Alzheimer’s Disease
Prototype of Cognitive Deterioration,
Valuable Lessons to Understand Human Cognition

Maryam Noroozian, MD

INTRODUCTION
With the aging of the population, more neuroscientists, neurologists, psychiatrists, and psychologists focus their research on age-related medical disorders in general, and more specifically dementia. Alzheimer’s disease (AD) is the most common cause of severe memory loss and cognitive deterioration in the elderly; the main goal of research on cognitive aging has been to find treatments for AD and other dementias. However, apart from the disease process, it is also crucial to understand the normal

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Memory and Behavioral Neurology Division, Department of Psychiatry, Roozbeh Hospital, Tehran University of Medical Sciences, 606 South Kargar Avenue, Tehran 1333795914, Iran
E-mail address: mnoroozi@tums.ac.ir

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process of cognitive decline with age: age is the greatest predisposing factor for a spectrum of neurodegenerative disorders. Thus, understanding what the brain goes through in the normal process of aging helps not only to improve the quality of life for the general population but may also ultimately help unravel pathologic changes that at present seem unrelated.\(^1\) AD is one of the most prevalent conditions in the elderly and the most common cause of memory impairment in old age.\(^2\) Nearly 40 years ago, dementia, and particularly AD, was first emphasized as a major public health problem.\(^3\) According to the World Health Organization (WHO), in the year 2011, 35.6 million people were affected by dementia.\(^4\) This number is destined to increase rapidly. The aging of the population affects both the incidence and the prevalence of this syndrome,\(^5,6\) thus, it has been estimated that, by the year 2050, 115.4 million people will be affected.\(^4\) In Western industrial nations, AD is the most common form of dementia\(^8\); thus, AD is the fourth cause of death (after cardiovascular disorders, cancer, and cerebral hemorrhage). Over the past 30 years, neuropsychological assessment has played one of the central roles in characterizing the dementia associated with AD. As well as being available, noninvasive, and inexpensive, it has helped identify the most significant cognitive and behavioral symptoms; it has also contributed greatly to the staging and tracking of the disease.\(^9-13\) At present, no curative treatments exist for AD. However, several promising strategies are being developed that may delay or even prevent the progression of AD.\(^14\) It is now known that decades before the onset of cognitive symptoms, such as episodic memory loss, AD-related neurologic changes begin to accumulate.\(^15,16\) Thus, intervention well before the onset of observable symptoms could provide a promising opportunity to slow the progression of the disease or minimize the damage, particularly if targeted at individuals with the greatest risk of developing AD.\(^17\) This article describes the neuropsychological profile of AD and its contrast with cognitive changes that occur in normal aging and in mild cognitive impairment (MCI) over the course of time.

**The Spectrum of Alzheimer's disease as a Prototype of Cognitive Disorder**

The first case of the disease was described by Alois Alzheimer's in November 4, 1906, in his lecture at the 37th Conference of South-West German Psychiatrists in Tübingen and the condition was later called AD by Emil Kraepelin.\(^18,19\) This first case (Aguste D) was a 51-year-old woman with progressive cognitive and behavioral impairment in middle age; however, in general, AD affects the elderly. The first clinical signs in most patients with AD are shown during the seventh decade. Early-onset cases are often familial; in many of these patients mutations have been discovered. In contrast, late-onset cases are sporadic, and their cause is still unknown. In both the sporadic and familial forms of AD there is a remarkably selective defect in declarative memory, which is discussed later.\(^1\) Recent research, which has increasingly focused on earlier stages of AD, has made clear that cognitive and behavioral symptoms of the illness can be preceded by biological markers by years.\(^9\) AD disorder is usually initially selective for limbic regions that subserve episodic memory, which in turn brings about circumscribed memory deficit in the early stages of the disease.\(^20-22\) Over time, with the progress of the disorder to other neocortical regions,\(^23-26\) further cognitive symptoms emerge and the full dementia syndrome manifests itself. The established research diagnostic criteria for AD dementia has served well since 1984; however, these recent discoveries have prompted its revision.\(^27\) In addition to defining the dementia of AD,\(^28\) the new criteria also incorporate a fuller spectrum of cognitive aging, and include an intermediate stage of MCI that precedes the full-blown dementia.\(^29\) A third, even earlier, stage of preclinical AD has also been identified.\(^30\)
The Structure and Function of the Brain Change with Age

Fig. 1 presents the different pathways in the brain aging process (from normal to MCI and AD). The quality of life in most people is not seriously compromised by age-related cognitive changes. However, in a subset of elderly people, cognitive decline reaches a pathologic level. Age-related declines in mental abilities are highly variable with regard to rate, severity, and type of cognitive capacity. First, there are considerable differences in the rate and severity of cognitive decline among individuals. Some rare individuals retain their cognitive functions throughout life, whereas others experience decline in mental agility: for some, the decline is gradual, for some rapid (Fig. 2). There are well-known instances of the former group: in his late 80s, Titian was still painting masterpieces, and they say Sophocles wrote *Oedipus at Colonus* in his 92nd year. The infrequency of cases with completely preserved function suggests that this retention of cognitive function may be suggestive of special properties in the life experiences or genes of the individual. Accordingly, great interest has been shown in studying these rare individuals, who retain nearly intact cognition well into their tenth or even eleventh decade. These centenarians might provide insight regarding environmental or genetic factors that protect against normal cognitive decline with age, or potentially even prevent the pathologic progression to dementia. Typically, personalities and interests are retained in those individuals who age normally; personality traits and interests include their levels of initiative, motivation, sociability, sensitivity to others, sympathy, affect, and behavior.

Second, averaged data gathered from many individuals show that although some cognitive capacities decline significantly with age, others are largely spared (Box 1, Fig. 3).

Alterations that occur with age in memory, motor activity, mood, sleep pattern, appetite, and neuroendocrine function result from alterations in the structure and function of the brain. The volume of the brain mildly shrinks in the elderly, a loss in brain weight is observable, and the ventricles are enlarged. These cellular changes lead
to alterations in the integrity of the neural circuits through which mental activities are mediated. Age-related cognitive decline is thought to be greatly contributed to by loss of synapses along with impairment in functioning of retained synapses. MCI is a constellation of changes at the lesser end of the pathologic range. MCI is characterized by memory impairments that the individual might find alarming but that are not serious enough to affect day-to-day life. Because of its subtlety, MCI is difficult to diagnose; neurologists have been convinced by longitudinal studies that it is a real condition and needs additional attention. Approximately 15% of individuals diagnosed with MCI develop AD within a few years of diagnosis, and another 50% eventually succumb to AD. In contrast, some individuals with MCI remain at a stable plateau for decades. At present, intense interest exists with regard to learning how to distinguish individuals with MCI who will progress to AD from those who will age normally (Box 2).


### Box 1
Aging brain

- Working and long-term memories, visuospatial abilities, and verbal fluency usually decline with old age. In contrast, there is minimal decline in measures of vocabulary, information, and comprehension in normal individuals well into their 80s.
- From college age onward, brain weight decreases 0.2% per year on average; this number is about 0.5% per year in the 70s.
- Widespread changes are detectable in white matter, which are especially notable in the prefrontal and temporal cortex. Considering the localization of encoding and storing memory functions in the frontal-striatal systems and the temporal lobes, it is possible that notable alterations in white matter may underlie age-related decline in executive functions and reduction in the ability to focus attention as a major cause of cognitive decline.

In most patients with dementia, memory problems are evident early in the course of their disease. Therefore, understanding memory is vital to explaining the neuropsychology of dementia. Learning and memory are crucial for people and animals to fully function and survive independently (Box 3).1

The nature and function of learning and memory can be investigated by observing the imperfections and errors in remembering. During the past several decades, significant progress has been made in the analysis and understanding of learning and memory. There are several fundamentally different types of memory, each of which has its own distinctive cognitive properties and is mediated by a specific brain region; thus, specific regions of the brain are more crucial for some types of storage. Memory can be classified along 2 dimensions: (1) the time course of storage, (2) the nature of the information stored (Box 4).

**MEMORY TYPES AND TIME COURSE OF STORAGE: SHORT-TERM VERSUS LONG-TERM MEMORY**

Historically, memory has been categorized into three temporal stages.36

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**Box 2**

**Mentalizing**

- The concept of mentalizing is defined as the ability to infer other people’s mental states.
- Using functional MRI (fMRI), a recent study has confirmed the results of previous studies indicating that mentalizing capacity decreases in older adults.34
- There was also an association between this decline and decreases in blood oxygen level–dependent response in the dorsomedial prefrontal cortex (PFC).
- Thus, the possibility is raised that PFC might be important for mentalizing, becoming less active with advancing age.

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**Fig. 3.** Average scores on several cognitive tests administered to a large number of people. Long-term declarative memory and working memory decline throughout life, and more so in advanced age. In contrast, knowledge of vocabulary is maintained. (Adapted from Park DC, Smith AD, Lautenschlager G, et al. Mediators of long-term memory performance across the life span. Psychol Aging 1996;11:621–37; with permission; and Kandel ER. The principles of neural science, 5th edition. New York: McGraw-Hill Education, 2013; with permission.)
Immediate Memory

Immediate memory comprises the amount of information a subject can keep in conscious awareness without having to actively memorize the information. Normal human beings can retain 7 digits in active memory span. Perhaps by coincidence, a local telephone number is also 7 digits. Most normal people can hear a telephone number, walk across the room, and dial the number without having actively memorized it. Implementing supraspan numbers (numbers of more than 7 digits) requires active memory processing, similar to unnatural tasks, such as reverse digit span. This first temporal stage corresponds with Baddeley’s concept of working memory. Attention disorders affecting digit span and focal lesions of the superior frontal neocortex affecting Brodmann areas 8 and 9 may extensively affect immediate memory. Many patients with aphasia secondary to left frontal lesions manifest impaired immediate memory. Individuals normally forget the items in immediate memory as soon as their attention switches to another topic unless they try actively to memorize them.

Recent Memory

The second stage of memory, which clinicians call short-term or recent memory, comprises the ability to register and recall items, such as words or events, after a delay of minutes or hours. This type of memory has such synonyms as declarative and episodic memory. The function of the hippocampus and parahippocampal areas of the medial temporal lobe is required by this second stage of memory for both storage and retrieval. The function of the amygdala, a structure adjacent to the medial temporal cortex, is not crucial for episodic memory, but seems essential for recalling

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**Box 3**

**Learning and memory**

- Learning refers to a change in behavior that results from acquiring knowledge about the world.
- Memory is the ability of the brain to store information for later retrieval and is the capacity by which that knowledge is encoded, stored, and retained to be later retrieved. Thus, memory is the necessary prerequisite that makes learning possible.
- Memory can be deconstructed into discrete encoding, storage consolidation, and retrieval processes.

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**Box 4**

**The so-called 7 sins of memory**

- Seven basic sins comprise the misdeeds of memory: transience, absentmindedness, blocking, misattribution, suggestibility, bias, and persistence.
- The first 3 denote different types of forgetting, the next 3 involve different types of distortions, and the seventh sin refers to disturbing recollections that are not easy to forget.
- Cognitive, social, and clinical psychology and cognitive neuroscience studies indicate that the 7 sins may only seem to reflect flaws in system design; instead, it is argued that the flaws are by-products of features of memory, which are otherwise adaptive.

Adapted from Schacter DL. The seven sins of memory: insights from psychology and cognitive neuroscience. Am Psychol 1999;54(3):182; with permission.
the emotional contexts of, and the reactions associated with, specific events and such reactions as fear or pleasure associated with those events. The familiar bedside test of asking the patient to recall 3 unrelated memory items at 5-minute intervals assesses episodic (short-term) memory; asking the patient about this morning’s breakfast or the result of yesterday’s football match is similar.

**Long-term Memory**

Remote memory refers to storage of long-known information such as a person’s first-grade teacher, where a person grew up, or the names of grandparents. The factual knowledge that is consciously recalled is known in current parlance as semantic memory.41

To test semantic memory, the patient is asked to recall a famous figure or event, such as presidents or wars; also, the patient’s knowledge of semantic information is assessed, such as the definitions of words and the differences between words. Semantic memory is different from personal long-term memory; the latter can be replenished continuously through daily life events.

**NEURAL BASIS OF MEMORY: HISTORICAL EVIDENCE**

In the mid-1950s, important new evidence began to emerge about the neural basis of long-term memory from studies performed on patients in whom bilateral removal of the hippocampus and neighboring regions in the medial temporal lobe was performed as treatment of epilepsy. The first and most thoroughly studied case was a patient called H.M. He is a historic case because his deficit for the first time linked clearly memory and the medial temporal lobe, including the hippocampus.1

After the surgery, H.M. ’s seizures were managed more effectively, but he had developed a distressing memory deficit (or amnesia). H.M. ’s deficit was highly specific. His working memory was still normal, for seconds or minutes, which indicated that the medial temporal lobe is not necessarily related to transient memory. Also, he had long-term memory for events that had occurred before the operation. He remembered his name, his previous job, and his childhood; however, he did not have robust recollection of memories in the years just before the surgery. In addition, he retained a command of language, including his vocabulary, which indicated that semantic memory was preserved. H.M. dramatically lacked the ability to move new information from working memory into long-term memory. He did not have the ability to retain information about people, places, or objects that he had just come across for lengthy periods. H.M. was able to repeat a new telephone number only immediately for seconds to minutes because his working memory was intact. If he was even briefly distracted, he forgot the number. H.M. could not recognize people whom he met after the surgery, even if he met them repeatedly. The physiologic findings are consistent with clinical observations: lesions in the right hippocampus cause problems with spatial orientation, whereas lesions of the left hippocampus affect verbal memory. Another critical observation regarding H.M. was that all types of long-term memory were not impaired. Despite H.M. and other patients with damage to the medial temporal lobe showing profound memory deficits, they were as able as healthy subjects to form and retain certain types of enduring memories. Such patients retained simple reflexive learning, including habituation, sensitization, classical conditioning, and operant conditioning.

The results from the observations of amnesic patients with damage to the medial temporal lobe, such as H.M., are suggestive that old memories are not stored in the medial temporal lobe itself. They are stored in various other cortical regions. Squire and Zola-Morgan42 and others, suggest that the medial temporal region may play
only a temporary role in the consolidation of memories, but, after a sufficiently long period, because memories can be retrieved directly from cortical regions, the medial temporal region is no longer needed. Their finding is consistent with the observation that remote memories are more readily recalled by amnesic patients compared with memories from the period just before they became amnestic. The activation of neocortical representations that were present during encoding is thought to be facilitated by medial temporal lobe activity (Box 5).

LONG-TERM MEMORY: EXPLICIT VERSUS IMPLICIT MEMORY

Considering whether or not conscious awareness is required for recalling a memory, two types of long-term memory are differentiated. Fig. 4 shows the classification of all types of human memory and the anatomic substrates.

Implicit Memory

Also known as nondeclarative or procedural memory, this type is an unconscious form of memory that underlies the task performance; it typically manifests in an automatic manner that requires little conscious processing from the individual. Different forms of implicit memory give rise to priming, skill learning, habit memory, and conditioning.

Explicit Memory

The other type comprises the conscious retrieval of previous experiences as well as conscious recall of factual knowledge about people, places, and things. This type is also referred to as declarative memory. Explicit memory is highly flexible; various pieces of information are registered in accordance with their associated circumstances, which also influence their retrieval. However, implicit memory is closely related to the conditions under which the learning originally took place.

DECLARATIVE (EXPLICIT) VERSUS NONDECLARATIVE (IMPLICIT) MEMORY

Memory is not a monolithic entity but comprises several separate entities that function in association with different brain systems. The main distinction is between the capacity for conscious recalling of facts and events (declarative memory) and a heterogeneous collection of capacities for nonconscious learning (nondeclarative memory), which are expressed through performance and cannot access any conscious memory material. Declarative and nondeclarative memory systems need to be distinguished not only in terms of anatomy but also in terms of operating characteristics, the kind of information processed, and the purpose served by each system.

<table>
<thead>
<tr>
<th>Box 5</th>
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<tbody>
<tr>
<td>Memory localization</td>
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<tr>
<td>• The function of the hippocampus and parahippocampal areas of the medial temporal lobe is required for both storage and retrieval parts of recent memory.</td>
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<tr>
<td>• The function of the amygdala seems to be essential for recalling the emotional contexts of the reactions, such as fear or pleasure, associated with specific events.</td>
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<tr>
<td>• Once a memory is well deposited in the neocortex, it can be retrieved without the hippocampal system being engaged. Thus the effects of medial temporal damage do not affect remote memory.</td>
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Fig. 4. Memory classification and the main localization of its subcomponents.
EXPLICIT MEMORY: EPISODIC VERSUS SEMANTIC MEMORY

The idea of a distinction between explicit memory (the memory of personal experiences or autobiographical memory) and semantic memory (memory for facts) was first developed by the Canadian psychologist Endel Tulving.44

Episodic Memory

Episodic memory serves to recall that a person saw the first snow of winter yesterday or that several months ago heard Beethoven’s Hammerklavier.1

Semantic Memory

Semantic memory is used to learn the meanings of new words or concepts.

In both episodic and semantic memory, the medial temporal lobe plays a critical role; this is evident in patients like H.M., who have difficulties in forming new conscious memories of their personal experiences or the meanings of new concepts and their retention.

EXPLICIT MEMORY PROCESSING INVOLVES AT LEAST 4 DISTINCT OPERATIONS

Two additional important things need to be considered about explicit memory.1 First, there exists no single long-term store for explicit memories in the brain. Instead, every item of knowledge is stored in a widely distributed manner among many brain regions and can be independently accessed (by visual, verbal, or other sensory clues). Second, at least 4 related but distinct types of processing mediate explicit memory: encoding, storage, consolidation, and retrieval.45

Encoding

Through this process, new information is attended and linked to existing information in memory. Determining how well the learned material will be remembered almost entirely depends on the depth of this process. The incoming information needs to be encoded thoroughly in order for a memory to persist and be well remembered; this is called deep encoding. This process is performed by attending to the new item of information and associating it with knowledge that is already well established in memory. Furthermore, memory encoding is stronger when there is high motivation for remembering. Different neurodegenerative conditions can affect functioning of memory in different ways. Patients with frontosubcortical atrophy have problems with encoding and initial learning; retention is left fairly intact. In addition, there exists normal recognition memory.46,47 In contrast, in patients with AD, normal immediate recall may be shown, but they may have difficulty retaining information over brief minutes-long delays; recognition tends to be poor in such patients as well. Functional MRI (fMRI) scans show that, when people engage in deep encoding (eg, attending to the meaning of information by judging whether a word is concrete or abstract), there is greater activity in the medial temporal lobe compared with when they engage in shallow encoding (eg, judging whether a word is registered in upper-case or lower-case letters). During deep encoding, there is enhancement in activity in parts of the left prefrontal cortex (PFC), which suggests that, for encoding episodic memory, frontal lobe and medial temporal lobe processing are involved. Moreover, it has been shown that, at the time of encoding, when subjects are studying words that they were later able to recall, there is enhanced activity in several regions of the left PFC. In comparison, there is greater activity in the right PFC during encoding of pictures that were later recalled compared with pictures that could not be recalled (Box 6).
**Storage**

This operation comprises the neural mechanisms and sites by which memory is retained over time. Remarkably, long-term storage seems to have an almost unlimited capacity; long-term storage has known limits with regard to the amount of information it can store. In contrast, working memory storage is very limited; at any given time, it is thought that human working memory can hold only a certain number of pieces of information.

**Consolidation**

Consolidation is the process that renders the information that is stored temporarily and is still labile more stable. In this process genes are expressed and proteins synthesized that bring about structural changes at the synaptic level.

**Retrieval**

Retrieval is the process by which stored information is recalled. In this process, different kinds of information that are stored in different sites are brought back to mind. Retrieval of memory closely resembles perception: it is a constructive process and can therefore be distorted, much as perception may be subject to illusions. Individuals can be reminded of how they initially encoded an experience through a retrieval cue.

**EPISODIC MEMORY**

Episodic memory refers to the system through which particular experiences or episodes are remembered. These memories are context dependent and are associated with a particular time, place, and feeling. In evaluating memory in patients with AD using clinical neuropsychological tests, it is clear that recall and recognition performance are impaired in both the verbal and nonverbal domains. Studies using postmortem examination, structural imaging, resting metabolism, and functional imaging have linked explicit memory deficits in AD to pathologic, structural, and functional abnormalities within the mesial temporal lobe (MTL). These findings are consistent with evidence that suggests MTL structures are crucial for new episodic memories to be formed (Box 7).

When examiners assess episodic memory in the clinic, they should use enough information to exceed immediate memory span. They should also consider initial
learning versus retention, and recall versus recognition separately. For bedside evaluation of memory, supraspan list learning tasks with delayed recall and recognition conditions (eg, California Verbal Learning Test-II [CVLT-II]\(^5^8\) and Rey Auditory Verbal Learning Test\(^5^9,6^0\)) are more suitable. Patients with AD manifest a general episodic memory deficit: such patients cannot benefit from cueing or inherent structure; their ability to recognize is as defective as their free recall performance. Rather than accelerated forgetting or disrupted retrieval, patients with AD show impaired learning. In addition, regardless of the perceptual modality of the stimuli implemented in episodic memory tasks, patients with AD manifest impaired performance. The relative irrelevance of delayed recall trials and perceptual modality is an important finding considering that these factors strongly influence clinical memory testing (Box 8).

It has been shown, through a comparison of patients with AD with amnestic patients with Korsakoff syndrome (KS) and demented patients with Huntington disease (HD) that patients with AD recalled significantly fewer words over a 2-minute delay.\(^6^2\) Although the subjects with KS and HD and the normal control subjects lost an average of 10\% to 15\% of the verbal information between the 15-second and 2-minute delay intervals, patients with AD lost an average of 75\% of the material. Severe recall deficits of the patients with AD have been shown, through similar studies, compared with the patients with frontotemporal dementia (FTD) and progressive supranuclear palsy (PSP)\(^6^3\) (Box 9).

Note that, in order to stage patients with AD across levels of severity, measures of episodic memory are not particularly useful, mainly because memory is much impaired early in the course of the disease. These findings support the observation that, in most patients with AD, memory is impaired preceding impairments in language and spatial function. There is substantial agreement that memory tests are significantly different among nondemented individuals who show mild memory deficits with a diagnosis of AD on follow-up, compared with those who also have memory problems but do not progress to AD within a few years.\(^6^4–6^8\)

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**Box 7**

**Episodic memory**

- The earliest neurofibrillary alterations, which are part of the disease process of AD, usually occur in structures in the medial temporal lobe (eg, hippocampus and entorhinal cortex).\(^9,2^0\)
- Hence, deficits in episodic memory, which are caused by medial temporal lobe atrophy and neuronal loss in the basal forebrain cholinergic system, characterize the early stages of AD.\(^5^7\)
- The impact of this disorder is interruption of the neural network that is critical for episodic memory function. Thus, the clinical hallmark of AD is a deficit in the ability to learn and remember new information.

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**Box 8**

**Delayed recall task**

- A study has assessed the effectiveness of using 3-word recall tasks (such as the task in the Mini–Mental State Examination [MMSE]) in order to assess recall performance. There was major variability among the subjects, and a significant share of normal subjects recalled zero or 1 word.\(^5^1\)
- When simple recall performance is interpreted as an index of memory, the investigators noted that caution must be taken. For bedside evaluation of memory, supraspan list learning tasks with delayed recall and recognition conditions are more suitable.
SEMANTIC MEMORY

Semantic knowledge comprises general knowledge about the world: facts, concepts, and information about objects, as well as words and their meanings. Semantic knowledge is distinguished from episodic knowledge in that it is typically not linked to the context in which the information was first acquired. All of the semantic knowledge that has been acquired over a lifetime is not stored in a single storage site. It is instead stored in a distributed manner among many brain regions, such as the neocortex, including the lateral and ventral temporal lobes, the visual association cortex for visual memories, and the temporal cortex for auditory memories. Thus, specific features (eg, form, color, or motion) are represented by various brain regions. Functional brain imaging research supports this view of multiple localizations of semantic memory. Patients have been reported to have an impaired knowledge about living things, whereas their knowledge about inanimate objects was spared and vice versa. Hence, it seems that the brain organizes semantic knowledge according to conceptual primitives (eg, form and function). Some categories mainly depend on information about form (eg, living things), whereas others depend on knowledge of function (eg, inanimate things). Therefore, loss of memory for particular semantic categories can result from focal brain damage, whereas knowledge of others is left intact. It is thought that the left lateral temporal cortex is where specific semantic knowledge of word meanings resides. Semantic memory plays an important role in several tests, as listed in Table 1. Before the diagnosis of AD can be made, changes in semantic memory can be detected; initially, patients cannot name low-frequency exemplars and later they go on to lose more common elements. It is concluded that, in AD, it is the impaired verbal fluency performance that is caused by loss of knowledge, rather than impaired initiation of retrieval. Contrary to early-phase dementia, and AD in particular, semantic memory, and certain forms of implicit memory, are thought to be relatively spared in normal aging. Another prominent influence of AD on mental status testing is a decrease in category fluency in the context of preserved letter fluency. In a study by Rascovsky and colleagues, verbal fluency results from 32 patients, whose AD was confirmed by autopsy, were compared with those of 16 patients with autopsy-confirmed FTD. Those with AD were more impaired in terms of semantic fluency than letter fluency (in which, within a certain time limit [usually 1 minute] as many words as possible are to be recalled beginning with a particular letter), whereas the pattern of impairment was reversed in those with FTD. Semantic category fluency deficits in AD may be suggestive of the gradual progression of AD in the temporal association areas that serve semantic memory. However, these tests do not usually serve to measure semantic memory. Thus, it could be argued that (purely) episodic memory processes should not be considered crucial for prediction, otherwise important information could be missed. Several studies suggest

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<td>Severity of delayed recall impairment in AD</td>
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- Patients with AD recalled significantly fewer words over a 2-minute delay. Hence the patients with AD lost an average of 75% of the material.
- In the Korsakov syndrome, Huntington dementia, and normal control subjects, the patients lost an average of 10% to 15% of the verbal information between the 15-second and 2-minute delay intervals, whereas patients with AD lost an average of 75% of the material.

Alzheimer's Disease: The Prototype of Cognitive Deterioration
Table 1
Cognitive domains and their assessment in an office visit

<table>
<thead>
<tr>
<th>Domain and Subdomains</th>
<th>Instructions for the Patient</th>
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| Orientation           | • Person: state name; name the present family members  
                        | • Place: name the county, state, town, hospital or clinic building, floor  
                        | • Time: state the year, month, date, day, time of day |
| Attention             | • Recite the days of the week or months of the year in forward then reverse order  
                        | • Spell a word (eg, world) in forward then reverse order  
                        | • Recite a string of numbers (presented at a rate of a number per second, starting with a short string and increasing string length by 1 number each time (eg, 2, 7...5, 8, 6...6, 9, 3, 4...))  
                        | • An impaired attention span is usually apparent during history taking. It can be tested more formally by having the patient repeat a series of numbers or count backward |
| Memory                | • Repeat a list of words immediately, and again after 10 min  
                        | • Digit span tests are widely used, with the forward digit span component used to assess immediate auditory memory |
| Immediate memory      | • At the beginning of the visit, tell the patient you will be hiding 3 objects in the room (eg, watch, pencil, and ruler). Then show the patient where you are hiding them, and ask the patient to try to remember the items and their locations. At the end of the visit, ask the patient to name the objects and to show (or tell) you where they are located  
                        | • Ask the patient to memorize 3 to 5 unrelated words and, after 5-min intervals, prompt the patient to repeat them |
| Recent memory         | • Ask the patient to say the patient’s (own, spouse, first child’s) birthday, the name of city where the person has done military service, name of the high school or college, an important social or political event in the past years (with regard to the patient’s education and culture). All of the personal information needs to be confirmed by the informant caregiver |
| Remote memory         | • The backward span component evaluating working memory (ie, the capacity to juggle information mentally). Research has shown that, on average, people can keep 7 ± 2 items in their short-term memory  
                        | • Recite a string of numbers using the method described earlier, but instructing the patient to recite the numbers in reverse order (eg, “If I say ‘7, 8, 3,’ you would say ‘3, 8, 7’”).  
                        | • Recite a string of numbers using the method described earlier, but instructing the patient to recite the numbers in numeric order, starting with the lowest number (eg, “If I say ‘7, 2, 5,’ you would say ‘2, 5, 7’”).  
                        | • Working memory is also assessed on the MMSE when the patient carries out serial 7s or spells “world” backward. Other bedside techniques include reciting the months of the year in reverse order |
| Working memory        | • Name several objects in the room, starting with high-frequency items (pen, pencil, watch, ruler, glasses) and moving to low-frequency items (glasses lens, watch clasp, tip of pencil) |

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Table 1 (continued)

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<tr>
<th>Domain and Subdomains</th>
<th>Instructions for the Patient</th>
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<tr>
<td><strong>Fluency</strong></td>
<td>• Recite as many words as possible in 1 min that start with a given letter (eg, C) or a given semantic category (eg, grocery store items)</td>
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<tr>
<td><strong>Reading</strong></td>
<td>• Read aloud simple sentences, words, or letters</td>
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<td></td>
<td>• Reading comprehension can be tested by having the patient follow written commands that were previously successfully executed as oral commands or by having the patient answer written yes-or-no questions, such as following a written command (eg, “Close your eyes”)</td>
</tr>
<tr>
<td><strong>Repetition</strong></td>
<td>• Repetition of high-frequency and low-frequency word combinations (eg, no ifs, ands or buts)</td>
</tr>
<tr>
<td><strong>Comprehension</strong></td>
<td>• Comprehension of single words (give the patient simple commands, such as “Show me your chin,” or have the patient say the word that a picture is illustrating), comprehension of complex syntax (eg, “Put your left hand on your right ear”), or follow a multistep verbal command (eg, “Touch your left ear with your right index finger then touch your nose”)</td>
</tr>
<tr>
<td></td>
<td>• Answer a complex question (eg, “If a lion and a tiger fight and the tiger eats the lion, which animal is still alive?”)</td>
</tr>
<tr>
<td><strong>Visuospatial</strong></td>
<td>• Ask the patient to copy the predrawn shapes on a page, starting with simple shapes (eg, a square, pentagon) and progressing to more complex shapes (eg, a cube, intersecting pentagons), building shapes with triangles or blocks, drawing a clock, and eventually a Rey-Osterrieth complex figure task</td>
</tr>
<tr>
<td><strong>Praxis</strong></td>
<td>• In most of the classifications, there are 3 types of testing: (1) gesture (“Show me how you would throw a ball”), (2) imitation (“Watch how I point upward, then you do it”), and (3) use of an object (“Here is a spoon. Show me how you would use it”)</td>
</tr>
<tr>
<td><strong>Limb-kinetic praxis</strong></td>
<td>With limb-kinetic apraxia the act is understood but motor execution is faulty. There is loss of hand and finger dexterity resulting from inability to connect or isolate individual movements</td>
</tr>
<tr>
<td></td>
<td>• Ask the patient to wave the patient’s hands as a goodbye (symbolic), touch the patient’s nose (nonsymbolic), transitive (ie, using tools and instruments; eg, a hammer or a hairbrush), and intransitive (ie, communicative gestures; eg, representational tasks such as waving goodbye and nonrepresentational tasks such as touching the nose and wiggle the fingers)</td>
</tr>
<tr>
<td><strong>Ideomotor praxis</strong></td>
<td>The ability to correctly form the necessary postures and movements to perform a task using a tool, which can be tested by:</td>
</tr>
<tr>
<td></td>
<td>• Asking the patient to pretend by showing you how to scramble an egg with a fork (a transitive task) or by asking the patient to show you how to salute (a nontransitive task)</td>
</tr>
<tr>
<td><strong>Ideational praxis</strong></td>
<td>The ability to correctly temporally sequence independent actions/task components to perform a goal. Ideational apraxia is present when the idea of the act (the neural representation of the act, or engram) is disrupted. The patient does not know what to do</td>
</tr>
<tr>
<td></td>
<td>• Ask the patient to verbalize, step by step, how to make a sandwich Error types include impairment in carrying out sequences of actions requiring the use of various objects in the correct order so as to achieve an intended purpose, and loss of tool action knowledge</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Domain and Subdomains</th>
<th>Instructions for the Patient</th>
</tr>
</thead>
</table>
| **Constructional praxis**<sup>a</sup> | • Draw a copy of crossed pentagons (as in MMSE) or copy a cube (as in the MoCA scale) or more complex task, such as the Rey-Osterrieth Complex Figure Test  
• Dressing praxis is a type of constructional praxis. Ask the patient to wear an inside-out jacket, and then button or zip it up |
| **Calculation** | • This can range from simple arithmetical (eg, “What is 9 plus 14?” “What is 28 minus 17?”) to calculations involving money (eg, “How many nickels are there in 65 cents?”), to figuring out the change (eg, “If you bought something that cost $3.73 and you paid with a $5 bill, how much change should you receive back?”), to calculating more complex bills involving percentages (eg, “If you went to a restaurant and the bill came to $120, how much total money would you leave if you wanted to also include a 15% tip?”) |
| **Executive Functions** | **Abstract thinking**  
• Identify the similarities between words (eg, “In what way are a banana and an orange alike?”)  
• Ask the patient to explain about the concept of a familiar proverb or metaphor (check with the informant whether this item is routine for the patient in terms of culture and education)  
• Abstraction can be assessed by asking for the meaning of common proverbs as well as asking the patient to delineate the similarity (eg, “In the most general sense, how are a bicycle and a train similar?”) and difference between 2 things (eg, “What is the difference between a lie and a mistake?”). Identify the similarities between words (eg, “In what way are a banana and an orange alike?”).  
• Abstract reasoning can be evaluated by asking patients to describe conceptual similarities or differences between word pairs (eg, dog–lion), give opposites (eg, healthy–sick), find analogies (eg, “Table is to leg as bicycle is to…”), or interpret proverbs (eg, “An old ox plows a straight row”) |
| **Sequencing and planning** | • Imitate hand movements in a sequence demonstrated by the examiner  
• Continue a sequenced drawing that is started by the examiner (eg, XOXO; ramparts) |
| **Reasoning/ problem solving** | • Provide solutions to everyday problems (eg, “What should you do if you are in a movie theater and you smell smoke?”) |
| **Set switching** | • Alternate between counting and reciting the alphabet (eg, “I want you to switch between counting in numeric order and reciting the alphabet, like this: 1-A-2-B-3… Now you try it”)  
• Alternate between counting by 6s and reciting the days of the week (eg, “I want you to alternate between counting by 6s and reciting the days of the week in order, like this: 0, Sunday; 6, Monday; 12… Now you try it”) |
| **Specialized Mental Functions** | **Visual Gnosis**<sup>b</sup>  
• Ask the patient to name the different segments of an object, name different parts of a schematic outline of an image or recognize each object in pictures of overlapping objects |

(continued on next page)
that, typically, normal elderly subjects perform better on the category fluency task than on the letter fluency task. The reverse pattern is seen in patients with AD: despite showing impairment in both types of performance, they perform better on letter fluency than on category fluency. This performance pattern usually helps differentiate patients with AD and normal elderly controls, and shows the clear semantic memory problems of patients with AD compared with normal elderly controls. In addition, the qualitative performance of patients with AD on the category fluency task may help detect these patients: in addition to naming few correct exemplars in general, they typically name the most common elements (ie, broad category information is preserved) and produce few different subcategories, few items per subcategory, and relatively numerous category labels. As mentioned before, to examine semantic memory, the most frequently and extensively used task is verbal fluency. Hodges and Patterson tried to explore how early in the course of AD, and how consistently, semantic memory problems occur. The patients with minimal AD showed impaired performance on various tests of semantic memory (eg, category fluency, naming, naming to verbal description, semantic feature questions) and on episodic memory (ie, delayed story recall). In patients with minimal AD, recognition memory was less impaired, which may be a better index of severity of the disease. Hodges and Patterson concluded that semantic memory is impaired very early in the course of AD, although patients with the same overall level of dementia showed considerable variability in the extent of semantic impairment. Other investigators who examined category fluency performance in patients with early AD have supported the findings regarding the early semantic memory impairment in AD. Other studies have confirmed that patients with early AD (mean Mini–Mental State Examination [MMSE] score: 23.7) are impaired in

<table>
<thead>
<tr>
<th>Domain and Subdomains</th>
<th>Instructions for the Patient</th>
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</thead>
<tbody>
<tr>
<td>Prosopagnosia</td>
<td>• Show an image of a famous or familiar person (for the patient) and ask the patient to say the person’s name</td>
</tr>
<tr>
<td>Simultanagnosia</td>
<td>• Describe a complex scene (eg, the Boston Cookie Theft picture) or identify a large object that is made up of smaller shapes (eg, an A made on a page with small As)</td>
</tr>
<tr>
<td>Color agnosia</td>
<td>• Ask the patient to name the color of such fruits as banana, carrot, lemon and so forth; name similar colors in terms of tonality or different shades of a color</td>
</tr>
<tr>
<td>Neglect</td>
<td>• Bisect a line drawn on a page</td>
</tr>
<tr>
<td></td>
<td>• Draw a clock face on a page</td>
</tr>
</tbody>
</table>

**Table 1** (continued)

<table>
<thead>
<tr>
<th>Domain and Subdomains</th>
<th>Instructions for the Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>General impression²⁵³</td>
<td>Note processing speed, psychomotor retardation</td>
</tr>
<tr>
<td></td>
<td>Note the patient’s mood, behavior, and frontal lobe signs</td>
</tr>
<tr>
<td></td>
<td>Note the patient’s movement disorders, eye movement, and pyramidal signs</td>
</tr>
</tbody>
</table>

**Abbreviation:** MoCA, Montreal Cognitive Assessment.

² Note that some overlaps exist between active cognitive domains in many of the mentioned tasks (eg, visuospatial, constructional praxis, and planning during the clock drawing task).

³ These tasks are helpful for the diagnosis of posterior cerebral atrophy or the occipital variant of AD.

*Adapted from* Dickerson B, Atri A. Dementia: comprehensive principles and practice. Oxford University Press; 2014, with permission.
several tasks of semantic memory. They also showed the impaired performance on a category fluency test and several tests of semantic knowledge (eg, Boston Naming Test, Wechsler Adult Intelligence Scale-Revised [WAIS-R] subtests Vocabulary and Similarities). Another study also found early semantic memory impairment and reported that very mild dementia was best detected by 3 tests assessing episodic memory, semantic memory, and visuospatial functioning (according to a stepwise discriminant analysis).

EPISODIC VERSUS SEMANTIC MEMORY IN ALZHEIMER’S DISEASE BIOMARKER RESEARCH

Aspects of memory functioning are used as part of tasks presented to participants in several fMRI studies. These studies frequently assess 2 general categories of memory performance: episodic memory (eg, discriminating between previously learned and novel stimuli) and semantic memory (recall of general facts and knowledge about the world that is not contextually specific; eg, making a categorical or attributional judgment to a presented item). Episodic memory impairment is a hallmark of AD, and thus most fMRI studies of AD risk have used episodic memory tasks. However, there may be challenges in the use of episodic memory tasks in fMRI studies that focus on prediction of MCI, AD, and risk factors for these conditions. Episodic memory is typically impaired not only in association with onset of MCI or AD but also in normal aging. Furthermore, episodic memory tasks might be fundamentally more difficult than semantic memory tasks, making individuals who are in the preliminary stages of cognitive decline exert greater effort and paradoxically display a greater blood oxygen level–dependent signal (a marker for metabolic activity) because of the greater cognitive challenge. In longitudinal studies that use episodic memory tasks, participants displaying a greater extent of activation are usually at the greatest risk of subsequent cognitive decline.

IMPLICIT (NONDECLARATIVE) MEMORY

Implicit memory systems such as procedural memory (remembering how to perform a skilled motor act) are less likely to be affected by amnestic or dementing illnesses. Although patients with AD consistently manifest impaired explicit (episodic or declarative) memory, they show intact implicit (priming or procedural) memory. The ability to play a musical instrument has been shown to be unforgettable in some musicians with AD. The dissociation between impaired and intact memory capacities seems to reflect the distinction between neural systems that are injured or spared in the early stages of AD. Nonconscious influence of past experiences on subsequent performance affects implicit memory. The hippocampus seems to be required for the recognition or recall of items. As discussed earlier, large areas of the neocortex specialized for specific cognitive functions, such as auditory or visual analysis, are involved as sites for storage of memories. Once items are processed in the neocortex and stored for a long period of time, they can be recalled even in the presence of hippocampal damage, as is the case with remote or semantic memories. Following hippocampal damage, a retrograde period of memory loss may extend back from minutes to years, and the patient cannot form new anterograde memories.

WORKING MEMORY

Miller and colleagues coined the term working memory and used it in 1960 in their classic book Plans and the Structure of Behavior; it was used in 1968 by Atkinson and
Shiffrin\textsuperscript{101} in an influential article and afterward adopted as the title for a multicomponent model by Baddeley and Hitch.\textsuperscript{102} Working memory refers to the system or systems that are thought to be essential for keeping things in mind while such complex tasks as reasoning, comprehension, and learning are being performed. The term working memory evolved from the earlier concept of short-term memory. These two terms are sometimes still used interchangeably (Box 10).

It has been proposed by Baddeley and Hitch\textsuperscript{102} that working memory could be categorized into 3 subsystems. (1) the first subsystem is concerned with verbal and acoustic information (the phonological loop); (2) the second subsystem is the visuospatial sketchpad providing its visual equivalent; whereas both are dependent on (3) the third attentionally limited control system, called the central executive. Baddeley\textsuperscript{103,104} later discussed the modification of his first model in a comprehensive article and has added a fourth component: the episodic buffer (Fig. 5).\textsuperscript{103}

\textbf{The Central Executive}

The central executive is the most complex component of working memory. As presented in the original model, it was assumed to be capable of attentional focus (eg, during dual tasks performed on 2 different modalities: one verbal, involving recalling digit sequences, and the other requiring visuospatial tracking), storage, and decision making.

\textbf{The Phonological Loop}

The phonological loop is the verbal subsystem that functions when people attempt to keep phonological information (speech, sign, lip reading, music, environmental sounds) in conscious awareness; for instance, when people mentally rehearse a phone number that they have just obtained from an operator. The verbal subsystem consists of 2 components that are interactive: a reservoir that stores phonological information and a rehearsal mechanism that keeps the stored information active for as long as it is needed.

\textbf{Visuospatial Sketchpad}

The visuospatial sketchpad is related to the characteristics of such variables as visual (information about the shape and color), spatial (the location of objects in space), and haptic domains (the kinesthetic and tactile information).

\begin{table}[h]
\centering
\begin{tabular}{|l|}
\hline
\textbf{Box 10} \\
\textbf{Short-term memory versus working memory} \\
\hline
- Short-term memory is the simple temporary storage of information, whereas working memory is a functional system that implies concomitant storage and manipulation.\textsuperscript{103} \\
- working memory is a common substrate to patients’ difficulty with multitasking. \\
- The forward digit span component of digit span tests is used to assess immediate auditory memory, and the backward span component evaluates working memory (ie, the capacity to mentally juggle information). \\
- Research has shown that, on average, people can keep $7 \pm 2$ items in their short-term memory. \\
\hline
\end{tabular}
\end{table}
The Episodic Buffer

The episodic buffer is assumed to hold integrated episodes or chunks of information in a multidimensional code. It acts as a buffer store, not only between the components of working memory but it also links working memory to perception and long-term memory. The episodic buffer does this through its capability to hold multidimensional representations; however, like most buffer stores, its capacity is limited.

In brief, this model presents a processing system in which a limited-capacity, language-based or visually based, immediate memory buffer holds the information that is the immediate focus of attention, while this information is manipulated by a central executive. Activated long-term memory influences working memory in many ways. For example, when a telephone number is spoken in a person’s native language, memory for it is substantially better than when a number is spoken in a foreign language. This difference reflects the influence of long-term phonological knowledge on short-term verbal memory. Furthermore, the capacity to remember and repeat a string of irrelevant words is about 5 items, but if the words comprise a meaningful sentence, the capacity expands to 15 words, which reflects a contribution from grammar and meaning, both of which depend on different aspects of long-term memory. Hence, neuroimaging studies of short-term or working memory tasks have also been shown to activate areas related to long-term memory. The mental manipulation deficit that patients with AD manifest may also express itself in working memory tests. Studies indicate that the working memory deficit in patients with AD is mild to begin with; this deficit primarily disrupts the central executive and relatively spares...
immediate memory. Working memory assessment has been used in the development and validation of a dual-task performance measure in order to detect AD in early stages. It is only in later stages of AD that all aspects of the working memory system become compromised. Mildly demented patients with AD often manifest impairment in complex attention tasks that depend on the efficient allocation of attention (eg, dual-processing tasks) or that require efficient disengagement from tasks and shifting of attention. In contrast, the ability to focus and sustain attention is usually not affected until later stages of the disease, which is evident when mildly demented patients with AD perform essentially normally on tests of immediate attention span compared with supraspan tests.

**MEMORY IN ALZHEIMER’S DISEASE**

Kramer and colleagues showed that, when conducting a dementia evaluation, delayed episodic memory needs to be examined as well and not just immediate memory. They established that hippocampal volume best predicts delayed recall, even after controlling for levels of initial acquisition. Numerous studies have found that patients with AD have greater memory impairments than other diagnostic cohorts. Despite diffuse cognitive changes being typical in AD, particularly in the middle and later stages, this condition is associated with 2 particularly distinct findings on mental status testing: rapid forgetting on tasks of episodic memory and decreased category fluency compared with lexical fluency. Rapid forgetting is reflective of impairment in consolidating new information into long-term memory. Thus, even though patients with AD can show relatively intact immediate recall, much of the information is lost after even the briefest of delays. With regard to memory function, patients with AD might partially or entirely forget important conversations, life events, dates, appointments, and obligations; misplace or lose belongings (and have difficulty retracing their steps; they may even put things in unusual places); be highly repetitive with questions and statements; and increasingly need to rely on external memory aids and others for tasks they used to perform efficiently and independently. In the moderate to severe stages of AD, severe memory loss is brought about by progression of memory dysfunction; also, there is difficulty with new learning in a way that only highly learned or overlearned material is retained, and new information is lost rapidly, including semantic knowledge and current and historical events (generally with a retrograde gradient). However, patients in the moderate stages of AD may still be able to remember details of events from decades ago. In severe dementia, no new learning occurs and no memory is formed; only patchy memory fragments remain. Patients increasingly lose not only personal and autobiographical information but also elementary semantic knowledge about the world. Although this general progression is characteristic, it is important to keep in mind that individuals with AD often have both patchiness and fluctuations in cognition, function, and behavior. They do experience islands of relative stability in some mental or daily functions and, occasionally, otherwise low function and confusion is interspersed with moments of clarity. In contrast, patients with normal cognitive aging might occasionally have difficulty recalling a name, appointment, or details of a conversation, but this piece of information is not entirely lost and can typically be remembered later. This phenomenon is like when a name or piece of information is not readily within reach, but ultimately, if the person waits long enough, it comes back around and is retrieved. Cognitively healthy individuals may also occasionally misplace items; however, with time, they usually are able to remember and retrace their steps. By definition, daily functioning is not consistently adversely affected by this type of memory change. Numerous studies have shown that patients with AD manifest impairment in episodic memory tests.
that use a variety of cognitive procedures (e.g., free recall, recognition, paired-associate learning) across virtually all modalities (e.g., auditory, visual, olfactory). Evidence from many of these studies suggests that the episodic memory deficit of patients with AD, in general, results from ineffective consolidation or storage of new information. Early studies that described the episodic memory deficit in AD used word list learning tasks, such as those from the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD)\textsuperscript{119} and the CVLT.\textsuperscript{120} These studies consistently showed that patients with AD rapidly forget information over time and are equally impaired (relative to age-matched controls) in recognition and free recall components of the tasks. This performance pattern is consistent with impaired consolidation rather than ineffective retrieval of new information.\textsuperscript{120} Indices of rapid forgetting have important clinical utility in detecting AD in an early stage and making differential diagnoses. It was shown by Welsh and colleagues\textsuperscript{119} that patients with very early AD could be differentiated from healthy elderly controls, using the amount of information recalled after a 10-minute delay on the CERAD word list learning task, with better than 90% accuracy. In this regard, this measure was superior to other measures derived from this task, including immediate recall on each of the 3 learning trials, recognition memory score, and the number of intrusion errors produced throughout the test. Other studies have shown that mildly demented patients with AD can be differentiated from healthy elderly controls using measures of rapid forgetting with 85% to 90% accuracy.\textsuperscript{10,119,121–123} An additional mechanism that contributes to episodic memory impairment in AD includes an increased sensitivity to interference caused by defects in the inhibitory processes that in the natural state help people to exclude intruding phenomena while trying to register something in the memory. In other words, the brain in AD is more susceptible to these intruding phenomena and cannot resist them, which leads to the production of intrusion errors\textsuperscript{120,124,125} and defective use of semantic information to bolster encoding.\textsuperscript{126,127} Several prospective longitudinal studies of cognitive function in nondemented older adults have shown that a subtle decline in episodic memory can be registered before the emergence of the obvious cognitive and behavioral changes that are required for a clinical diagnosis of AD.\textsuperscript{128–132} Some of these studies suggest that, several years before the development of the dementia syndrome, memory performance may be poor, but stable, and then rapidly decline in the period immediately before the diagnosis of AD dementia. Two studies\textsuperscript{131,133} have shown that episodic memory was mildly impaired 6 years before the onset of dementia, but changed little over the next 3 years. Chen and colleagues\textsuperscript{134} showed that, in individuals who were either asymptomatic in the first place or met the criteria for MCI at enrollment to the study, a significant and steady decline occurred in episodic memory on delayed recall conditions of word list and story memory tests.\textsuperscript{134,135} Moreover, normal elderly individuals typically have difficulties with free recall conditions,\textsuperscript{136,137} but they show normal benefit from (semantic) cueing and intrinsically structured material.\textsuperscript{138–140} Compared with younger subjects, they show less efficiency in their recognition performance; however, this difference is negligible compared with the impairment they show on free recall tasks.\textsuperscript{141} Taken together, more studies suggest that, to predict the imminent onset of dementia in an elderly individual, registering an abrupt decline in memory might serve better than poor but stable memory ability.\textsuperscript{9} Recall performance of patients with AD is not improved by semantic cueing, possibly because of deficient semantic encoding.\textsuperscript{89,142,143} Patients with AD are suggested to have a specific deficit in the ability to evaluate semantic relations. They are no longer able to discriminate between 2 related concepts, because they have lost the attribute knowledge that distinguishes these.\textsuperscript{83} No relative better performance can be seen in patients with AD on verbal recognition tasks compared with recall tasks.\textsuperscript{143–148} Greene and colleagues\textsuperscript{149} found that patients with AD seem incapable of learning because of deficient
encoding rather than because of impaired retrieval, because their free recall performance is as weak as their recognition performance; they are expected to be equally impaired on visual and verbal recognition trials. Furthermore, patients with AD show poor performance on the recognition of pseudowords.\textsuperscript{150} In a study, they seemed not to be able to constrain irrelevant associations.\textsuperscript{151} Many false-positive errors were shown by patients with AD because of their inability to discriminate between different semantic relations in the material that was presented to them: they were sensitive to category membership of words but, within a given category, they could not discriminate between different semantic attributes of words.\textsuperscript{152} Contrary to early-phase dementia, AD in particular, semantic memory (in particular, but also certain forms of implicit memory) is alleged to be relatively spared in normal aging.\textsuperscript{75,76} Another aspect of semantic memory deficit in AD is the patients’ consistent deficiency on verbal fluency, compared with normal elderly controls.\textsuperscript{79,80,83–85}

**PRECLINICAL ALZHEIMER’S DISEASE**

The period of cognitive decline that precedes the onset of AD is referred to as the preclinical phase of dementia.\textsuperscript{153} At present, preclinical AD is a heatedly debated topic in dementia research. Two of the best studies in determining the characteristics of this phase and its practical implications were done by Elias and colleagues\textsuperscript{154} and Linn and colleagues,\textsuperscript{155} who worked on the Framingham cohort. With the advancement of research with respect to prognostic methods and therapeutic interventions, early detection of AD will be increasingly important.\textsuperscript{129,155} Therefore, it is important for the timeline and the earliest evidence of cognitive decline that signals the preclinical phase of AD to be determined, and for the specific neuropsychological tests that have clinical applications for predicting this disorder to be identified. Deficits on the following tests may indicate the development of AD,\textsuperscript{17} several years before the diagnosis: verbal and visuospatial episodic memory\textsuperscript{155–159}; abstract reasoning\textsuperscript{129,160}, new learning\textsuperscript{161}; verbal abilities, including category and letter fluency\textsuperscript{130,159,162}; and visuospatial and executive functioning.\textsuperscript{129,159} Relations between measures of attention (eg, digit span forward and backward) have been seen in some studies\textsuperscript{163} but not in others.\textsuperscript{158,164} Moreover, delayed story recall,\textsuperscript{154,165} similarities in WAIS-R,\textsuperscript{154,166} verbal paired-associate learning,\textsuperscript{155,166} delayed free recall and recognition of words,\textsuperscript{133,155,157,165,167} recall of tactile memory, immediate visual memory,\textsuperscript{168} and Digit Symbol in WAIS-R\textsuperscript{166} have been shown to be valuable tests. There is also impairment in semantic memory in a very early stage: in patients with minimal AD\textsuperscript{84} MMSE\textsuperscript{169} is more than 23. Thus, it could be argued that, compared with (purely) episodic memory, semantic memory performance might be a better early marker for AD; episodic memory performance is left relatively intact by semantic processing capacities, as in free recall of lists of words that are inherently unstructured. A finding that supports this suggestion is that there is impairment in free recall conditions of normal elderly controls. However, in contrast with the performance of patients with AD, elderly controls show normal performance on tasks sensitive to semantic processing capacities.

Weingartner and colleagues\textsuperscript{71} investigated semantic memory in patients with preclinical AD (using a category fluency task, 2 years before the diagnosis) and concluded that one of the early cognitive symptoms of AD is alterations in the extent to which uncommon exemplars of semantic networks are available.

**PRINCIPLES OF COGNITIVE ASSESSMENT**

Frequently, cranial nerves, reflexes, eye movements, and sensorimotor function seem to be intact in patients with neurodegenerative disease, particularly in the early stages.
Thus, to formally assess the cognitive, psychiatric, and behavioral abnormalities that define many dementing disorders, clinicians are in need of more effective neuropsychological tools. The regional variability in neuropsychological testing protocols and in the relative influence of various portions of the dementia evaluation on determining the clinical diagnosis has been recognized as a limiting factor in more effectively characterizing and treating AD.

Cognitive function is assessed by various scales, which are subject to educational and cultural bias. All of these scales have been designed to measure different cognitive domains, including memory, language, visuospatial functions, calculation, abstract thinking, planning, and other executive functions. Validation studies with proper methodological design are necessary to measure the cutoff point in any population in terms of culture adaptation and educational impact before any diagnostic decision.

Crum and colleagues\textsuperscript{170} examined the distribution of MMSE scores in 18,056 adult participants. As measured by the MMSE scores, cognitive performance varied in accordance with both age and education level (Box 11).

The study of Crum and colleagues\textsuperscript{170} emphasizes that, to interpret the MMSE scores, age and education need to be taken into account. However, it is important to bear in mind that the MMSE was primarily designed to quantify the severity of dementia and not to make differential diagnoses.

**FUNCTIONAL STATUS**

To diagnosis dementia, it is necessary to detect impairment in both cognition and everyday functioning. Functional status refers to the capacity to perform effectively such activities of daily living as food preparation, management of medication, driving,

### Box 11

**Mini Mental State Examination (MMSE)**

- Perhaps the most widely used cognitive rating scale is the MMSE. Although this scale is extremely useful, it is weighted significantly toward aspects of memory and attention. The language tasks are fairly insensitive; there is limited assessment of visuospatial ability, and executive performance is not tested.
- There is an inverse relationship between age and MMSE scores and a positive relationship between years of education and MMSE scores.
- The impact of age: the median MMSE score of those participants aged 18 to 24 years was 29, whereas the median score for individuals more than 80 years of age was 25 in the study by Crum and colleagues.\textsuperscript{170}
- The impact of educational level: the median MMSE score for participants with at least 9 years of formal education was 29, whereas the median score for those with 0 to 4 years of education was 22.
- The strength of tests like the MMSE lies in that they provide researchers with composite scores that can be used as markers of disease severity over time.
- Healthy older adults perform in a fairly stable manner in MMSE, whereas, over time, MMSE scores of patients with AD decrease at an average rate of around 3 points per year.\textsuperscript{171}
- The patients with dementia with Lewy bodies performed worse than patients with AD on attention and construction items, whereas patients with AD performed worse on the MMSE on temporal orientation items and memory items (delayed recall).\textsuperscript{172}
- It needs to be taken into consideration that MMSE is not particularly sensitive indicator for manifestations in early stages of the disease.\textsuperscript{173}
Memory and executive functioning bear the strongest relationship to functional abilities as components of the mental status examination. Executive dysfunction often brings about impairments in planning, organization, and insight, all of which are likely to have an effect on people’s ability to care for themselves. Another study determined that, among several elements of executive functioning (e.g., working memory, generation, inhibition, planning, and sequencing), inhibition was the one most strongly related to impairments in instrumental activities of daily living in patients who were at risk of decline in cognition and function in future. Apart from executive dysfunction, apathy (a frontally mediated behavior) was also associated with impairment in instrumental activities of daily living. Extensive research efforts have been directed toward developing strategies that could predict risk of developing AD before the appearance of observable symptoms. The efficacy, invasiveness, and ease of implementation of existing approaches vary for early detection of AD. Studies that investigate patients with preclinical AD (as the previous stage before MCI) generally recruit a large cohort of nondemented older subjects, who are subjected to a battery of neuropsychological tests at several times of measurement. In the process of neuropsychological evaluation, it is important to precisely evaluate the level of education and schooling, culture, social status, and job exposures. To elaborate, in developing countries, patients are not familiar and comfortable with the setting of these types of assessments. Therefore, to reduce false-positive results, it is important to take into consideration consequences of such conditions; namely anxiety, reduced concentration, and their negative impact on the subjects’ scores.

Early to middle stage Alzheimer’s dementia has the hallmark of a relatively preserved ability to immediately register new information but significant storage loss for the information when the patient is tested after an adequate delay that is not significantly amenable to cues or recognition by multiple-choice/forced-choice testing (Box 12).32

Box 12
Important consideration in delayed recall assessment

- It is important that patients are able to immediately register or encode the material, as well as having good hearing; this can be checked by asking the patient to repeat the presented items before the main test (at least once, and preferably twice, or more when a greater learning load is demanded).

- If the patient is not able to adequately register this material for any reason, then memory storage capacity cannot be reliably assessed.

- Once the patient has been mentally engaged with other tasks (i.e., after a delay, ideally of at least 5 minutes) that do not require substantial learning and remembering of material that has the potential to interfere with this material/information, the patient should be asked to recall the specific information.

- Patients should not be allowed to rehearse the presented materials, a verbally presented word list or story, or to redraw a previously copied figure.

- When expressive language function can significantly interfere with verbal recall during memory testing, there are other alternatives to redrawing previously copied figures, which include testing recognition memory through presenting lists of words, patterns, or pictures, or hiding objects in particular locations in the examination room and asking the patient to remember and later show the locations.

Note that standard cognitive testing sometimes does not verify the memory complaints of patients. Memorization in complex three-dimensional environments is required for acquisition of information in everyday life. Among the hallmarks for the early clinical manifestations of dementia are impairment of episodic memory and spatial orientation. To assess memory in specialized clinical settings, list learning paradigms such as the Auditory Verbal Learning Test and the California Verbal Learning Test are used. However, such assessments have been criticized for not representing naturalistic conditions and being irrelevant to everyday life. Various cognitive domains that should be evaluated in the diagnostic process of dementia in clinical assessment are presented in Table 1.

THE NEUROPATHOLOGIC BASIS OF ALZHEIMER’S CLINICAL PRESENTATION

The neuropathologic hallmarks of AD, namely neuritic plaques and neurofibrillary tangles, first appear in the entorhinal cortex and hippocampus, and subsequently spread to other MTL and neocortical sites. Some brain regions, including primary sensory and motor cortices, are relatively spared. Within modality-specific neocortical areas, there is an increase in the scale of pathologic changes from primary to secondary to tertiary cortices. Thus, the increase in pathologic changes in AD occurs in a hierarchical manner through the ventral visual pathway. To learn the sequence of the symptoms it is vital to understand this pattern of disease progression. It has been revealed in patients with early-stage AD, through using fMRI that, compared with healthy age-matched neurologically normal control subjects, a dissociation exists in AD between impaired explicit memory encoding in MTL and fusiform regions and intact implicit encoding in earlier-stage occipital cortex. During episodic memory encoding in AD, decreased MTL activation has been observed.

Orientation

Patients with dementia show disorientation to place and time but not to person. With regard to spatial and temporal orientation, patients with AD have increased difficulty when they need to keep track of dates, the passage of time, and geographic relations and locations. Initially, this manifestation of disorientation might present as being disoriented only about the day and date, but, as AD progresses into the moderate and later stages, this confusion could progress to forgetting about the month, season, and year. In later stages, increasing confusion occurs about spatial location (eg, hospital or town) and patients can easily forget where they are or how they have arrived there. In normal cognitive aging, it is common not always to immediately remember the date (or even day of the week); however, in such cases the individual eventually remembers. It is also common to sometimes become distracted or become lost; to look for a car in the parking lot; become confused about a particular travel route; or have to ask for directions, need a map, or need a GPS (global positioning system). Although attention to some of these phenomena may have limited utility in detecting subtle signs of early dementia, they can still provide useful information for staging and tracking patients who are in the middle to late stages of dementia. Also, they may be beneficial in patients with mild dementia who have a greater disorientation, show impairment in forming new memories, or have a lack of insight and awareness into their cognitive problems. Also, through assessment of arousal and orientation, the clinician may be provided with an indication that an underlying medical complication that manifests as confusion and delirium is causing acute or subacute change or fluctuation in mental status.
Attention

Attentional disturbances are frequently the first nonmemory impairments that develop in patients with AD. Therefore, an increasing number of investigations have attempted to identify the specific features of attention that are affected in the disease (for reviews, see Refs. 110,111,193,194).

Although impairment in delayed recall may serve as an indicator of hippocampal dysfunction, immediate recall impairment may indicate problems in other brain regions involved in attention and organization.113 The word attention is an umbrella term that refers to many different cognitive abilities, such as orientation to sensory stimuli, maintenance of the alert state, and orchestrating the computations needed for performing the complex tasks of daily life.195 This last category also comprises the abilities to switch between tasks and to inhibit prepotent responses, also skills that are sometimes referred to as executive functions.195,196 Although the core of AD is associated with memory impairments, evidence has accumulated over recent years that indicates early deficits in attention.194,196–198 In early AD, hypometabolism is seen in some of the brain areas most important for attention. Moreover, attention is influenced by acetylcholine levels, which are decreased in AD.199,200 These observations have led some researchers to propose that memory problems in AD may result in part from a cholinergic attention disruption.201 The memory deficit in AD has been related chiefly to lesions of the hippocampus and medial temporal structures, whereas the attention deficits are thought to denote lesions of cortical association areas in the parietal and frontal lobes.202–204 The pattern of attention impairments as observed in AD has been classified by Perry and Hodges111 in terms of 3 broad subtypes.

Selective attention

Selective attention is the ability to focus on a single relevant stimulus or process while irrelevant stimuli are ignored. This ability includes ignoring perceptual distractors (ie, perceptual filtering) as well as the suppressing responses that conflict with the person’s goals (ie, conflict resolution). Selective attention comprises various cognitive processes by which individuals are able to choose which stimuli to process and which to ignore. Thus, selective attention is fundamental for goal-directed behavior. Using the visual search task, selective attention in the visuospatial domain has been extensively studied.103 In this task, reaction time increases with an increase in the number of distractors when the search is demanding with regard to attention. Possible deficits in selective attention were explored by Fernandez-Duque and Black197 in patients with early AD, healthy elderly, and young adults under low memory demands; their study assessed perceptual filtering, conflict resolution, and set switching abilities. Neither evidence of impaired perceptual filtering nor evidence of impaired conflict resolution was found in early AD. In contrast, these patients did manifest a global cost in set switching, which was consistent with their not being able to maintain the goals of the task (mental set). These findings are important with regard to the impairment in executive attention, dual tasking, and working memory in AD.197 However, it is not clear whether this deficit in the patients with AD is caused by their slowness in shifting attention from one item to another or to the processing of each item being ineffective.44,104

Divided attention

Divided attention is the ability to allocate attention to multiple stimuli or processes at the same time.205 Neuropsychological studies of attentional systems in AD show that early in the course of the disease divided attention is affected,202–204 whereas sustained attention remains preserved until later stages.110,205 It has been observed
that the histologic changes of AD are more pronounced in the parietal than in the frontal lobe during the early clinical stages of the disease. This observation points to the possibility that divided attention depends on the function of the posterior parietal attention site. Another study has shown the role of frontal cortices as well as parietal dysfunction in the impairment of divided attention in probable AD. To investigate the nature of the divided attention deficit in AD, most studies have used dual-task paradigms, in which tasks are performed both singly and in combination. In these studies, relative to healthy elderly controls, patients with AD have consistently shown a disproportionate impairment in simultaneous performance of 2 tasks. In patients with mild AD dual-task performance is also impaired.

**Sustained attention**

Sustained attention is the ability to maintain attentional focus over time. Studies have shown that, although sustained attention is relatively well preserved early in AD, selective attention and divided attention were predominantly prone to disruption. Patients with mild AD do not show impairments on a simple test of sustained attention that makes little demand on memory, such as digit span forward. However, such patients show selective impairments on more complex attentional tasks. Given that AD is associated with impairments in both selective attention and divided attention, it is critical to understand how, in these patients, declines in the component processes of selective attention (eg, spatial attention, perceptual filtering, and inhibitory control) interact with the impairments in the executive processes that coordinate dual-task performance. The functional neuroanatomy of attention is still much debated. Hypotheses range from models of attention monitored by a single central processor to network hypotheses. Using PET study in the healthy elderly, a study has shown both sustained and divided attention to elicit activation of the right parietal (inferior lobule) and the right frontal (middle gyrus), whereas the anterior cingulate gyrus was activated only during sustained attention. In patients with AD, only medial frontal structures were activated. Compared with the healthy elderly, more cortical sites differed statistically in patients with AD during divided than during sustained attention. The activation patterns elicited by attention in this study supports the neuropsychological data suggesting that divided attention is more impaired than sustained attention in early AD. Hence the evaluation of attention in general and divided attention specifically may provide important insight into the neural mechanisms of attention, and may aid early diagnosis and treatment of AD; therefore, studies on attention are important from both theoretic and clinical standpoints.

**DUAL-TASK DEFICIT IN ALZHEIMER’S DISEASE**

Once these findings are taken together, it could be deduced that the dual-task deficit in AD is caused more by a specific inability to effectively coordinate processing across attentional networks than by a general deficit in cognitive function or reduction in available attentional resources. Furthermore, this impairment has been interpreted as a deficit in a specific dual-task coordination function of the central executive component of working memory. This specific deficit in dual-task coordination in patients with AD suggests that being able to execute 2 competing tasks concomitantly may prove to be a particularly sensitive indicator of subtle changes in cognitive status. Dual-task impairments on selective attention tasks could be manifested in different ways with regard to behavior. First, dual-task conditions could bring about an overall increase in rate of error and/or response time, because coordinating and executing performance of the selective attention task become more
difficult under dual-task conditions. Patients with AD also manifest impairment in rescaling the focus of attention, because, compared with healthy individuals, they benefit less from cues providing only imprecise information about the target location in the search display. Maintaining a mental set is an ability related to working memory capacity; this ability may be compromised both in individuals experiencing healthy aging and those with AD. Furthermore, poor set switching performance in neuropsychological tasks can well predict the progression of the disease in patients at the preclinical stage. The Trail Making Test, Part B, is one of these predicting tasks; letters and numbers are randomly distributed on a sheet of paper. The patient is asked to trace the items in an ascending manner and alternate between letter and number. In the case of healthy adults, performance in this task is related to performance in experimental set switching tasks. There exists a consistency between these findings and the hypothesis that, even at very early stages of AD (including the prodromal stage called MCI), the ability to maintain mental set may be affected. As a group, patients with MCI may be impaired in response inhibition and set switching; however, a considerable number of patients seemingly show only deficits in episodic memory. These latter meet the criteria for amnesic MCI (MCI-a). Note that even the patients with MCI-a are a heterogeneous group, and patients reveal subtle deficits of attention in experimental designs. In one such study, researchers divided patients with MCI-a into 2 groups: those who had mostly hippocampal atrophy, and those who had mostly small vessel cerebrovascular disease (as registered by white matter hyperintensities on brain MRI). Both groups were equally impaired with regard to episodic memory; however, subjects with small vessel disease showed more significant impairment in tasks that required them to maintain a mental set, such as working memory and continuous performance tasks. In a study by Festa and colleagues, the findings are merely suggestive that a deficit in the ability to maintain a mental set is already detectable at very early stages in the disease. Their finding raises an important question: whether or not deficits in mental set maintenance could help predict who is at risk to progress from a preclinical stage to full-flown clinical manifestations. The difficulty in maintaining mental set also helps explain the deficit that exists in areas of higher cognition in AD. Dual-task studies have contended that it is not the increased perceived load by the patients that results in dual-task deficit in AD, but that it is caused by a deficit coordinating the two tasks. Although task coordination is a concept in need of further development, one of its constituent parts might be the ability to maintain a mental set about task A while task B is being performed. This concept forms a testable prediction: whether AD deficit in dual task is mediated, at least in part, by the inability to maintain set. In sum, the literature regarding early AD is suggestive of the existence of deficits in a variety of selective attention tasks; however, not much is known about the precise mechanisms underlying those deficits.

VISUOSPATIAL FUNCTION

Visuospatial function comprises the abilities to identify, integrate, and analyze space, and visual form, details, structure, and spatial relations in several (usually 2 or 3) dimensions. Moreover, visuospatial skills include spatial navigation; perception of distance, depth, movement, and visual relations; visuospatial construction; and mental imagery. Assessment of visuospatial function is extremely useful and should thus be included in every mental status examination to detect organic brain disease. Complex nonverbal cognitive functions are required for constructional abilities; these abilities also involve the integration of occipital, parietal, and frontal lobe functions.
Nevertheless, the parietal lobes are the principal cortical areas that are involved in visual-motor integration. According to the cognitive map theory and similar studies, representation of spatial locations are stored in the hippocampus. The hippocampus is also the critical structure for the memorization of verbal and nonverbal lists of items. It is not clear whether the learning of verbal material that occurs in spatial surroundings is different from classic word list learning. One of the crucial abilities for the preservation of autonomy in old age and AD is the ability to remember information and events while simultaneously moving in a complex environment. At some point in the course of the disease, patients with AD often show deficits in visuospatial abilities. Patients have also been reported to manifest visuospatial deficits early, even in preclinical stages. Changes in visuospatial function are detectable on visuoconstructional tests and the tasks that require visuoperceptual abilities and visual orientation. This visuoperceptual deficit may partly arise from the loss of effective interaction between distinct and less damaged cortical information processing systems. Studies have shown that, compared with controls in a visual search task, when patients with AD are asked to quickly identify targets from the aggregation of 2 or more features that are processed in different cortical regions (eg, color and shape), they have disproportionately greater response times than when they are asked to identify targets exclusively from a single feature. In the course of normal aging, deficits are also observed in visual information processing and in selective and divided attention, but these deficits are intensified in individuals with AD. In addition, visual motion detection has been shown to deteriorate in some individuals with MCI and more in patients with a diagnosis of AD dementia, which suggests that this symptom may serve as an independent marker to detect those who potentially have AD.

Note that intact visuospatial functioning is essential for driving. Thus, given the safety implications, it is essential to question patients and their caregivers in detail regarding recent changes in driving ability. With regard to visual and spatial relationships, patients with AD, even in the mild stages, can have difficulty understanding or interpreting visual images and spatial relationships, and navigating through space. They may not be able to appreciate the big picture or notice objects that are right in front of them; they may also have difficulty judging distances, colors, and contrasts, and reading. Such problems can be a predominant and presenting sign of AD in some individuals (ie, patients with the visuospatial variant of AD). These problems can readily translate into substantial difficulties with work and particularly with driving. Gross visuospatial dysfunction can be indicated by evidence of the patient’s trouble navigating through space (eg, frequently bumping into things). Often, this early functional disability results in life-threatening complications caused by wandering and getting lost while driving. Therefore, regardless of the degree of verbal memory impairment, as a symptomatic variant of MCI, this navigational impairment is a harbinger of AD-related cognitive decline. However, it is important to bear in mind that the eyesight might be undergoing changes in individuals who are undergoing normal cognitive aging, as opposed to how their brain is integrating and interpreting visual images. For example, they may be shortsighted or have lost their visual clarity, because of cataracts, and have low visual acuity, caused by changes in the retina. In addition, compared with younger controls, older individuals react more slowly to peripheral stimuli; patients with AD show an even greater impairment. The increased incidence of car crashes in patients with AD dementia may be accounted for by these visual deficits. There is an identical pattern of difficulty in associating visual scenes and locations in normal aging and AD; the difficulty becomes complicated in AD by the loss of navigational capacities that are verbally mediated.
Compared with normal controls, patients with mild AD present equal performances on simple copying tasks, such as drawing a clock or a triangle.\textsuperscript{236,237} However, among mildly to moderately impaired patients, visuospatial impairments are commonly observed.\textsuperscript{238,239} To assess visuospatial problems, patients can be asked to copy pre-drawn shapes on a page, starting with simple shapes (eg, a square or pentagon) and progressing to more complex shapes (eg, a cube or intersecting pentagons), to build shapes with triangles or blocks, and draw a clock. Also, visuospatial construction can be tested by asking the patient to imitate the construction of different interlocking finger patterns that the examiner has made. Another approach for assessment of visuospatial function\textsuperscript{181} is checking navigation ability, which is impaired early in the course of AD.\textsuperscript{182} Assessment of patients at various levels of severity,\textsuperscript{240} as well as longitudinal data collected from the same patients,\textsuperscript{239} indicates that, over time, performance on clock drawing to command becomes progressively worse, and that conceptual errors are particularly sensitive to the overall change in the severity of dementia. The sensitivity of clock drawing to command in patients with mild AD has led investigators to probe whether this task might also be sensitive to individuals in the prodromal phase of AD. However, several studies have indicated that clock drawing to command is not efficient for the identification of MCI cases.\textsuperscript{241,242}

**VISUAL GNOSIS**

Agnosia, derived from agnosis, or nonknowledge (Greek: nosos meaning disease and gnosis meaning knowledge), is the loss of the ability to recognize objects, persons, sounds, shapes, or smells, without the specific sense being defective. Anosognosia is the lack of awareness of, or denial of, the existence of a deficit or handicap; this feature is seen often (but not necessarily), and early, in several dementias, particularly AD and behavioral variant of FTD (bvFTD).\textsuperscript{32} Agnosia is a failure of recognition that cannot be explained by impaired primary sensation (tactile, visual, auditory) or cognitive impairment. It has been described as perception stripped of its meaning. Agnosia is different from anomia; the patient with agnosia not only fails to name an object but also cannot recognize it in a group or match it to a picture. In cases of tactile agnosia (astereognosis), touch threshold is normal but patients cannot recognize what they are touching. There exist comparable agnosias in the visual and auditory spheres. However, as the responsible lesions are usually bilateral, only rare cases of visual and auditory agnosias are seen. Simultanagnosia is the inability to recognize the meaning of a whole scene or object, despite its individual components being correctly recognized; individuals with this condition literally cannot see the forest because of the trees. To test simultanagnosia, the patient could be asked to identify on a page specific targets of various sizes, such as letters, numbers, or shapes; affected patients may be able to identify smaller individual targets but not bigger ones. Usually, language is processed in the left hemisphere and spatial information in the right hemisphere. Right hemispheric (particularly parietal) lesions impair spatial perception and manipulation. Patients with such lesions have difficulty reading maps or finding their way around (topographagnosia), or difficulty copying simple pictures or shapes or drawing simple objects such as a flower (constructional apraxia or apractagnosia).\textsuperscript{1} It is important to assess anosognosia, and the patient’s overall insight, in order to advise the caregivers about the best approaches to the patient’s care and safety measures (like driving, handling guns, and cooking). To assess anosognosia, facts need to be compared with the patients’ insights, perceptions, and understanding of their condition (deficits, disabilities, and behaviors, and their impact on others), current stations in life, and the reason for and context of the medical evaluation.
Posterior Cortical Atrophy: Occipital Variant of Alzheimer’s Disease

Although rare, AD can initially show relatively circumscribed posterior cortical atrophy (PCA), and the dementia can be dominated by higher order visual dysfunction.\textsuperscript{162} Patients with the clinical syndrome of PCA have relatively preserved memory functions, intact language, and preserved judgment and insight. However, such patients usually have prominent visual agnosia, constructional apraxia, and some or all of the features of Balint syndrome, which include optic ataxia, gaze apraxia, and simultanagnosia. Another key feature of this variant of AD is navigational impairment, which presents with disorders of spatial cognition, memory, and orientation\textsuperscript{163,243–245}; this impairment is linked to the accumulation of AD neurologic disorder in peristriate cortices.\textsuperscript{77} Components of Gerstmann syndrome may also be found in PCA, including acalculia, right-left disorientation, finger agnosia, and agraphia. Also, visual field defect, decreased visual attention, impaired color perception, or decreased contrast sensitivity may be present.\textsuperscript{130} Usually, the clinical syndrome of PCA is associated with AD; however, this syndrome may also occur in association with neuropathologic changes of cortical Lewy body disease or Creutzfeldt-Jakob disease. Disproportionate atrophy and pathologic lesions are detected through neuropathologic examination in the occipital cortex and posterior parietal cortex.\textsuperscript{163,246} Particular involvement of the dorsal visual stream has also been reported in studies using PET. In PCA caused by AD, neurofibrillary tangles and neuritic plaques in the posterior cortical regions are identical, with regard to their quality, to those in typical AD.\textsuperscript{246} Using PET imaging with Pittsburgh compound-B ([11C]-PIB), an agent that binds to β-amyloid in the brain, it has recently been shown that pathologic features of AD in PCA have a disproportionately posterior cortical distribution.\textsuperscript{247}

ARITHMETICAL ABILITY

Such common daily activities as handling money or consulting timetables,\textsuperscript{248} apart from numerical and arithmetical processing (eg, comprehension of number meaning, simple calculation) are in need of executive control, set shifting, inhibition of interference, as well as temporary maintenance of information in short-term memory. In early stages of AD, patients show episodic memory deficits, along with functional impairment in everyday life activities including numerical activities.\textsuperscript{46} In a recent study, patients with mild to moderate AD showed intact basic numerical skills (number comparison, transcoding, simple calculation), but performed very poorly in tasks such as checking the television program or calculating the money change.\textsuperscript{47} There was a correlation between the patients’ performance in these everyday numerical situations and their global cognitive status and measures of executive functioning. Early in AD, attentional and executive deficits present; these deficits manifest after impairments in episodic memory but before visuospatial and language disorders.\textsuperscript{111} Among the first signs of AD, deficits in more abstract numerical processing (eg, dot counting, written complex calculation) have also been reported.\textsuperscript{87,88,249} Daily-life financial abilities\textsuperscript{32} may also be impaired in individuals with MCI. Patients with MCI typically have memory loss and show reduced performance on neuropsychological testing.\textsuperscript{68,91} Also, mild deficits in episodic memory and executive functions, such as inhibition of interference and allocation of attention, have been described in MCI.\textsuperscript{247} Activities of daily living, as tested by routine assessment, are usually found to be intact. However, slight impairments have been recently described in tasks related to high-order financial capacities, such as financial conceptual knowledge, bank statement management, and bill payment.\textsuperscript{32} It has been shown that executive dysfunction may play a critical role in the functional change in MCI. To
test arithmetical processing in routine neuropsychological assessment, well-structured
test batteries are used in which, for example, knowledge of addition and multiplication
facts \((2 + 3 = 6, 4 \times 3 = 12)\) is tested by separate tasks. However, it is rare for people to
be asked to solve series of addition or multiplication problems in real-life situations.
Instead, it is typically required to shift between operations. A result acquired through
routine laboratory testing may therefore not accurately reflect the individual’s arithmet-
ical ability in daily life. Moreover, it is assumed that arithmetical knowledge of addition
and multiplication facts is stored in long-term memory in highly interrelated associative
networks. However, because attentional and executive deficits are shown early
in AD, patients may find difficulties with tasks that put high demand on these func-
tions. With regard to MCI, minor executive deficits have also been reported. A recent
study on arithmetic by Zamarian and colleagues showed that, in the mixed and the
Stroop-like conditions, patients with MCI may manifest reduced performance. This
finding may help in developing a diagnostic tool to differentiate mild AD or MCI from
healthy aging. Zamarian and colleagues showed that both patients with AD and
MCI have intact arithmetical knowledge retrieval from long-term memory in the blocked
condition. However, whenever a load was put on executive functions, patients with AD
showed impairment, whereas patients with MCI successfully shifted between opera-
tions (mixed condition) but, if required to inhibit overlearned associations (Stroop-like
condition), they had difficulties. These findings, in line with previous studies, signify
the contribution of attentional and executive functions in arithmetic and are suggestive
of the potential importance of assessing arithmetical processing not only in blocked pre-
sentations but also in mixed presentations. There is a high ecological value in the mixed
condition because it mimics daily-life arithmetical activities (eg, checking the grocery
bill). As shown by recent outcomes, patients with AD and MCI who are in the normal
range in routine neuropsychological (blocked) arithmetical assessments might experi-
ence difficulties if extra requirements are demanded from nonnumerical resources,
which means they may not process arithmetic efficiently in real daily-life situations.

**Praxis**

Praxis denotes the performance of a learned motor act. In its broadest sense, apraxia
refers to impaired learned skilled movements that cannot be explained by weakness,
incoordination, abnormal tone, bradykinesia, movement disorder, dementia, aphasia,
poor cooperation, sensory loss, lack of comprehension, or inattention. Apraxia
can be defined as the loss of the ability to execute purposeful, previously learned
movements, despite the presence of the desire and the physical ability to perform
such movements. Apraxia is common in AD, and usually develops after the estab-
ishment of the impairments of memory and language. Apraxia also occurs in HD, cort-
icobasal ganglionic degeneration, and occasionally in Parkinson disease. Failure to
perform an act is not necessarily evidence of apraxia. In order for apraxia to be diag-
nosed, the act must be performed incorrectly, or components of the act must be per-
formed imprecisely. There might be omissions in parts of the act, or the acts may be
sequenced abnormally or incorrectly oriented in space. A complete assessment of
apraxia should include these subcomponents: imitation of gestures, use of imagined
objects, orobuccal movements, and a sequencing task such as the Luria 3-step com-
mand (fist, edge, palm) (see Table 1).

Apraxias are traditionally classified as limb-kinetic, ideational, and ideomotor.

**Limb-kinetic apraxia**

With limb-kinetic apraxia the act is understood but there is fault in motor execution.
Hence, there is loss of hand and finger dexterity resulting from inability to connect or
isolate individual movements. All types of movement are affected: symbolic, nonsymbolic, transitive (ie, using tools and instruments; eg, a hammer or a hairbrush), and intransitive (ie, communicative gestures; eg, representational tasks such as waving goodbye and nonrepresentational tasks such as touching the nose and wiggling the fingers). Movements of the mainly distal finger and hand are coarse and mutilated. All cases that were pathologically confirmed have shown a degenerative process involving frontal and parietal cortices or primary motor cortex.

**Ideomotor apraxia**

In ideomotor apraxia, a disorder of goal-directed movements, there is impairment of pantomiming ability to use tool; hence, patients know what to do but not how to do it. Such patients are able to accurately describe using a hammer but might be unable to imitate its use and, if given a hammer, to use it correctly. Transitive movements are more affected than intransitive. Voluntary automatic dissociation is present; therefore, that deficit is more apparent in clinical settings than in everyday life. Ideomotor apraxia signifies a difficulty in producing gestures caused by an inability to translate the concept of a motor sequence into the corresponding motor action; this happens because of functional disconnection of the idea of the act and the motor components of its execution. Ideomotor praxis can be tested by evaluating the ability to correctly form the necessary postures and movements to perform a task using a tool (see Table 1).

Anatomically diverse lesions mainly in left hemisphere typically involve parietal association areas and white matter bundles connecting frontal and parietal association areas. Another classification for apraxia is described as ideomotor, dressing, and constructional apraxia. One study performed on patients with AD and age-matched controls of apraxia showed that, on the tests of ideomotor and ideational apraxia, all types of movements were not affected to the same degree. Limb transitive movements were especially susceptible, whereas limb intransitive, buccofacial, and axial movements were relatively intact. No significant difference existed between performance on verbal command and imitation; however, considerable improvement was observed with the use of objects.

**Ideational (conceptual) apraxia**

These patients do not know what to do. Content errors are readily evident. This terminology can be puzzling, not only because, among investigators, definitions of ideational and conceptual apraxia vary but also because some scholars are debating a distinction between the two. Error types include impairment in carrying out sequences of actions that require the use of various objects in the correct order, in order to achieve a purpose, and loss of tool action knowledge. This apraxia can be tested by asking the patient to verbalize, step by step, how to do a job (eg, make a sandwich).

Qualitatively, disorders of skilled movement in AD were similar to the apraxic syndromes caused by left parietal damage. This study suggested that apraxia in AD may reflect posterior left hemisphere cortical involvement and may be apparent even in patients who manifest good language functions. In an anterograde and neuropathologic study, Giannakopoulos and colleagues investigated the neuroanatomic correlates of apraxia in 23 patients with clinically obvious AD. Their results suggest that ideomotor and dressing apraxias are associated with mild damage of the anterior cingulate cortex, whereas constructional apraxia is related to the disruption of cortical pathways that mediate visuospatial cognition in AD. However, this study included limitations: the neuropathologic analysis addresses only the left hemisphere whereas there is some evidence pointing to the role of the right hemisphere in dressing apraxia.
and drawing disability, and in the impairment in the production of intransitive movements following verbal commands. Moreover, depending on the neuropsychological tests selected, the definition of apraxia may vary in patients with AD. Although refined criteria exist for bvFTD, its differentiation from AD remains problematic at early clinical stages. Although apraxia is not considered as a supportive feature aiding the diagnosis of bvFTD, it is so considered for AD. However, only a few studies have attempted to quantify praxis disturbances in mild disease stages; the specificity of these attempts remains indistinct for AD compared with bvFTD. In cortical dementias, breakdown in the praxis circuit is one of the early dysfunctions and results in perplexity, awkwardness, omission, substitution errors, toying behavior, and unrecognizable gestures in response to command. Attention to the organicity of these phenomena helps diagnosis to be made in early stages, which consequently helps in adopting appropriate therapeutic measures and slowing the progression of the disease. Cotelli and colleagues conducted a study on 300 patients with dementia to test for ideational, ideomotor, limb-kinetic, buccopharyngeal, dressing apraxia, and constructional apraxia, and gait apraxias, in addition to recording rare apraxias if present. Patients with AD manifested apraxias in all the phases of the disease: ideational, ideomotor, dressing, and constructional apraxias in the early phases and buccopharyngeal and gait apraxia in the late phases. Late in the disease, patients with FTD showed buccopharyngeal and gait apraxias. Limb apraxias were seen in cortical basal ganglionic degeneration; diffuse Lewy body disease showed more agnosias and fewer apraxias. The most common apraxias were ideational and ideomotor.

**Dressing apraxia**

Dressing apraxia comprises a particular form of apraxia confined to the use of clothing and is often associated with focal lesions in the right parietal lobe.

**Constructional apraxia**

Constructional apraxia signifies a visuospatial disorder that is characterized by impairment in the spatial organization that is required when fragments of objects are assembled to form a single entity. This impairment is thought to be related to parietal-occipital cortex disorder; however, this view has been challenged. Usually, apraxia develops in late stages of AD, although reports have been made of patients with early constructional and ideomotor praxis disability.

**LANGUAGE DISORDERS**

Aphasia is a disturbance of language, in which the patient shows an impaired production and/or comprehension of spoken language that cannot be explained by an impairment of the neural apparatus for hearing, vision, or vocalization. Overall, language difficulties in AD often present as new problems with word finding, expression, comprehension, reading, writing, repetition, naming, and understanding the meaning of words. Patients may have difficulty following or joining a conversation; they may frequently have long pauses in the middle of a sentence, struggle with vocabulary, and use wrong or imprecise words (e.g., call a watch a “hand clock,” or frequently use “thing” instead of the correct word). Over time, the patients’ speech becomes increasingly inarticulate, it may lack information content, become simplified, agrammatic, and short. As the disease progresses, they also require frequent repetition and use of simple and short sentences in order to comprehend. Early on, this language problem can be confused with hearing problem. Older individuals experiencing normal
cognitive aging frequently complain of the inability to retrieve the right word or name, which invariably comes back later. This difficulty is not sufficient to affect consistent, efficient, and successful communication.

**Language Evaluation**

To evaluate the patient’s speech and language, gross signs of the motoric aspects of speech (eg, dysarthria; speech rhythm, prosody, and volume) as well as multiple aspects of language function need to be noted. These language functions can broadly be conceptualized as receptive language abilities (ie, the ability to process and understand written or spoken language) and expressive abilities (ie, the ability to express ideas in verbal or written language). It is important to make a distinction between whether a patient has a motor speech disorder (eg, dysarthria) or aphasia, which is a communicative disorder. It might not be possible or appropriate to reach a perfect analysis of language function in a screening mental status examination format; however, a gross evaluation of expressive abilities can be attained. Close attention also should be paid to several features of the patient’s spontaneous and conversational speech, including intonation, prosody, typical phrase length, the presence of grammatical terms, the presence and type of paraphasia, word-finding ability, and how well the patient seems to comprehend the content of what is being said. In addition, reading and writing also need to be assessed. Assessment of 6 basic elements of language can help identify clinical subtypes of aphasia: spontaneous speech, speech comprehension, naming, repetition, writing, and reading.

**Spontaneous Speech**

Abnormality in the patient’s spontaneous speech may be observed in several ways.

**Fluency**

Fluency (ie, the quantity of speech produced over time) may be reduced. Fluency is an aspect of executive function, because it requires implementing organized search and retrieval strategies. Fluency can be assessed by asking the patient to generate words beginning with specified letters or belonging to certain semantic categories. Problems with semantic categories often suggest AD or Semantic Dementia (SD), whereas difficulty with letter prompts (phonemic cueing) suggests frontal and/or subcortical deficits.

**Semantic fluency**

Semantic fluency is often evaluated using the category of animals. Typically, nonverbal fluency tasks (eg, design fluency, Ruff Figural Fluency Test) present patients with boxes containing dots and the patients are then asked to generate as many novel designs as possible. The fluidity, speed, and ease with which patients express themselves in conversation are parameters that can be noted in order to assess fluency. If the patient has lengthy pauses or is hesitant in word finding or word substitutions, a nonfluent or dysnomic language disorder might be present (ie, if psychomotor processing is not also assumed to be generally affected to the same degree).

**Verbal fluency**

Verbal fluency is an aspect of language ability that conceptually is under both domains of executive and language function. Formal evaluation of verbal fluency is included on several of the standardized measures summarized later (eg, Saint Louis University Mental Status Examination [SLUMS], Montreal Cognitive Assessment [MoCA], Addenbrooke’s Cognitive Examination Revised [ACE-R]). Typically, verbal fluency is assessed by asking patients to say as many words as they can think of.
that begin with a certain letter (letter or phonemic fluency task) or that belong to a certain semantic category (eg, animals, vegetables, tools; semantic category task). It is also informative to pay attention to the pattern of verbal fluency deficits. For example, in early AD, language dysfunction is often seen as a verbal fluency profile with worse performance on semantic tasks than letter fluency, which is likely to reflect temporal cortical dysfunction. In contrast, profiles of impaired word finding and naming (but improved naming when provided with hints or cues), and worse performance on letter fluency than semantic category fluency, are seen in early-stage patients with vascular cognitive impairment or other disorders that prominently affect frontoparietal language systems (eg, agrammatic or logopenic variants of primary progressive aphasia). If a patient’s primary symptom is language difficulty, it is essential to perform a more detailed language assessment, which is usually performed by a specialist.

**Prosody**

Prosody (ie, the musical qualities of speech: pitch, accent, and rhythm) can also be impaired. Thus, dysprosody is an impairment of speech melody, inflection, and rhythm.

**Paraphasia**

Paraphasia is defined by substitution of incorrect words for correct ones.

Patients with literal (or phonemic) paraphasia use words that resemble the intended word phonetically but contain 1 or more substituted syllables (eg, “hosicle” instead of “hospital”). Patients with verbal (or semantic) paraphasia use words that are real but that are unintended (eg, “hotel” instead of “hospital”). In some patients, paraphasic mistakes occasionally contaminate speech; in others, they almost fully replace it. Even when paraphasia is absent, it may be difficult to grasp the content of aphasic speech. Logorrheic but empty speech, as well as hesitation before certain words, may be indicate a severely restricted vocabulary.

**Paragrammatic**

Paragrammatic speech preserves a facade of syntax despite profoundly restricted semantic content. By contrast, agrammatic (or telegrammatic) speech omits relational words (such as prepositions or conjunctions).

**Speech Comprehension**

Abnormalities of speech comprehension, whether mild, moderate, or even severe, cannot be revealed through casual conversation with the patient. Particular testing is required. Clinicians should not depend on the patient’s verbal responses to commands or questions in order to assess speech comprehension. A wrong answer could signify a paraphasic error rather than the patient’s failure to comprehend. If the patients follow a command, whether simple or complex, it can be presumed that the command was understood. However, failure to follow a command could signify conditions other than impaired comprehension; for example, paralysis, apraxia, pain, or negativism. Asking yes-or-no questions is a more reliable method of testing speech comprehension. Even patients whose speech output is severely restricted can usually indicate affirmative or negative. Both the patient and the examiner must be aware of the correct answers. Another way to test speech comprehension is to ask the patient to point to objects or body parts. Similar to abnormal speech output, semantic and syntactic (relational) comprehension can be dissociated. Syntactic comprehension can be assessed by asking the patient to handle objects. For example, after the patient has identified a comb, a pen, and
a key, the patient could be asked to put the key on top of the comb or the comb between the key and the pen. The patient’s comprehension can be assessed by asking a question with complex grammatical constructions in need of processing of the sentences or asking the patient to perform a multistep command, preferably across midline. It is important to bear in mind that during longer verbal statements challenge both language abilities and working memory are involved; thus, if a patient does not manage to perform such a task, further testing is needed to better define the nature of the deficit.

**Naming**

If patients have adequate vision, they can be challenged with confrontation naming (ie, being shown objects, body parts, colors, or pictures of actions). A range of anomalous responses indicate anomia (the loss of the ability to recall or recognize the names of things). Some patients show paraphasias. Some hesitate and struggle to find the correct word (tip-of-the-tongue phenomenon). Rather than naming an object, some patients describe it. For example, instead of saying “necktie,” the patient says, “It’s what you wear around your neck.” Naming ability can briefly be assessed by asking the patient to name a few objects, starting with higher-frequency items and progressing to lower-frequency words (Box 13).

**Repetition**

One of the most important elements of language, which has an important role in differentiating types of dementia, is repetition. Evaluation of repetition is done by asking the patient to repeat sentences such as, “The cat always hid under the couch when dogs were in the room.” Patients may particularly have difficulty repeating syntactically complex sentences (eg, “If he were to come, I would go out”). Errors most often consist of paraphasic replacements.

**Writing**

In general, compared with reading, writing is more vulnerable to disruption; coordination of both central (spelling) and more peripheral (letter formation) components is involved in writing. Testing of writing begins by having patients sign their names. More specific tests of writing include dictated sentences, words, or letters, as well

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**Box 13**

**Tip-of-the-tongue syndrome (TOTs)**

- TOTs is a striking state of awareness; it is a common and dramatic word-finding failure, in which a person is temporarily unable to produce a well-learned word, despite being certain of knowing the word.

- Contradictory results are shown by the body of evidence for the nature of TOTs and its relationship with AD.

- For younger adults, episodes of TOTs occur about once a week and increase to about once a day for older adults. 

- TOTs is a phenomenon universally experienced by people of all languages and cultures; it is experienced by monolinguals and bilinguals, children, college-aged students, and older adults.

- TOTs are also detectable in several neurologic conditions, including AD, anomic aphasia, and temporal lobe epilepsy (see Brown and Schwartz and Brown).
as spontaneous writing; for example, describing what is seen in a room (see Table 1).³²

Reading
At first, the level of literacy should be assessed. The failure of comprehension is usually accompanied by an inability to read aloud; however, the reverse is not necessarily true. Reading ability is tested by having the patient read aloud simple sentences, words, or letters. Reading comprehension can be tested by having the patient follow written commands that were previously successfully executed as oral commands or by having the patient answer written yes-or-no questions (see Table 1).³²

Dysgraphia
Several problems can be caused in daily living by neurologic damage and cognitive dysfunction, such as loss of memory, and difficulties of written and oral communication.²⁸⁰,²⁸¹ Reading and writing can be directly assessed; patients can be asked to read a paragraph and to write a whole sentence. To test repetition, medium to long phrases or sentences are used. Agraphia is an acquired impairment in writing. The term alexia signifies a loss of reading ability in a previously literate person. One of the best studies on dysgraphia was performed by Onofri and colleagues,²⁸² in whose comprehensive article the history of dysgraphia is also reviewed. As early as 1907, Alzheimer’s²⁸³ had observed in patients abnormal graphic gestures, which indicated that a unitary process does not constitute handwriting, but that a coordination of linguistic and visual-spatial abilities is required,¹⁹³ which reflects brain damage in different associative areas, such as parietal, temporal, occipital, and frontal regions,²⁸⁴ in patients who are subsequently diagnosed with AD.²⁰⁸ Lambert and colleagues²⁸⁵ discussed a wide variety of agraphia syndromes, including a considerable number of patients with selective damage to one of the central or peripheral components, as well as patients who manifested multiple writing impairments. A positive correlation was registered between the severity of the dementia and spelling/writing measures. As observed in early AD,²⁸⁴ agraphia or dysgraphia comprise a progressive disorganization and degeneration of the various components of handwriting;²⁸⁶ these include the complexity of the structure of sentences,²⁸⁷ the diversity and the accuracy of words used,²¹⁰ punctuation,²⁰⁹ organization,²¹⁰ the production of grammatically incorrect sentences,²¹¹,²¹² the length of the sentences,²¹¹ the amount of written information,²¹² the morphology of the letters,²¹¹ and spelling,²⁸⁶ graphic and spatial layout of letters, and their arrangement in texts.²⁸⁹ The possibility that agraphia/dysgraphia may be an early sign of degenerative dementia was examined by Fukui and Lee²⁹⁰; they reported on the simultaneous or subsequent emergence of nonfluent aphasia, ideomotor apraxia, executive dysfunction, and asymmetric akinetic rigid syndrome. Their observations indicate that degenerative processes engage the parietal-occipital-temporal regions, basal ganglia, and striatofrontal projections. Within the AD population, it has been observed that writing impairment is heterogeneous. Nevertheless, certain aspects of the writing process are more vulnerable than others and may be regarded as diagnostic signs.²⁹¹ The understanding of disease progression may be facilitated through the identification and staging patterns of writing impairments/deficits during different phases of AD; they may also provide conditions for the development of applicable interventions. The relationship between cognitive impairment and the performance of handwritten scripts was examined by Onofri and colleagues²⁸² by asking patients with AD to do some letter writing to a close relative. Agraphia or dysgraphia is often observed in early AD; therefore, it encompasses a progressive disorganization and degeneration of the various components of
handwriting. The investigators showed that affected brain regions underlie functions in cognition, language, and motor domains, which are disturbed in AD. Dysgraphia manifests in the earlier as well as the later stages during the clinical course of AD; it is associated with deficits in attention, motor, and memory functions that develop during progression of the disorder. It has been suggested that, compared with anomia, dysgraphia is a more sensitive indicator for language deficits in AD. In one study using Hangul (the Korean alphabet), PET imaging of glucose metabolism indicated that the hypometabolism in the right occipitotemporal lobe and left temporoparietal lobe was related to writing impairment. Observations by other researchers have shown that dysgraphia associated with deficits in semantic memory, seem to correspond with current notions concerning the progressive performance impairments of patients with AD within language and cognition domains from a staging perspective. It has been concluded that the heterogeneous profiles of dysgraphia with primary signs of writing impairment in AD originate from changes in different regions of the brain networks that subserve writing and spelling performance. There is evidence for altered parietal-motor connections in AD; therefore, the possibility of related motor deficits in dysgraphia ought to be taken into account. It has also been found that, at an early stage of the disease, impairment occurs in the sensory-motor plasticity in the motor cortex of AD. It can be inferred from such findings that assessment of dysgraphia could serve as an additional diagnostic tool, providing evidence of compromised functioning in motor, cognitive, and emotional domains.

**Alzheimer's Disease: Involvement of Language or Working Memory?**

Impairments in working memory have dramatic consequences, therefore it has been suggested that the language impairments in patients with AD result from reduced working memory capacity. Other researchers have suggested that, in addition to having compromised working memory function, patients with AD have lost core linguistic knowledge. In all cases, researchers have formed several assumptions about what linguistic working memory is. These assumptions centrally include the notion that damage can occur in the knowledge of language and working memory capacity independently.

**Language and Semantic Knowledge**

On tests of object naming, verbal fluency, and semantic categorization, mildly demented patients with AD often show impairment. There is evidence that these impairments reflect decline in the structure and content of semantic memory. As the neurologic disorder of AD impinges on the temporal, frontal, and parietal association cortices, in which knowledge for particular items or concepts are thought to be diffusely stored, the knowledge and associations between them may be disrupted. Impairments in confrontation naming and verbal fluency are evident in mildly to moderately impaired patients with AD. It has been argued by some clinicians that these deficits result from a broader impairment in semantic memory. Several studies that probed for knowledge of particular concepts across different modes of access and output (eg, fluency, confrontation naming, sorting, word-to-picture matching, and definition generation) have provided evidence for a deterioration of semantic memory in AD. These studies assume that loss of knowledge, and not impaired retrieval of intact knowledge, leads to consistency of performance across items. For example, if the concept of a horse is lost with a patient, the patient should not be able to name a picture of a horse, generate “horse” on a verbal fluency test, sort horse into its proper category as a domestic animal, and so on. Using a range of tasks that include category fluency, category membership, confrontation naming,
and similarity judgments, semantic memory abnormalities in patients with AD have been documented. However, other studies that have used a variety of tasks, including recognition naming, category-naming fluency, drawing fluency, and category membership judgments, have failed to reveal such category-specific differences. It has been suggested that inconsistent findings regarding category-specific semantic loss in patients with AD relate to the fact that, for category-specific judgments, some brain regions are more critical than others, and the presence of a deficit depends on the anatomic distribution of disease in the specific patients examined. It is also assumed that loss of knowledge of the attributes and associations that define a particular semantic category reduces the ability of patients with AD to efficiently generate words from a small and highly related set of exemplars during tests of verbal fluency. Thus, patients with AD show more impairment on category fluency (eg, generating lists of animals) than letter fluency (eg, generating words beginning with a specific letter). The fact that patients with AD are more impaired on the fluency task, which places greater demands on the integrity of semantic memory, is consistent with the assumption that their structure and organization of semantic memory has deteriorated, rather than having a general in ability to retrieve or access semantic knowledge. It is suggested by studies of semantic memory in patients with AD that some conceptual domains may be more impaired than others; in particular, that patients with AD have a specific impairment in the conceptual domain of living things. For example, in studies assessing confrontation naming and picture recognition, patients with mild to moderate AD performed significantly worse in the category of living things than in the category of nonliving things.

**VISUAL FUNCTION**

Visual sensory functions are reported to be impaired in AD, including spatial contrast sensitivity, color, stereopsis, temporal resolution, and motion. Visual attention and higher visual functions such as reading, route finding, object localization, and recognition can also be affected in AD. Through a better understanding of these vision-related deficits, diagnosis, interpretation of cognitive scores, and interventions could be aided to improve functional capacity in patients with AD. On tests of static spatial contrast sensitivity, visual attention, shape from motion, color, visuospatial construction, and visual memory, patients with AD have been shown to perform significantly worse. AD affects several aspects of vision, which is compatible with the hypothesis that visual dysfunction in AD may contribute to declines in performance in other cognitive domains.

**EXECUTIVE FUNCTION**

Executive functions generally mean higher-level cognitive functions that are involved in the control and regulation of lower-level cognitive processes and goal-directed, future-oriented behavior. Having been dubbed the most subtle and central realm of human activity, executive function is particularly important to assess because it is affected in most types of dementia. The term executive function is an umbrella term denoting various complex cognitive processes and subprocesses. Most attempts to define executive function end up with a list of examples (such as decision making, task switching, planning, organization, fluency, abstract reasoning, solving novel problems, modifying behavior in the light of new information, generating strategies, or sequencing complex actions and skills such as mental flexibility and response inhibition) or that other useful umbrella term, working memory, which indicates that executive function is in no way a unitary concept.
summarized executive function as “a product of the coordinated operation of various processes to accomplish a particular goal in a flexible manner.” It is the responsibility of executive control systems to achieve a specific goal through this flexible coordination of subprocesses. The neuropsychological literature is in agreement that successful performance on tests of executive function is critically dependent on the frontal cortex; the terms executive function and frontal lobe function are often used interchangeably. Moreover, PFC has been indicated to be critical for performing executive function tasks, through lesion studies and structural and functional neuroimaging studies. However, it has recently been suggested that this view is simplistic; more recent theories point to the critical involvement of subcortical regions as well. Direct assessment of the neuronal basis of executive functions has been made possible through advances in neuroimaging. Perhaps unsurprisingly, these complex processes seem to be subsumed by distributed circuitry structures rather than discrete structures. It is not necessary to evaluate specialized cognitive functions during all screening mental state examinations in the primary care setting. However, in certain primary care situations, some tests of specialized cognitive functions can be included and should often be included in screening by subspecialists. These tests include assessment of calculations, reasoning, problem solving, abstraction, agnosia, neglect, praxis, insight, and judgment. Some of these domains that include calculations are to be as complex as the patient’s level of education or highest function allows. The ability to generate verbal or nonverbal responses is another aspect of executive functioning. Verbal fluency is discussed earlier, but the executive component of these types of tasks is that they require the patient to generate novel responses in accordance with a set of rules (eg, to say or write words or create designs following a rule set). Executive function impairments are evident on these tasks in a reduction of ability or inability to generate responses, difficulties maintaining cognitive set (eg, when instructed to say as many “A” words as possible, a patient says a word beginning with another letter), and perseverative errors (ie, repeating previously stated responses). Impairments in executive functions that are responsible for the mental manipulation of information, concept formation, problem solving, and cue-directed behavior manifest early in the course of AD and are often evident in the MCI stage. Initially, an alteration in executive function ability was not recognized among patients with AD, because early studies did not implement sensitive tests of executive function. Once sensitive tests of executive function began to be used to evaluate mildly impaired patients with AD, these impairments became apparent. For example, mildly impaired patients showed impairment on tasks that involved coordinating 2 concurrent tasks, as well as tasks that required shifting between stimulus dimensions. Mildly to moderately impaired patients also show executive function deficits. Several studies have tried to determine whether impairment in executive function precedes significant deficits in spatial and language function or coexists with them. These studies have compared very mildly impaired patients with AD with controls on tasks assessing a range of cognitive domains. It was reported by Grady and colleagues that deficits on tasks of memory and executive function preceded impairments in language. Lafleche and Albert attempted to describe the specific aspect of executive function in which very mildly impaired patients with AD showed impairment. The investigators assessed a spectrum of executive abilities, including set shifting and self-monitoring (ie, the concurrent manipulation of information), cue-directed attention (eg, the ability to use cues to direct attention), and concept formation (eg, abstraction). The tasks that required set shifting and self-monitoring revealed the most significant deficit.
By contrast, patients did not show major impairment on tasks that assessed cue-directed attention and verbal concept formation. Similarly, no impairment was registered in performance on the tests of confrontation naming, figure copying, and sustained attention. These findings, taken together, suggest that very early in the course of the disease selected aspects of executive function are affected, particularly those involving set shifting and self-monitoring.

However, no consensus exists regarding whether during prodromal AD executive function deficits are prominent. The inconsistencies among studies are, at least partially, caused by the shortage of studies that have examined a wide variety of cognitive domains, and thus the types of associations that can be found are limited. Several studies have reported that, in the prodromal stage of AD, executive function abnormalities are shown. Other studies have reported that people destined to develop AD are more likely to show declines in confrontation naming (eg, Ref.356). These discrepancies remain to be resolved. The brain abnormalities associated with executive function deficits that are seen among individuals destined to develop AD are also unclear. At least 2 potential neurobiological explanations have been put forth. During prodromal AD, findings from functional imaging indicate that dysfunction exists within a brain network that involves the dorsolateral PFC and the anterior cingulate. An alternative possibility is that the disruption of the corticocortical connections that are seen in AD, and that are not specific to the frontal lobes, may be responsible for executive dysfunction. In addition to difficulties with delayed memory recall, executive function deficits predict subsequent progression to AD dementia. A well-controlled study has shown that very mildly demented patients with AD were significantly impaired relative to cognitively normal controls on tests that required set shifting, self-monitoring, or sequencing, but not on tests that required cue-directed attention or verbal problem solving. Thus, this study suggests that reduced ability to mentally manipulate information may be a particularly early feature of AD. Similarly, several other studies have also shown that patients with AD are impaired on difficult problem-solving tests that require mental manipulation, such as the Tower of London puzzle, the modified Wisconsin Card Sorting Task, tests of relational integration, and other tests of executive functions such as the Porteus Maze Task, part B of the Trail Making Test, and the Raven Progressive Matrices. It has been hypothesized that these deficits in executive functioning reflect features of AD, especially neurofibrillary tangle burden, in PFC. This regional PFC disorder is particularly noticeable in a subset of patients with AD who predominantly present executive dysfunction in an early stage. This finding again highlights the influence of anatomically specific findings on the disruption of distinct neocortical networks. Among the cognitive domains, some might be less known to neurologists, such as mental flexibility and the inhibition response (Box 14).

**MENTAL FLEXIBILITY**

One of the best tests to evaluate attention and cognitive flexibility is the Trail Making Test, which is widely administered. In the part A of this test, patients are asked to connect a series of numbered circles arbitrarily distributed on a page. In part B, the patient is asked to alternate between connecting numbers and letters in a series (see Table 1). The scores are derived from the time the patient takes to complete each part. This test is principally sensitive to the progressive cognitive decline in dementia. Poor performance on part B by an elderly person is likely to be associated with problems performing complex activities in daily living.
INHIBITION RESPONSE

Through inhibition the patient is required to suppress an overlearned response or a noticeable environmental stimulus. To assess inhibition, Stroop interference tests are widely used. In this paradigm, patients are shown a series of color names printed in different color ink (e.g., the word “RED” printed in blue ink). The patient is supposed to inhibit the overlearned tendency to read the word and instead name the color of the ink in which the word is printed. In other tasks, such as opposite responding, patients are required to inhibit their response to a salient stimulus and provide a competing response. Executive functions can be informally assessed by observing for signs of disinhibition, such as frequently interrupting or making socially inappropriate comments. Moreover, patients with executive dysfunction also commonly have difficulty shifting from one task to another. This difficulty can be observed during interview: when the topic of conversation or task changes, the patient might show difficulty, be perseverative, or have poor mental flexibility. Elements of executive function can be formally assessed by asking the patient to alternate between reciting or drawing lines on a piece of paper between 2 sequences (e.g., alternate between counting by 7s and recite the months of the year; alternate between stating the letters of the
With regard to executive and administrative functions, reasoning, judgment, insight, and decision making, patients with AD experience progressive difficulties that often manifest in daily challenges. Such challenges are faced in organization, planning, problem solving, social interactions, doing or completing familiar tasks at home and at work, and making suitable judgments and decisions, and include the patients’ appreciation of the extent and nature of their cognitive, functional, and behavioral changes and limitations. Some individuals experience changes in their ability to develop and follow a plan; work with numbers and money; follow a familiar recipe; or keep track of and manage monthly bills, finances, and tax records. Patients may become less efficient or effective while accomplishing tasks that they previously did, or may have great difficulty learning how to handle new tools or procedures. For example, relative to the past, the work they produce may consistently be of inferior quality, to accomplish a task might not be as effortless or as time-efficient as before, or they may be unable to satisfactorily learn a new system or procedure (eg, writing a report, managing a budget, learning a new computer program or work flow at work). They may also frequently have difficulty with concentration, be easily distractible, and often lose their train of thought. In addition, they may manifest deterioration in their ability to comprehend information, manipulate it, and make important connections and deductions necessary to make reasoned judgments and appropriate decisions. For example, they may have poor judgment when dealing with money; give large amounts to telemarketers, strangers, or associates; make poor purchases; display major changes in their spending; and not fully grasp that their ability to function and make decisions has changed (ie, have anosognosia). In addition, they may be less able to temper their affect, have poor impulse control and insight with regard to their behavior, and become less aware of proper grooming and hygiene. Differentiation of the age-related cognitive deficits from very mild AD is one of the great challenges that clinicians face. Normal cognitive aging does not preclude occasionally making an error while balancing the checkbook; being late with a check; having to look up a recipe; needing greater time or help to use a new device, tool, or program; having to be reminded of details of a conversation; or sometimes losing concentration and being distracted during a task. However, the frequency of these occurrences is significantly greater in AD. Making an occasional poor decision, being easily distracted (especially in the context of multitasking or not being present in the moment), or making an occasional careless mistake is normal.

**SUMMARY**

Neuropsychology has made a crucial contribution to the characterization of the dementia associated with the neurologic disorder of AD, its differentiation from cognitive changes associated with normal aging, and its distinction from dementias related to other types of neurologic disorder. The earliest neuropsychological symptoms of a dementia reflect their associated neuroanatomic systems; however, the relationship between the symptoms and the underlying disease is less obvious. Therefore, in early stages, neuropsychological profiles are most informative. It is true that the accumulation of fluid and neuroimaging biomarkers will improve diagnosis and ultimately be used to measure the efficacy of the treatment. However, neuropsychological characterization continues to be of essential importance in understanding the individual patient’s deficits and be valuable as a noninvasive, inexpensive and available method. The implementation of such an approach might be influential in the development of
more sophisticated diagnostic procedures and aid in more appropriate selection of nonpharmacologic and/or pharmacologic interventions.

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