefit from honing their clinical skills in neurobehavioral assessment. A systematic approach to cognitive and behavioral assessment increases differential diagnostic specificity, helps focus appropriate therapeutic interventions, and improves the quality of life for patients and their families. This article highlights practical approaches to neurobehavioral assessment in support of differential diagnosis and therapeutic monitoring in general neurology practice.


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## INTRODUCTION

The seeds of contemporary cognitive and behavioral neurology arose about a half-century ago in the fertile soil of Boston led by Norman Geschwind. This renaissance in behavioral neurology advanced work from the middle to late 19th century, first in aphasiology (Broca and Wernicke) and later in dementia (ie, Pick and Alzheimer). The necessity of a detailed neurologic and neurobehavioral examination accrued from a forced dependence on inferential data in the absence of direct visualization of the brain. Over the last several decades, brain imaging has revolutionized the daily practice of neurology and is on the cusp of advancing structural, functional, and molecular diagnostic tools that will marry clinical diagnostic assessment with objective biomarker data in dementia, traumatic brain injury, and other neuropsychiatric disorders. In current neurology practice, cognitive, functional, and behavioral assessment is far from standardized. In a tertiary memory disorder clinical practice setting, there is much greater diagnostic yield from obtaining a detailed and comprehensive history than from ordering a battery of esoteric tests. Accordingly, this article focuses on the basic elements of a comprehensive neurobehavioral assessment that are amenable to general neurology practice settings.

## HISTORY

The primary focus of clinical neurobehavioral assessment is a change from a previous level of functioning, which includes cognitive and functional abilities,

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**KEY POINTS**

- The primary focus of clinical neurobehavioral assessment is a change from a previous level of functioning, which includes cognitive and functional abilities, mood, emotional responsiveness, and social behavior.
- A marked discrepancy between a patient's and informant's portrayal of clinical cognitive changes sets the stage for clinical hypothesis testing based on the degree of agreement with formal cognitive testing.
- Impaired awareness of cognitive deficits is difficult to measure clinically but has important implications for how challenging complying with appropriate restrictions or supervision for activities, such as driving and managing finances, can be for the patient.

mood, emotional responsiveness, and social behavior. The clinical history is often the most critical data source for a neurobehavioral evaluation and typically requires an informant who knows the patient well in order to ensure an accurate rendering. Knowing the reason for the evaluation helps determine strategy regarding how to engage the patient and informant. For example, a patient who is unaware that he or she is being evaluated for a memory problem needs to be interviewed (and debriefed) differently from one who is concerned about his or her own memory functioning. In the former case, it is often helpful to speak with the informant separately or, alternatively, allow the informant an opportunity to discretely communicate sensitive information. Although informants generally provide a reliable history, at times their frustration and distress may lead to their overstating symptom severity in patients. In such circumstances it is often productive to focus attention on helping them cope with caregiving demands. Rarely, informants may have nefarious financial motives for exaggerating clinical symptoms and associated disability in order to obtain guardianship. Conversely, patients with either depression or morbid anxiety may be hypercritical of their self-perceived cognitive status and exaggerate cognitive changes.

A marked discrepancy between a patient's and informant's portrayal of clinical cognitive changes sets the stage for clinical hypothesis testing based on the degree of agreement with formal cognitive testing. For example, if an informant's report of the patient's deficits is supported by cognitive testing and the deficits reported are greater than the patient's self-report, it is reasonable to infer that the patient has impaired awareness of his or her deficits. This finding is suggestive of a neurodegenerative disorder such as Alzheimer disease or traumatic brain injury, where deficit awareness is often compromised.[1] Impaired awareness of cognitive deficits is difficult to measure clinically but has important implications for a patient's ability to comply with appropriate restrictions on driving or accept supervision for activities such as managing finances. Conversely, a patient may report a greater cognitive symptom burden than a reliable informant, with cognitive testing aligning more with the latter's assessment. This profile is more likely to be associated with a mood disturbance, anxiety symptoms, or elevated level of stress. Although the term ''worried well'' is sometimes used in this context, in certain cases it may be appropriate to pursue a more in-depth neuropsychological evaluation to ensure that early signs of a neurocognitive disorder are not being missed. This is particularly true in highly educated individuals, where ''normal'' performance on standard cognitive screening tests may be misleading.

Other historical data may help elaborate a differential diagnosis, including temporal onset and course, hereditary factors, and comorbid medical conditions (**Table 1-1**). A positive family history deserves close attention, particularly if autosomal dominant inheritance is suspected. Within a given family, a wide range of phenotypic variability may be seen with autosomal dominant mutations. For example, an autosomal dominant mutation on chromosome 9 associated with the expansion of a hexanucleotide repeat (chromosome 9 open reading frame 72 [c9orf72]) is the most common cause of both familial ALS and familial frontotemporal degeneration.[2] Affected members within a family can exhibit clinical features on a spectrum between these two disorders. Sleep disturbances such as insomnia, restless leg syndrome, and sleep apnea are common comorbidities in neurobehavioral disorders, and rapid eye movement (REM) behavior disorder is a hallmark of synucleinopathies.[3]

**TABLE 1-1 Diagnostic Elements in the Clinical History**

| |
|---|
| ▶ **Initial/Concomitant Symptoms** |
| Cognitive: Memory, language, visuospatial, executive (eg, judgment) |
| Functional: Work, managing finances, driving, shopping, household chores |
| Neuropsychiatric: Apathy, depression, anxiety, psychosis, impulsivity, disinhibition |
| Motor: Tremor, rigidity, incoordination, balance difficulty, dysarthria, weakness |
| ▶ **Temporal** |
| Onset: Abrupt, subacute, insidious |
| Course: Static, progressive, fluctuating, improving |
| ▶ **Traumatic** |
| Altered consciousness (eg, dazed, confused, groggy, ''saw stars'') |
| Loss of consciousness (duration) |
| Amnesia (retrograde/anterograde) |
| Neurologic sequelae (eg, headache, nausea, vertigo, vision change, sleep alteration) |
| ▶ **Individual** |
| Age, gender, cultural background |
| Educational level, learning disability, premorbid personality |
| Social circumstances, financial resources, occupational activities |
| ▶ **Genetic** |
| Family history suggesting autosomal dominant inheritance |
| Familial cases suggesting polymorphism association (eg, apolipoprotein E4 [*APOE*] in Alzheimer disease) |
| ▶ **General** |
| Medical conditions (eg, hypothyroidism, vitamin deficiency, peripheral vascular disease) |
| Neurologic conditions (eg, transient ischemic attack, stroke, seizure, head trauma) |
| Sleep disturbances (eg, sleep apnea, insomnia, sleep-associated movement disorder) |

**KEY POINTS**

- Documenting a careful history of head injuries and their associated acute (eg, alteration or loss of consciousness) and chronic (eg, headaches, vertigo) accompaniments will likely play an increasing role in understanding complex relationships between mechanical brain injury and neurodegenerative disorders, such as frontotemporal degeneration and ALS.
- A hallmark of neurobehavioral assessment is its multidimensional and integrative nature.

A history of mild repetitive traumatic brain injury or concussions draws scrutiny as a risk factor for a later-developing dementia syndrome: chronic traumatic encephalopathy.[4] Head injuries associated with falls, automobile or bicycle accidents, recreational activities (eg, skiing, sledding), military activities, sports-related injuries, and other home- or work-related accidents may cause or exacerbate neurologic disorders such as headaches or seizures. Documenting a careful history of head injuries and their associated acute (eg, alteration or loss of consciousness) and chronic (eg, headaches, vertigo) accompaniments will likely play an increasing role in understanding complex relationships between mechanical brain injury and neurodegenerative disorders, such as frontotemporal degeneration and ALS.

## CLINICAL ASSESSMENT

A hallmark of neurobehavioral assessment is its multidimensional and integrative nature. Among dementias, the high prevalence of Alzheimer disease and its cardinal manifestations of short-term memory and other cognitive disturbances weight clinical assessment heavily toward

cognitive symptoms. However, recently revised diagnostic criteria for Alzheimer disease now recognize noncognitive symptoms such as depression and apathy as primary disease manifestations,[5] and other neuropsychiatric symptoms are often the most prominent changes in disorders such as dementia with Lewy bodies and frontotemporal degeneration. Moreover, recent dementia quality measures developed by the American Academy of Neurology (AAN) and other stakeholders highlight a broad range of clinical parameters that support comprehensive care to improve clinical outcomes (**Table 1-2**).[6]

Among these 10 quality measures, which are used as part of Physician Quality Reporting System (PQRS) and Meaningful Use (MU) requirements, numbers 2 to 6 under Evaluation and Treatment Strategies emphasize the multidimensional aspects of care. In addition to the standard cognitive assessment, there is also the provision for neuropsychiatric and functional assessments, as well as screening for depression and managing neuropsychiatric disturbances. Moreover, other AAN quality measures for Parkinson disease[7] and ALS[8] include provisions for cognitive and psychiatric symptom assessment. The former also highlights assessing sleep-wake disturbances such as REM behavior disorder and daytime somnolence as common associated clinical manifestations.

## Cognitive Assessment

The examiner can evaluate cognitive symptoms both informally through a clinical interview and objectively by assessment with neurocognitive testing. The Ascertain Dementia 8 (AD8), an 8-item measure of informant-reported changes in cognitive functioning, is a well-validated and widely used historical cognitive screening instrument (**Supplemental Digital Content 1-1**, *links.lww.com/CONT/A140*).[9]

The AD8 was derived from semistructured interviews involving a large research data set and includes historical features that were most strongly

**TABLE 1-2 Dementia Quality Measures from the American Academy of Neurology[a]**

| |
|---|
| ▶ **Evaluation and Treatment Strategies** |
| Measure 1: Staging of Dementia |
| Measure 2: Cognitive Assessment |
| Measure 3: Functional Status Assessment |
| Measure 4: Neuropsychiatric Symptom Assessment |
| Measure 5: Management of Neuropsychiatric Symptoms |
| Measure 6: Screening for Depressive Symptoms |
| ▶ **Safety Issues** |
| Measure 7: Counseling Regarding Safety Concerns |
| Measure 8: Counseling Regarding Risks of Driving |
| ▶ **Patient-Centered Care Strategies** |
| Measure 9: Palliative Care Counseling and Advance Care Planning |
| Measure 10: Caregiver Education and Support |

[a] Detailed information on these measures can be found at *www.aan.com/uploadedFiles/Website_Library_Assets/Documents/3.Practice_Management/2.Quality_Improvement/1.Quality_Measures/1.All_Measures/Dementia%20measure%20set%202014%20transition.pdf*.

associated with Alzheimer disease. An informant typically completes the screening questions, although patients can self-report if no informant is available.[10] The AD8 content includes memory, orientation, and other faculties, including executive, motivation, praxis, and functional ability (eg, managing money). A score of 2 or higher (out of 8 total items) on the AD8 is highly predictive of dementia (sensitivity 0.85, specificity 0.86). Inquiring about the patient's ability to manage finances deserves special attention because financial capacity is often affected early in the course of mild cognitive impairment (MCI), Alzheimer disease, and other forms of dementia, and the potential consequences of poor financial management can be devastating.[11]

Performing cognitive testing in clinical practice is a challenge that varies in proportion to the length and complexity of required testing and available testing resources. The standard single-system neurologic examination generally covers level of arousal, attention, orientation, speech, language, recent and remote memory, and general fund of knowledge and is useful only for general screening. These data should also be supplemented by observations regarding affect (eg, blunted, expansive, pseudobulbar), mood state (eg, hypomanic, sad, anxious), motivation (eg, apathetic, disinhibited), distractibility, fidgetiness, restlessness, perseveration, obsessive thinking, paranoid or psychotic thinking, impulsivity, or other behavioral phenomena noted to be present. Beyond this, clinical cognitive assessment is used for a variety of purposes, ranging from screening for possible dementia using tests such as the Mini-Cog,[12] to performing a comprehensive neuropsychological evaluation. The latter typically involves several hours of testing using age- and education-adjusted normative data, yielding a quantitative psychometric assessment. Behavior and psychological rating scales are also often included to evaluate for depression, anxiety, and effort (eg, malingering).

All screening cognitive tests have limitations and require specific knowledge regarding test administration and scoring in order to be valid. More detailed and sophisticated cognitive tests generally require more training of the examiner. A screening test such as the Mini-Cog may yield a negative screen based on the patient recalling all three words, yet indicate a potential problem in a patient with, for example, Parkinson disease, who may have difficulty drawing a clock. When administering cognitive tests, it is crucial to document any potential confounds to the validity of the test, such as hearing or vision problems, motor dysfunction, language barrier to understanding instructions, and psychological factors such as effort, motivation, depression, and anxiety.

A fundamental limitation regarding clinical cognitive testing is that it is generally not reimbursable. One exception is to administer a battery of cognitive tests and bill as a separate neurobehavioral status examination (*Current Procedural Terminology* [*CPT*] code 96116). This approach requires a physician or advanced practice practitioner to conduct most of the testing, which may not be feasible in many clinical practice settings. Another alternative is to have an office staff person supervise testing the subject in a computer-administered test battery such as CNS Vital Signs.[13] This assessment consists of seven neuropsychological tests that yield five domain scores: memory, psychomotor speed, reaction time, cognitive flexibility, and complex attention, with scaled percentile performance indices generated automatically. While this approach collects data on a battery of tests with minimal supervision, lack of training qualifications and clinical diagnostic standards for data interpretation currently limit its utility. Computer-based test materials offer the prospect of improving

**KEY POINTS**

- Inquiring about the patient's ability to manage finances deserves special attention because financial capacity is often affected early in the course of mild cognitive impairment, Alzheimer disease, and other forms of dementia, and the potential consequences can be devastating.
- When administering cognitive tests, it is crucial to document any potential confounds to the validity of the test, such as hearing or vision problems, motor dysfunction, language barrier to understanding instructions, and psychological factors such as effort, motivation, depression, and anxiety.

**KEY POINTS**

- The Montreal Cognitive Assessment (MoCA) test is a comprehensive cognitive screening test with multiple alternate forms and an expanding normative database.
- The MoCA test represents a distillation of a neurobehavioral status examination battery and requires specific training in test administration and scoring.

standardization and scoring of clinical cognitive testing, which, combined with the establishment of robust training and application criteria, may eventually support higher levels of reimbursement.

The prevailing standard for cognitive assessment in neurologic practice is to administer brief cognitive tests such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA).[14–16] The primary aim of such testing is to evaluate cognitive symptoms reported to be present in daily activities, as opposed to screening for cognitive impairment.[17] Although the MMSE is the historical gold standard for clinical cognitive assessment, it was copyright protected more than 25 years after its initial publication and now requires payment on a per-use basis (*www.parinc.com*).

Although the MMSE is fairly well suited to screening for and tracking Alzheimer disease over time, it is not particularly useful for identifying MCI or non–Alzheimer dementias. However, in depressed or disinhibited patients, the content of the sentence they compose (eg, "I am depressed" or "I love you") may, at times, provide useful diagnostic data.

An extended 50-point version of the MMSE, the Mini-Mental State Examination Extended (MMX), was developed, which requires minimal additional time, yields standard MMSE scores, and is sensitive to MCI and non–Alzheimer dementias (**Table 1-3**).[18] The additional 20 points of the MMX test are derived from a combination of alternate scoring criteria and some brief additions **(Table 1-4)**. Alternate scoring involves scoring the sum of serial 7s subtraction and WORLD backward scores (5 additional points, 10 points total) and using a 4-point scoring scheme for the intersecting pentagon figure (3 additional points, 4 points total). Additional items include adding *pen clip* or *pen holder* and *watchband* or *watch strap* to naming (2 additional points), reproducing the intersecting pentagon figure from memory (4 additional points), and long-delayed spontaneous recall of the three words with multiple-choice recognition for any that are not recalled (6 additional points). In the MMX delayed recall/recognition test, 2 points are given for each word that is recalled, and for those that are not, 1 point is given if correctly identified from among three choices. This test may also provide useful qualitative information to help discriminate Alzheimer disease and amnestic MCI from other types of cognitive impairment, as these patients also tend to do poorly on multiple-choice recognition testing.

The MoCA is a comprehensive cognitive screening test with multiple alternate forms and an expanding normative database (*mocatest.org*). The MoCA is sensitive to detecting cognitive disturbances in Parkinson disease and MCI.[19,20] Studies in community samples suggest that it may have lower specificity in less-educated subjects (ie, high false-positive rates), a trade-off to being sensitive to early cognitive impairment. A dementia cutoff score lower than 26 may need to be used in selected clinical populations.[21] The five-word recall test is more challenging than the three-word test on the MMSE and includes qualitative measures for cued recall and multiple-choice recognition. The MoCA represents a distillation of a neurobehavioral status examination battery and requires specific training in test administration and scoring. Untrained examiners commonly fail to instruct the test subject to *remember* the five-word list after repeating the list over two trials, as this script is not printed on the test form. This omission invalidates the test as it was designed and may contribute to false-positive results.

The St. Louis University Mental Status (SLUMS) examination is a 30-point cognitive screening test that includes a

**TABLE 1-3 Brief Cognitive Screening Instruments**

| Test | Format and Content | Comments |
|---|---|---|
| Mini-Mental State Examination (MMSE) | 30-point scale<br>Orientation, memory, attention, praxis, language, constructions | Old standard assessment for Alzheimer disease, not sensitive to mild cognitive impairment and non–Alzheimer disease disorders, withdrawn from public domain |
| Mini-Mental State Examination Extended (MMX) | 50-point scale (MMSE with an additional 20 points)<br>Constructions, language, verbal/nonverbal memory | Yields standard MMSE with little effort, sensitive to mild cognitive impairment and non–Alzheimer dementia, MMSE forms are copyright protected, requiring pay per use |
| Montreal Cognitive Assessment (MoCA) | 30-point scale<br>Memory, constructions, executive, visuospatial, language | Sensitive to mild cognitive impairment and non–Alzheimer dementia, alternate forms; requires training; may see false-positive results in subjects with less than a college education |
| St. Louis University Mental Status (SLUMS) examination | 30-point scale<br>Memory attention, language, praxis, abstraction, calculations | Word list and paragraph recall, emphasizes practical cognitive functions, belongs to the public domain, alternative to MMSE |

five-word memory list and story recall, as well as fluency, orientation, clock drawing, and other executive cognitive tasks.[22] The SLUMS has been shown to have similar characteristics to the MoCA with respect to identifying MCI and dementia.[23] The SLUMS includes a word-based arithmetic problem and paragraph

**TABLE 1-4 Mini-Mental State Examination (MMSE) Versus the Mini-Mental State Examination Extended (MMX)**

| | MMSE (30 Points) | MMX (50 Points) | Added Points |
|---|---|---|---|
| **Alternate scoring** | | | |
| Mental control | WORLD backward *or* serial 7s subtraction (5 points) | WORLD backward *and* serial 7s subtraction (10 points) | +5 |
| Figure copy | 0–1 Point | 0–4 Points[a] | +3 |
| **Additions** | | | |
| Naming | Pen (1 point) | Pen *clip (holder)* (1 point) | +2 |
| | Watch (1 point) | Watch*band (strap)* (1 point) | |
| Figure recall | NA | 0–4 points[a] | +4 |
| Three-word delayed recall/recognition | NA | Spontaneous recall (2 points each)<br>Multiple choice[b] (1 point each) | +6 |

NA = not applicable.
[a] One point for each pentagon, one point if there is any overlap, one point if the overlap is four-sided.
[b] Used only for words not recalled (eg, carrot [choices: celery/carrot/cabbage], robin [choices: robin/sparrow/bluejay], hammer [choices: wrench/screwdriver/hammer]).

**KEY POINT**

- Single-domain cognitive tests may be useful as adjuncts to cognitive screening or as part of a more comprehensive neurocognitive evaluation.



recall test that may better reflect real-world functioning (ie, ecological validity).

Single-domain cognitive tests may be useful as adjuncts to cognitive screening or as part of a more comprehensive neurocognitive evaluation. Clinical tests of attention, memory, language, visuoperceptual, and visuomotor (eg, figure copy) function are generally sensitive to corroborating reported deficits in these domains. By contrast, executive dysfunction, which encompasses a wide array of cognitive/behavioral/motor processes such as working memory, planning, sequencing, and abstract conceptual thinking, may be more challenging to demonstrate. Fluency testing is a combined language and executive task that involves asking subjects to name as many items from a given class or category as they can in 1 minute using stimuli such as animals (semantic) or a letter (S or D). Semantic fluency is often selectively impaired in Alzheimer disease or the semantic variant of primary progressive aphasia, whereas selective impairment in letter fluency is more suggestive of frontal subcortical network dysfunction as seen in frontotemporal degeneration or dementia with Lewy bodies.[24,25] For either test, unwitting repetitions provide a backdoor view of memory function, and strategies the patient employs in word generation may paint a portrait of other higher cognitive functions as well.

Short forms of the Boston Naming Test are also useful for aphasia screening.[26,27] Confrontational naming is usually markedly impaired in the semantic variant of primary progressive aphasia, where errors typically involve semantic relatedness (eg, saying airplane for helicopter). The Northwestern Naming Battery is a more recently developed naming assessment that includes both verbs and nouns, assesses both production and comprehension, and has been developed for patients both poststroke and with primary progressive aphasia.[28] A brief summary of commonly used single-domain cognitive tests is shown in **Table 1-5**.

## Functional Assessment

The assessment of functional abilities is indirectly related to specific cognitive

**TABLE 1-5 Single-Domain Cognitive Tests**

| Domain | Test Description (approximate normal range) |
|---|---|
| Working memory | Digit span forward (7 ± 2) |
| Divided attention | Digit span backward (6 ± 2) |
| | Months in reverse order (15–20 sec) |
| Orientation | Time (date, month, season, year) |
| | Location (building, floor, city, state) |
| Fluency | Category: number of animals named in 1 min (18 ± 6) |
| | Letter: number of S words named in 1 min (12 ± 2) |
| Language (naming) | 15-item Boston Naming Test |
| Constructions | Copy cube or intersecting pentagons |
| Visuomotor | Clock drawing (including drawing the hands as 10 minutes after 11) |
| Executive | Trails B (letter-number tracing), age-dependent |
| Verbal memory | 3–5 word list (spontaneous/cued recall) |

domains and reflects the collective practical impact of cognitive dysfunction. High-level daily functional abilities (instrumental activities of daily living) include managing finances, shopping, operating a motor vehicle, and performing household chores. Whether or not cognitive symptoms are clinically significant underscores the categorical distinction between dementia and MCI, which can be ambiguous at times. The Functional Activities Questionnaire (FAQ) is a brief informant-rated 10-item measure of instrumental activities of daily living that is part of the uniform data set for Alzheimer disease research centers (**Figure 1-1**).[29] Basic activities of daily living such as dressing, bathing, and toileting tend to be preserved early in the course of dementing disorders but, over time, become important determinants of overall care needs and disposition.

## Neuropsychiatric Assessment

Neuropsychiatric symptoms overlap with idiopathic psychiatric disorders in conditions such as depression, anxiety, and psychosis, but differ in that they occur by definition in the setting of a neurologic disorder. Other symptoms such as apathy, disinhibition, and agitation typically accompany or are associated with neurobehavioral disorders such as dementia and traumatic brain injury. Mood disturbance may be a primary manifestation of neuropsychiatric disorders and is a common comorbidity of neurologic conditions. The term *pseudodementia*, which refers to cognitive dysfunction attributed to a mood disturbance, was used historically as a counterpoint to ''true'' dementia (eg, dementia versus pseudodementia). This wayward construct has given way to recent findings that depression is an independent risk factor for dementia. From a clinical perspective, it is useful to think of depression as a multidimensional syndrome with variable features and severity, as opposed to a condition that is either present or absent. Components of depression include hedonic state (eg, sadness), level of effort/motivation, neurovegetative changes (eg, sleep/appetite), and comorbidities such as anxiety, irritability, and agitation. The Patient Health Questionnaire-9 (PHQ-9) (**Figure 1-2**[30]) and 15-item Geriatric Depression Scale (GDS-15) (**Figure 1-3**[31]) are two of the more widely used scales for clinically assessing depression. One recent study showed the GDS-15 to be more sensitive as a depression screen than the PHQ-9 in a cohort of subjects with Parkinson disease.[32]

The Neuropsychiatric Inventory (NPI) developed by Cummings and colleagues[33] is the gold-standard assessment for neuropsychiatric symptoms in dementia and has been widely used as an outcome measure in Alzheimer disease clinical therapeutic trials. However, as an informant-based interview, the test is not well suited for standard clinical practice. A derivative clinical form of the NPI, the Neuropsychiatric Inventory Questionnaire (NPI-Q),[34] uses a questionnaire format where caregivers rate 10 behavioral domains, as well as eating and sleep-related behaviors, in terms of symptom severity in the patient along with associated caregiver distress (**Supplemental Digital Content 1-2**, *links.lww.com/CONT/A141*). The NPI-Q is also used in multicenter Alzheimer disease research studies (administered as an interview to increase data quality) and includes symptoms that aid in the differential diagnosis of frontotemporal degeneration (eg, apathy, disinhibition, aberrant motor behavior, appetite or eating changes) and dementia with Lewy bodies (eg, hallucinations, anxiety, and sleep disturbances) **(Case 1-1)**. Neuropsychiatric symptom burden in subjects with MCI increases the risk of progressing to Alzheimer disease.[35]

**KEY POINT**

- From a clinical perspective, it is useful to think of depression as a multidimensional syndrome with variable features and severity, as opposed to a condition that is either present or absent. Components of depression include hedonic state (eg, sadness), level of effort/motivation, neurovegetative changes (eg, sleep/appetite), and comorbidities such as anxiety, irritability, and agitation.

## Functional Activities Questionnaire

| Activity | Score (0 to 3)<br>0 = independent<br>1 = mild difficulty<br>2 = requires assistance<br>3 = dependent |
|---|---|
| 1. Writing checks and maintaining other financial records | |
| 2. Assembling tax or business records | |
| 3. Shopping alone | |
| 4. Playing a game of skill | |
| 5. Making coffee or tea | |
| 6. Preparing a balanced meal | |
| 7. Keeping track of current events | |
| 8. Attending to and understanding a television program, book, or magazine | |
| 9. Remembering appointments, family occasions, and medications | |
| 10. Traveling out of the neighborhood | |
| **Sum scores (0 to 30)**<br>Score >8 = functional impairment | |

**FIGURE 1-1** Functional Activities Questionnaire.

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# PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

| **Over the last 2 weeks, how often have you been bothered by any of the following problems?** *(Use "✔" to indicate your answer)* | **Not at all** | **Several days** | **More than half the days** | **Nearly every day** |
|---|---|---|---|---|
| **1.** Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| **2.** Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| **3.** Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| **4.** Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| **5.** Poor appetite or overeating | 0 | 1 | 2 | 3 |
| **6.** Feeling bad about yourself — or that you are a failure or have let yourself or your family down | 0 | 1 | 2 | 3 |
| **7.** Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| **8.** Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |
| **9.** Thoughts that you would be better off dead or of hurting yourself in some way | 0 | 1 | 2 | 3 |

**FOR OFFICE CODING** __0__ + _____ + _____ + _____

**=Total Score:** _____

**If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?**

| **Not difficult at all** | **Somewhat difficult** | **Very difficult** | **Extremely difficult** |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

**FIGURE 1-2** Patient Health Questionnaire-9 (PHQ-9).

Reprinted from Kroenke K, et al. J Gen Intern Med.[30] *link.springer.com/article/10.1046/j.1525-1497.2001.016009606.x.*

## Geriatric Depression Scale: Short Form

Choose the best answer for how you have felt over the past week:

| Question | Answer |
|---|---|
| 1. Are you basically satisfied with your life? | YES / **NO** |
| 2. Have you dropped many of your activities and interests? | **YES** / NO |
| 3. Do you feel that your life is empty? | **YES** / NO |
| 4. Do you often get bored? | **YES** / NO |
| 5. Are you in good spirits most of the time? | YES / **NO** |
| 6. Are you afraid that something bad is going to happen to you? | **YES** / NO |
| 7. Do you feel happy most of the time? | YES / **NO** |
| 8. Do you often feel helpless? | **YES** / NO |
| 9. Do you prefer to stay at home, rather than going out and doing new things? | **YES** / NO |
| 10. Do you feel you have more problems with memory than most? | **YES** / NO |
| 11. Do you think it is wonderful to be alive now? | YES / **NO** |
| 12. Do you feel pretty worthless the way you are now? | **YES** / NO |
| 13. Do you feel full of energy? | YES / **NO** |
| 14. Do you feel that your situation is hopeless? | **YES** / NO |
| 15. Do you think that most people are better off than you are? | **YES** / NO |
| **Score (number of answers in bold)** | |

Answers in **bold** indicate depression. Score 1 point for each bolded answer.

A score >5 points is suggestive of depression.
A score ≥10 points is almost always indicative of depression.
A score >5 points should warrant a follow-up comprehensive assessment.

**FIGURE 1-3** Geriatric Depression Scale: Short Form.

Reprinted from Sheikh JI, Yesavage JA, Clin Gerontol.[31]

## Case 1-1

A 68-year-old right-handed man developed cognitive, behavioral, and motor changes over a 1- to 2-year period. His past medical history was notable for obstructive sleep apnea that had been diagnosed approximately 15 years earlier, and he had used the continuous positive airway pressure (CPAP) machine regularly since then. However, he reported a history of loud snoring for 25 to 30 years prior to being diagnosed with obstructive sleep apnea. Neuropsychiatric evaluation yielded the diagnoses of bipolar disorder and obsessive-compulsive disorder, which were treated with serial additions of clomipramine, valproic acid, and lamotrigine. Neurologic evaluation revealed gait disturbance and brain MRI showed prominent ventriculomegaly, raising the possibility of normal-pressure hydrocephalus (NPH) **(Figure 1-4)**. However, he showed no response to either a high-volume lumbar puncture or a subsequent 48-hour lumbar drain procedure. Examination revealed the following: a Mini-Mental State Examination (MMSE) score of 25 out of 30 (1 out of 3 recall, 3 out of 5 WORLD, poor pentagon copy), a Mini-Mental State Examination Extended (MMX) score of 38 out of 50, and verbal fluency: animals 17, F-words 7; clock drawing: intact. On the Neuropsychiatric Inventory Questionnaire (NPI-Q) completed by his daughter, the patient reportedly exhibited moderate symptoms of apathy, euphoria, disinhibition, irritability, and appetite changes (craving sweets). Neurologic examination was notable for hypomimia, intact extraocular movements, no dysarthria, stooped posture, decreased left arm swing with ambulation, and reduced stride length.

Over the next several months, serial medication changes included discontinuing clomipramine, valproic acid, and lamotrigine and adding sertraline, resulting in significantly improved motor, behavioral, and cognitive symptoms. He exhibited some residual obsessive symptoms, but was able to resume living independently without any appreciable decline for several years.

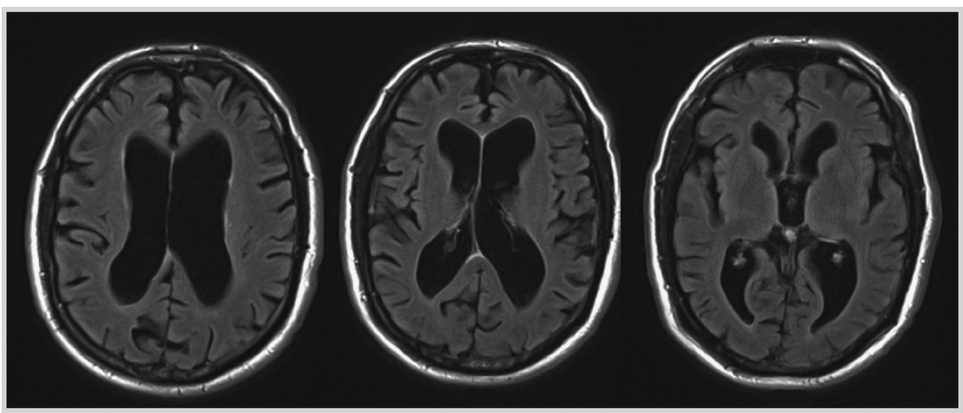

**FIGURE 1-4** Imaging of the patient in **Case 1-1.** Axial fluid-attenuated inversion recovery (FLAIR) MRI showing minimal frontal and temporal lobe atrophy. There is also subcortical atrophy, characterized by enlarged ventricles.

**Comment.** This patient was variably diagnosed with a neuropsychiatric disturbance based on prominent changes in behavior and possible NPH based on motor and cognitive signs as well as brain imaging that was suggestive of this disorder. He was duly evaluated for NPH and failed to improve with a lumbar drain. His overall presentation met criteria for behavioral variant frontotemporal degeneration, with congruent MRI findings. However, his motor dysfunction and cognitive symptoms improved dramatically with medication adjustments, suggesting an iatrogenic etiology. The conundrum of this case is why his MRI appeared so abnormal, particularly suggestive of NPH.

It is noteworthy that obstructive sleep apnea and NPH may have a shared pathophysiologic substrate, with pressure waves associated with obstructive sleep apnea contributing to loss of ventricular compliance seen in NPH. Moreover, repeated episodes of hypoxia and hypercarbia associated with obstructive sleep apnea may cause oxidative stress that preferentially affects frontal and temporal lobe regions that regulate mood, motivation, and executive functions.[36]

## Neurobehavioral Screen

Patient's name: _____ Date: _____

Informant's name: _____ Relationship: _____

The items below reflect possible **changes** in the patient from their old, usual self.
Check the appropriate box to indicate if there has been a change in any of these areas or not, and add any comments (eg, mild, moderate, severe).

| | No Change | Change | Comment |
|---|---|---|---|
| **Cognitive** | | | |
| Difficulty remembering recent or upcoming events | ☐ | ☐ | |
| Getting lost or not knowing where they are | ☐ | ☐ | |
| Difficulty keeping track of time | ☐ | ☐ | |
| Difficulty finding appropriate words | ☐ | ☐ | |
| Difficulty making decisions or problem-solving | ☐ | ☐ | |
| **Functional Activities** | | | |
| Difficulty writing checks, paying bills, etc. | ☐ | ☐ | |
| Difficulty driving a car | ☐ | ☐ | |
| Difficulty shopping alone | ☐ | ☐ | |
| Difficulty performing household tasks | ☐ | ☐ | |
| Difficulty pursuing hobbies and leisure activities | ☐ | ☐ | |
| **Social Activities** | | | |
| Difficulty holding a conversation | ☐ | ☐ | |
| Decreased social activity with family or friends | ☐ | ☐ | |
| Less cooperative, more difficult to get along with | ☐ | ☐ | |
| Less aware of how others feel, hurtful | ☐ | ☐ | |
| Less concerned about dressing or grooming | ☐ | ☐ | |
| **Behavioral** | | | |
| Sad, depressed | ☐ | ☐ | |
| Anxious, worried | ☐ | ☐ | |
| Impatient, fidgety | ☐ | ☐ | |
| Less interested in hobbies or social activities | ☐ | ☐ | |
| Acts impulsively, disinhibited | ☐ | ☐ | |
| Increased or decreased appetite, weight change | ☐ | ☐ | |
| Increased or decreased sleep, daytime fatigue | ☐ | ☐ | |

**FIGURE 1-5** Neurobehavioral screen.

## CONCLUSION

This review has focused on delineating the various elements of a comprehensive neurobehavioral assessment, including a systematic approach to history taking and involving clinical history assessments that assay cognition, functional abilities, and behavior. An informant generally provides these data components due to the limited reliability of a patient with impaired memory and insight. The instruments reviewed use a questionnaire format that the caregiver can complete in the waiting room or while the physician is performing a cognitive assessment on the patient. Conducted in parallel, a comprehensive screening history and general cognitive assessment (which clinic staff can administer) can be accomplished in real time prior to, or in conjunction with, physician involvement. Although this review covers domain-specific screening questionnaires that are widely used in research studies, an informal hybrid form may be adequate to support clinical care **(Figure 1-5)**.

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**KEY POINT**

- Conducted in parallel, a comprehensive screening history and general cognitive assessment (which can often be administered by clinic staff) can be accomplished in real time prior to, or in conjunction with, physician involvement.

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