Keep in Mind

- Is dementia inevitable? How does healthy "normal" aging differ from dementia?
- Are dementia and Alzheimer's disease synonymous?
- Does Alzheimer's disease selectively affect "memory" structures of the brain?
- Why is Alzheimer's disease so difficult to diagnose?

Overview

Elderly adults are the fastest growing segment of the U.S. population. In 1900, 4% of the population was older than 65. As of the 2000 census, this number has mushroomed to 12.4%, or 34.9 million people. In the year 2030, estimates suggest 20% of the population will be older than 65, constituting approximately 70 million people (Administration on Aging, 2000). The 85-and-older group is expected to double its current size. This trend toward an aging population is found throughout Western industrialized countries. These numbers reflect increased life expectancy and medical advances. However, diseases of aging become a great concern.

Tremendous research effort is focused on understanding the neurologic conditions that target older people. Among these conditions are a group of disorders, collectively known as the **dementias,** that cause global declines in cognitive and behavioral functioning. They have no one cause, and most causative factors are still not fully understood. Moreover, many dementias have no known cure. Dementia is often progressive, eventually affecting numerous higher mental facilities. It is often considered a "thief of the mind," first robbing one aspect of cognition such as memory, communication ability, or visuospatial skills, but then returning to steal other aspects of mental functioning.

With a top-heavy population of aging baby boomers, the problem of identifying dementia and providing medical and psychological services to patients and families is becoming increasingly important. About 10% of Americans older than 65 live in specialized settings (such as residential care facilities or assisted living), and more than 1 million live in nursing homes. Older people account for more than 40% of hospitalization days in acute-care hospitals. They buy 25% of all prescription drugs and use 30% of the total health budget. Clinical neuropsychologists contribute valuable assessment skills to distinguish normal aging from dementia. They also play an important role in health care decision making, helping match level of care to an older patient's actual needs.

This chapter examines the differences among normal aging, mild cognitive impairment (MCI), and dementia, and addresses questions regarding the aging brain and neuropsychological functioning. For example, is there an inevitable cognitive decline with age? This question can be addressed by considering the neuropsychological profiles of both healthy older adults and those with dementia. We examine dementias in both this and the next chapter. This chapter presents an in-depth evaluation of the most common dementia syndrome: Alzheimer's disease (AD). This cortical dementia is examined from a neuropathologic, neuropsychological, and behavioral perspective. Chapter 15 presents the subcortical dementias of Parkinson's disease, Huntington's disease, and Creutzfeldt–Jakob disease.

Normal Aging

Defining "normal aging" is a challenge. Stereotypes and concerns abound as people face getting older. Socially, we may fear becoming isolated with adjustment to retirement and death of friends or a spouse. Physically, age brings the threat of increased ailments and chronic illness. Cognitively, the possibility of memory problems, mental slowing, and dementia looms. These concerns are often amplified by myths of aging, painting people older

Figure 14.1 (a) Tina Turner, one of the world's most successful female rock artist, performs at age 65. (b) Dr. Ruth Patrick, one of the world's leading biologists, is still active at age 94. ([a] © Heinz Award photo/Lynn Keith; [b] REUTERS/Alexandra Beier.)

than 65 as unattractive, dull, sickly, and unproductive (Dychtwald & Flower, 1989). Stereotypes of aging, however, can be shattered by examples of highly functioning people. From rock performers such as Tina Turner to renowned scientists like Ruth Patrick (Figure 14.1), we witness the great range of physical, social, and mental ability of people older than 65 and ask, What can we learn from those who age well?

One of the challenges for brain scientists is that the range of cognitive variation for people older than 65 is wide compared with people in their 20s, 30s, 40s, and 50s. Some of this increased variation is due to the incidence of brain diseases of aging, such as the dementias or strokes, and some of this may be due to "age-related" declines in cognition that affect people differentially as they age. A large part of what clinical neuropsychologists are asked to do is to aid in determining the difference between normal cognitive declines due to the aging brain and brain diseases. Inherent in this is whether problems such as forgetting of names can be considered "normal age-related" or as the harbinger of AD. Scientists have wondered whether age-related declines in cognition will inevitably lead to dementia (that is, is normal aging and dementia on a continuum?) or whether there is a qualitative difference between a disease state and the aging brain. This issue is explored within this chapter and in Chapter 15.

This section reviews both cognitive and brain changes associated with normal aging in humans. By considering both cross-sectional and longitudinal studies, as well as studies that compare normal aging with dementia, a picture of normal aging, cognition, and the brain emerges.

COGNITIVE CHANGES ASSOCIATED WITH AGING

Why is there such a range of functioning in people older than 65? Does everyone lose some cognitive functions even if they do not have degenerative brain disease? Is cognitive decline uniform, or are certain areas more likely to decline than others? What is the trajectory of cognitive decline? Finally, are there protective factors against cognitive decline and disease?

Numerous examples exist of people who stay active and working in their fields well past the age of retirement. Whether a scientist, a musician, or a mechanic, these people have developed an expertise and an accumulated body of knowledge related to their work. In fact, all people are likely to develop areas of expertise over their lifetimes related to work, hobbies, or talents. This **crystallized intelligence** consists of stored knowledge and habitual ways of acting or solving problems built up over a lifetime. By rehearsal, practice, and use, certain domains of knowledge become strengthened and are more easily accessible and perhaps less subject to decay. Verbal scales of intelligence tests typically measure general crystallized intelligence not related to a specific work domain. They measure factual knowledge, such as vocabulary definitions, or general information learned in school. Crystallized intelligence represents an accumulation of acquired skills and general

information and is more related to formal education or diverse social experiences. Research using the Wechsler Adult Intelligence Scales (WAIS-R) suggests that levels of crystallized intelligence show only slight changes as we age (Kaufman, Reynolds, & McLean, 1989). It has also been theorized that higher levels of crystallized intelligence or general knowledge may provide a protective factor, or "functional reserve" (in this case, a "cognitive reserve"), against dementia that allows the brain to compensate in the presence of declines presented by aging or disease.

Two series of studies lend credence to the idea that a protective cognitive reserve may start early in life. The first of these is provided by the longitudinal study of aging and AD called the *Nun Study*. David Snowdon of the University of Kentucky has followed 678 Roman Catholic sisters who agreed to regular cognitive and medical assessments and brain donation at death. Snowdon and his colleagues seek to shed light on the factors that lead to increased longevity, as well as on the determinants of AD and other brain disorders such as stroke. What is unique about this research is the availability of records from young adulthood and throughout the time each nun resided in the convent. In one study, Snowdon and colleagues (1999) examined the linguistic complexity of autobiographies written as the nuns entered the convent between ages 18 and 32. Women who scored lower on "idea density" (that is, the number of different ideas discussed) early in life also showed lower cognitive functioning after age 75. Also, autopsies of a small sample of nuns indicated that the women who had brain markers of AD showed lower "idea complexity" as young women than those who did not have brain pathology.

Snowdon's studies used "idea density" as a proxy for intelligence, but researchers from Scotland (Whalley, Starr, Athawes, Hunter, Pattie, & Deary, 2000) were able to actually assess the relation between a standardized general intelligence test, administered at age 11, and signs of dementia more than 50 years later. Children who had higher mental ability were less likely to have dementia when they were located again at age 72. Interestingly, there was no relation between mental ability and decline for those who had been diagnosed with an early-onset (before age 65) dementia. Early-onset dementias, as discussed later, may be caused by disease processes that are different than late-life cognitive decline.

Both the Nun studies and the Scottish studies show a correlational link between early intelligence and the health of the aging brain. One possible explanation is that a "cognitive reserve" serves as a reservoir to resist the effects of aging. If this is so, it is not yet known whether cognitive reserve is, for example, a reflection of having more neurons and glial cells in crucial areas or the result of wider or more efficient semantic networks. In addition, the positive correlation between intelligence and the aging brain may be related to other factors associated with longevity. Those with higher intelligence may be more likely to seek and follow health information, have higher paying jobs, adhere to a better diet, and have better access to health care.

Even people who show little signs of cognitive decline, however, are likely to notice changes in **fluid intelligence.** Areas of fluid intelligence involve novel reasoning and the efficiency of solving new problems or responding to abstract ideas. Fluid intelligence has also been conceptualized as a measure of adaptability. Fluid intelligence is most directly related to the influences of changing biological factors and is relatively unaffected by higher levels of experience or education. The most reliable declines in cognition show up in three areas of intellectual activity, all of which are considered fluid markers of intelligence: (1) processing speed, (2) abstract and complex new problem solving, and (3) memory and new learning.

Tests of fluid intelligence (for example, Wechsler's Digit Symbol and Block Design) generally require both novel processing and the ability to complete a task quickly. Studies of aging suggest that performance on tests of this type declines across the life span (Salthouse, 1991). Behavioral slowing also occurs and may partly contribute to poorer performance on a number of tests of fluid intelligence where speed is a factor, but age-related decline is still observed on novel problem-solving tasks even in the absence of speed demands.

Studies of aging suggest that older people are more likely to have more difficulties in many aspects of memory. Early research in aging and memory suggested that the main problem for older people was information retrieval. Poorer performance occurs with free recall, compared with recognition, with less contextualized information, and when more effort is involved. However, new learning may also be difficult because of problems in encoding, particularly with intentional encoding. In fact, some of the retrieval issues relating to poorly remembered contextual information may be due, in part, to poor encoding of context at the outset. Once information is encoded, however, healthy older adults seem to show similar semantic storage in long-term memory as younger adults. Semantic storage can be conceptualized as drawing more heavily on crystallized intelligence and knowledge structures (Bäckman, Small, Wahlin, & Larsson, 2000). There also appears to be little effect of aging on procedural and implicit memory tasks, although these may be performed more slowly.

It has been predicted that older adults would perform more poorly on prospective memory tasks because of a high degree of self-initiation required in remembering to do something in the future (for example, McDaniel &

Einstein, 2000). However, because prospective memory requires both remembering "what" is to be done and "when," it appears that older people have more trouble with the "what" or content that may have more to do with basic encoding, storage, and retrieval mechanisms in retrospective memory (for review, see Henry, MacLeod, Phillips, & Crawford, 2004). Although older people may perform more poorly on laboratory prospective memory tasks, they do much better on real-life tasks, such as keeping appointments or remembering to post mail or return phone calls; tasks for which motivation may be different or external reminder aids may come into play (for review, see Henry et al., 2004).

A number of researchers suggest that working memory (WM) capacity declines with age. Interestingly, short-term memory, or the ability to recall strings of digits, does not appear to decline with age. However, this is a more passive task than WM, where information must not only be held but also manipulated and processed in a more complex manner.

How stable is cognitive functioning among those 75, 85, or older? Does the pattern look the same as one continues to get older? Do initial losses of function stabilize, is there a gradual decline, or is there an acceleration of loss in some areas of functioning? In a review of studies of longitudinal aging, it appears that the pattern of preserved crystallized intelligence over fluid intelligence does not hold in those adults older than 75 (Bäckman et al., 2000), and all intellectual abilities show a decline in group studies.

However, a series of interesting studies conducted in Sweden document the neuropsychological performance of the oldest segment of the population. In one study, researchers gave neuropsychological tests twice, 2 years apart, to more than 300 people between the ages of 84 and 90 (Johansson, 1991). This study of the oldest old (84–90 years old) found surprising stability in neuropsychological functioning between the first and second test sessions. Researchers expected that functioning of people at this advanced age would decline over 2 years. However, two thirds of the sample (66%) remained at the same cognitive level, whereas 31% declined (Johansson, Zarit, & Berg, 1992). Almost half (42%) remained in the normal range of functioning during the 2-year time period. This finding was surprising not only in that a large portion of the sample showed stability of cognitive function over time but also that a significant portion of quite elderly adults still had "normal" cognitive function.

Johansson and his colleagues (Johansson, 1991) suggest that cognitive changes were more related to terminal decline, or proximity to death, than to chronologic age. Among other neuropsychological tests, these examiners administered the digit span task, at regular intervals, to normally aging Swedes older than 70. This requires repeating increasingly longer series of digits either in sequential or reverse order, respectively, until the testee misses them. For the 70- to 88-year-olds studied over time, Johansson examined two groups: those who died before age 85 and those still living. Those alive at age 85 showed a consistent performance as they aged; those who died before age 85 started showing a drop in backward digit span by age 75 and marked declines in both forward and backward span lengths by age 79.

What then is the secret of people who are active and productive well into their later years? In recent years, much focus has been on what can be termed the "use it or lose it" hypothesis. This idea suggests that by keeping mentally active, or by increasing mental exercise, older people may be able to stave off mental decline and diseases of aging. The question is, does mental exercise, such as doing crossword puzzles, starting a new hobby, or memory training help to slow or reverse the affects of aging? This hypothesis has also been called the *differential-preservation* hypothesis (Salthouse, Babcock, Skovronek, Mitchell, & Palmon, 1990) because it is assumed that the large age differences in cognitive functioning seen in the oldest adults are due to differences in their current levels of mental activity and mental exercise. This is in contrast with the *preserved-differentiation* hypothesis (Salthouse et al., 1990) that is more in line with the idea of "cognitive reserve" discussed earlier in this section. In other words, it may be that the range of cognitive differences found among older people are because those who showed higher cognitive ability to begin with continue to show this pattern as they age. In a recent review and commentary on this issue, Salthouse (2006) suggests that the research on "mental exercise" or training as a strategy has not yet demonstrated convincing results. For example, research focused on training people on various cognitive tasks, although showing some immediate benefits in targeted task performance, has not shown to be generalizable to other tasks, often in the same cognitive domain. Also, the effects of training are not convincingly sustained over time compared with those who were not trained. Therefore, although there is much optimism in the popular press about our potential ability to stave off the general effects of aging through mental exercise, this idea does not yet appear to be supported.

Although the mechanisms are not yet known, people who continue to be active well into their 70s, 80s, and 90s may be the best at resisting both declines in fluid and crystallized intelligence. They may have started out with a higher level of crystallized intelligence, and thus are provided with a certain degree of cognitive reserve. They may have learned a great deal in their life, which also provides

them with strong crystallized semantic networks. Although aspects of fluid intelligence such as speed and flexibility of thought may decline, many older people do maintain an active and independent lifestyle well into their later years.

BRAIN CHANGES ASSOCIATED WITH AGING

Variation in functional abilities with aging is a clue that the brain may not decline in a uniform manner. But how does it age, and when is change noticeable? By reviewing both global (structural and neuronal) and regional brain changes affected by aging, as well as considering the trajectory of decline and factors that impact brain aging, a picture emerges of how the brain changes as people grow older.

The aging brain undergoes visually apparent gross structural changes such as diminution in size and weight, flattening of the cortical surface, and expansion of the cerebral ventricles. The loss of weight and volume occurs in a general linear trajectory (for review, see Raz, 2000). One of the first recognizable global indexes of brain health or shrinkage is widening of the ventricles. If the brain loses volume in any area, the ventricles reflect this. However, this gross marker does not necessarily imply that the brain loses volume equally across all areas.

Concomitant changes occur at the neuroanatomic and biochemical levels. Neurons undergo significant structural changes with aging. Aging cells may shrink and die, lose some of their dendritic processes, and develop a yellowish brown pigment that accumulates in cells of the cortex and cerebellum and may have to do with "wear and tear" (Bourne, 1973; Kemper, 1994). Observations of cortical thinning may have led to one of the myths of human neurobiology, namely, that throughout adulthood people lose a great number of neurons from their brains each day. Better measurement methods indicate that this is exaggerated, and that much cortical thinning may be due to neuronal shrinkage rather than loss (for review, see Haug, 1985). Although some markers of neuronal abnormalities such as **neurofibrillary tangles** and **senile plaques** (see Figures 14.6 and 14.7) are hallmarks of AD and other dementias, they also occur in older people without frank evidence of cognitive dysfunction.

Images of aging brains often show white matter abnormalities indicating attenuation of myelin around the axons of neurons. This observation has led a number of researchers to question whether white matter (that is, myelinated axons) or gray matter (that is, cell bodies) may succumb more quickly to the aging process. Cerebrovascular disease and hypertension, both more common in older adults, are associated with white matter abnormalities (for example, Strassburger et al., 1997), but these comorbid problems of aging do not appear to fully explain white matter aging. In an analysis of studies across the life span, gray matter suffers a linear decline from infancy through old age, whereas white matter shows an inverted U-shaped function with increasing white matter into young to middle adulthood, followed by a plateau and then a decline into old age (for review, see Raz, 2005).

The brain shows differential changes with aging. Although some brain areas appear more vulnerable to the effects of aging, there are islands of relative preservation. The hippocampus, the frontal lobes, and specific association areas of the temporal and parietal lobes are more vulnerable, whereas the occipital and somatosensory cortices are relatively preserved. The frontal cortex is one of the cortical areas most affected by aging. The most likely set of age-related neuronal changes specifically affects the prefrontal cortex (Esiri, 1994). Neuronal loss in this area may account for some of the fluid intelligence changes in cognitive functions occurring in older people.

Because cognitive functioning varies widely among older people, it is also reasonable to assume that there is a range of individual variability in physical brain changes. When assessing the degree of cortical **atrophy** caused by advancing age, gross inspection of the brain demonstrates wide variation (Figure 14.2). In the Swedish study (Johansson, 1991), 85% of elderly adults' brains appeared to have little to no evidence of cerebral atrophy. However, all did show some neuropathologic markers usually associated with dementia, including signs of ischemia (that is, insufficient blood supply), neurofibrillary tangles, and senile plaque formations. In individuals older than 85, gray matter atrophy is often apparent on computed transaxial tomography (CT) in both demented and nondemented people. White matter attenuation (thinning of the white matter) relates to cognitive changes associated with fluid intelligence, such as slowed speed of behavior, poorer spatial ability, poorer arithmetic, and memory recognition skills (Johansson, 1991).

Genetic and environmental factors also play a role in an individual's vulnerability to brain aging. A variety of genetic factors have been implicated in the dementias discussed in this and the next chapter. Some of these genetic factors may also prove to accelerate the aging process in people who do not develop a full-blown dementia. For example, a specific allele of apolipoprotein E (that is, ApoE4) has been implicated in some forms of AD. However, ApoE4 may also be implicated in general problems of white matter maintenance through its action on the cholesterol system of the fatty oligodendrocytes that make up the myelin sheath and through a disruption in the

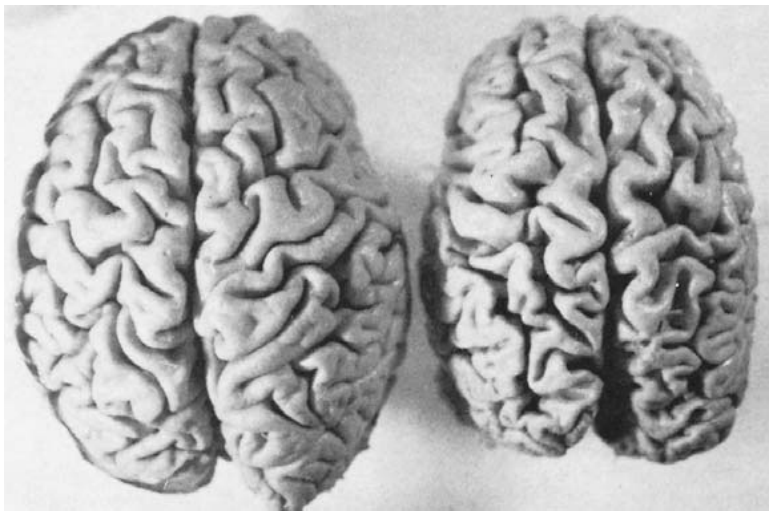

Figure 14.2 Normal brain (left) and brain showing widespread cortical atrophy (right). Note the thinner gyri, wider sulci, and widening of the interhemispheric fissure on the right. Cortical atrophy indicates loss of neuronal connections but not necessarily clinical dementia. (Reproduced from Bigler, E. D. [1987]. The clinical significance of cerebral atrophy in dementia. *Archives of Clinical Neuropsychology, 2,* 178, by permission. Copyright © 2000 Elsevier Science.)

maintenance of intracellular calcium balance (Masliah, Mallory, Veinbergs, Miller, & Samuel, 1996; Raz, 2000).

It is generally accepted that prolonged stress has negative effects on health. However, studies of stress and aging suggest that stress may age both immune and brain cells. Immune cells contain chromosomes with end caps termed *telomeres.* Telomeres shorten as cells reproduce and are a measure of the life of the cell. In a study of women who were continually under high stress levels because of caring for chronically ill children, it was found that their telomeres had undergone the equivalent of 10 more years of aging as compared with women who were living less stressful lives (Epel et al., 2004). Stress also appears to affect certain brain areas. For example, people who have high basal cortisol levels (a biochemical marker of stress) show reduced hippocampal volumes over time (Lupien et al., 1998).

Whereas stress may negatively impact the brain and cognition, aerobic activity appears to enhance it. Older people who engage in regular aerobic activity perform better than sedentary people on a wide range of cognitive tasks (for review, see Colcombe & Kramer, 2003). In direct measures of brain density, it has also been reported that exercising older adults showed reduced loss of gray matter in frontal, temporal, and parietal areas, as well as less reduction in white matter tracts in both anterior and posterior brain areas (Colcombe et al., 2003).

Mild Cognitive Impairment

People who show more than age-related cognitive decline, but do not meet the criteria for dementia, have been the focus of active research interest in recent years. The term ***mild cognitive impairment*** **(MCI),** although somewhat controversial and nonspecific, has come to imply an intermediary, and perhaps transitional, stage between normal aging and dementia. The use of this term has been somewhat controversial because it may be used in an overgeneralized fashion to refer to any number of cognitive changes, but it can be useful if it is well defined. Research also suggests that the presence of MCI is a risk factor for dementia.

Theoretically, MCI can affect many areas of cognition, but most research has focused on memory, or the *MCI-amnestic* type. This criterion identifies memory impairment (for example, Petersen et al., 1999) as the primary cognitive abnormality. In comparison with age-matched control participants, those with MCI-amnesia show deficits in both encoding and retrieval (Bennett et al., 2002; Wang & Zhou, 2002). In comparison with individuals with AD, those with MCI show similar memory deficits but do not show the same level of decline in other areas of cognition (Petersen et al., 1999). Following the initial focus on the MCI-amnestic group, other nonamnestic MCI subtypes have been identified based on

other variations in cognitive decline (Petersen, 2004, 2005). Imaging studies also suggest that this MCI group shows hippocampal and brain atrophy that is worse than would be expected in normal aging but is not as marked as that seen in AD (Jack et al., 2000, 2004, 2005).

A major reason for targeting those with MCI is to determine their risk for progressing to AD or another dementia. Indeed, longitudinal research has suggested that the MCI-amnestic group is at a greater risk for development of a dementia at an accelerated rate (Bennett et al., 2002; Daly et al., 2000; Flicker, Ferris, & Reisberg, 1991; Ganguli, Dodge, Shen, & DeKosky, 2004; Lopez et al., 2003). Through the identification of this group, at a high risk for dementia, therapeutic interventions can potentially be started earlier and biomarkers for various types of dementias can be studied.

SUMMARY

The findings from various researchers in aging and cognition suggest that both crystallized and fluid intelligence are important for successful functioning in advanced age. Ability, level of education, and knowledge gained early in life appear to provide some buffer against later brain disorders. Not everyone ages cognitively at the same rate, and many people retain high abilities into advanced age. Some individuals may suffer devastating effects, both physical and cognitive, whereas others suffer relatively few effects. Therefore, among groups of older people, age is not the only, or best, predictor of cognitive decline or mortality. The process of aging increases the probability of cognitive problems. Aging also results in brain and neuronal changes, but physical changes do not by themselves always differentiate between normal aging and dementia because of a wide range of individual differences and differences in functional cognitive reserve. Different measures of functional capacity may well be the key to identifying those at greatest risk for cognitive impairment. Advanced imaging methods correlated with neuropsychological functioning hold promise for more precisely relating structure to function. This will also aid in identifying people at greatest risk for development of dementia, such as those with MCI, and in ultimately answering the following question: What is the difference between normal aging and dementia?

Defining Dementia

With public and scientific attention focused on dementia, one might expect general agreement when referring to dementia and subtypes of dementia such as AD. Given the cornucopia of terms used to refer to dementia and subtypes of dementia, however (Table 14.1), there can be confusion. Professionals and laypeople alike may confuse dementia—the behavioral syndrome—with one particular condition, such as AD. Patients and families often label dementing conditions as "hardening of the arteries," "senility," or "old-timers' disease," which often reflects a perception that the problem is inevitable in aging. In the most generic sense, dementia refers to a behavioral syndrome, and not one disease or cause. It denotes conditions that may have a variety of causes. Some dementias may be treatable, and others may not be treatable. Some stem from disease processes that inevitably become worse, and some from toxic exposure or injury, resulting in a behavioral decline that plateaus.

The dementia syndrome is a cluster of behavioral symptoms that may or may not point to a disease, but dementia is not a disease entity in and of itself. The various subcategories of dementia usually relate to the suspected disease, cause, or primary site of damage (for example, cortical versus subcortical). Researchers have found well over 50 causes of dementia (see Table 14.1). Among the

Table 14.1 *Representative Causes of Dementia*

Progressive Dementias

Cortical dementias
- Alzheimer's disease
- Motor neuron disease
- Pick's disease
- Progressive aphasia
- Wilson's disease

Subcortical dementias
- Huntington's disease
- Parkinson's disease
- Progressive supranuclear palsy
- AIDS dementia
- Creutzfeldt–Jakob disease

Mixed dementias
- Lewy body dementia
- Vascular dementias
- Binswanger's disease

Potentially Static Dementias

Toxic conditions
- Alcoholic dementia
- Heavy metal poisoning (such as lead and mercury)

Infectious conditions
- Herpes encephalitis

Miscellaneous conditions
- Tumor
- Normal pressure hydrocephalus
- Trauma

Potentially Reversible Dementias

Systemic illness
- Severe anemia
- Uremia

Deficiency states
- B_{12} deficiency

Endocrine disorders
- Addison's disease
- Thyroid disorders

Drug toxicity
- Anticholinergics
- Antipsychotics

most well known are the degenerative dementias caused by a progressive and unrelenting disease process such as AD or Parkinson's disease. Neurologists traditionally have categorized these disease processes as cortical, subcortical, or mixed, depending on the degree to which they affect gray or white matter areas of the brain. Vascular, infectious, and toxic conditions, as well as a variety of other brain conditions, may also result in dementia.

Some of these conditions are progressive, whereas others, such as the dementia resulting from herpes encephalitis, may be static, rarely worsening over time. Although most dementing conditions encountered by neuropsychologists represent persistent or progressive states, or both, researchers have also documented "reversible" or temporary dementias. Reduced metabolic efficiency accompanies aging, making older adults especially susceptible to conditions and substances that they might have tolerated when younger. For example, symptoms of dementia can stem from adverse reactions to medications (such as sedative-hypnotics and anticholinergic drugs), nutritional disorders (such as thiamine deficiency and pernicious anemia), metabolic disorders (hypoglycemia, hypercalcemia, kidney failure), psychiatric disorders (severe mood disorders, psychosis), and other conditions such as anesthesia or surgery. However, when these conditions are treated, the dementia is usually reversible and the patient returns to baseline.

Table 14.2 ***Diagnostic Criteria for Dementia***

Criteria	DSM-IV-R	NINCDS-ADRDA
Memory impairment	R	R
Impairment of additional area of cognition (such as language, construction, praxis, or executive functioning)	R	D
Confirmed on mental status tests	NS	R
Impaired/decline in social or occupational function	R	NS
State of consciousness unclouded	R	R
Evidence of specific organic factor etiologically related to the disorder or absence of conditions other than organic mental syndrome	R	NS

Note: DSM-IV-R = *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Revised; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; R = required; D = desirable but not required; NS = not specified.

Source: Adapted from Rebok, G. W., & Folstein, M. F. (1993). Dementia. *Journal of Neuropsychiatry and Clinical Neurosciences, 5,* 265–276; and Katzman, R., Lasker, B., & Bernstein, N. (1988). Advances in the diagnosis of dementia: Accuracy of diagnosis and consequences of misdiagnosis of disorders causing dementia. In R. D. Terry (Ed.), *Aging and the brain* (Vol. 32, pp. 17–61). New York: Raven Press.

DIAGNOSTIC CRITERIA FOR DEMENTIA

No one set of criteria represents definitive agreement regarding the diagnosis of dementia. Somewhat varying diagnostic standards are described in the *Diagnostic and Statistical Manual* (4th ed., revised; DSM-IV-R) and by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) (Table 14.2). However, experts agree about some of the major features of dementia. The first is that dementia results in a *loss of cognitive or intellectual function.* This feature implies a decline that is acquired and unusual. It is acquired because people born with impaired intellectual function, having developmental disorders such as mental retardation, do not have dementia simply by virtue of poor intellect, although they too can experience development of dementia. The loss of cognitive or intellectual functioning must also be unusual or outside of the realm of what would be expected with normal aging. As we have discussed, aging may bring about some cognitive decline, particularly in memory and areas of fluid intelligence. But the decline associated with dementia represents a marked change from previous levels of intellectual and memory ability. Although the most well known subtypes of dementia have a predilection for the elderly and result in progressive deterioration, this broad definition of dementia could hypothetically refer to the sudden loss of intellectual function from head injury in a 17-year-old.

Although patterns of impairment may differ, the second area of diagnostic agreement in dementia involves *multiple areas of cognitive impairment.* The abilities impaired in dementia may represent all cognitive functions or may present different patterns of neuropsychological disability. Both sets of criteria for dementia identify memory impairment as a prominent and necessary feature. However, it is the multiple and often diffuse cognitive decline that characterizes dementia. It is not uncommon to see impairment in abstract thinking and problem solving, impaired judgment, and other problems of higher cortical functioning.

In summary, the term *dementia* in its broadest sense refers to a group of conditions and diseases that share some similar neuropsychological and behavioral symptoms, although the underlying causes may vary widely. The prime identifying feature is a decline in multiple areas of cognitive functioning, including memory. Beyond this initial definition of dementia, however, lies what is probably most important in working with patients with dementia—an understanding of the different neuropsychological presentations of dementia subtypes.

SUBTYPES AND CLASSIFICATIONS OF DEMENTIA

Cortical versus Subcortical

Traditionally, the primary demarcation among subtypes of dementia has followed the attempt to distinguish between cortical and subcortical dementias. **Cortical dementias** primarily affect, or start out by affecting the cerebral cortex, or gray matter. AD is typically included within this category. With **subcortical dementias,** the disease state predominantly affects the white matter, or neuronal connections between cortical areas, and gray matter structures below the cortex. The term *subcortical* was first used to describe the neuropathology and accompanying pattern of cognitive deficits associated with progressive supranuclear palsy (Albert, Feldman, & Willis, 1974). Since that time, it has expanded to include Huntington's and Parkinson's diseases and may also refer to diseases such as acquired immune deficiency syndrome (AIDS)–related dementia and some depressions. The difficulty with this differentiation, both neuroanatomically and behaviorally, is that these disorders do not conform to strict cortical–subcortical boundaries in the brain. For example, AD typically causes significant cortical neuronal loss and atrophy, but also specifically attacks the hippocampus, a subcortical limbic system structure. In contrast, diagnosticians usually identify Parkinson's disease by the subcortical structure that it targets, the substantia nigra, although evidence suggests that it also affects some higher cortical functions such as executive functioning. Even when evidence indicates that a disease targets only subcortical structures, "cortical" effects may appear because of the disconnection of neural pathways in the white matter that connect the gray matter areas. Although we use the terms *cortical* and *subcortical* dementia as general categories, you must loosely interpret them to imply a major or primary area of damage rather than an exclusive area of damage.

Static versus Progressive

All dementias that result from a disease process are progressive. Diseases such as AD, Pick's, Huntington's, or Creutzfeldt–Jakob inevitably follow a continuous cognitive and behavioral decline. Other conditions, however, may cause a static or steady-state cognitive disorder. A neurotoxic substance (such as lead or alcohol) or infection (such as herpes encephalitis) continues to cause brain damage as long as it is present. But when the condition is arrested, the resultant dementia usually plateaus.

Both static and progressive dementias can begin with a sudden change of functioning, over days or weeks, or a more insidious or gradual onset, over the course of months or years. Lead poisoning may impact the brain for a period of years before obvious impairment appears. Herpes encephalitis, in contrast, is an acute infectious condition with sudden and dramatic effects on the brain. Progressive dementias can also vary in their course. The progression, as in the case of AD, is gradual. However, there may be long periods during which the decline plateaus. Vascular dementias often produce a stepwise progression, as **multiple infarcts (multi-infarct dementia)** or strokes occur at different times. Only repeated neuropsychological testing and keen observation by the neuropsychologist, patient, or family can demonstrate the progression of the dementia.

Reversible versus Irreversible

Researchers have focused primarily on irreversible and progressive dementias. However, clinicians are likely to see a variety of patients with dementia-like symptoms that may remit with time. Part of the diagnostic problem with the so-called reversible dementias is that these people may actually have **delirium** rather than dementia. Delirium does not signal dementia, but rather is a transient cognitive problem associated with an acute confusional state. Typically, individuals with delirium have poor attention, disorganized thinking, perceptual disruption, disorientation, memory impairment, and an altered state of consciousness. Because delirium and dementia share memory impairment and disorientation, they can be easily confused. However, with delirium, the symptoms develop over a period of days or hours and are caused by specific organic problems such as overmedication or an acute or worsening medical condition. Many medical problems listed in Table 14.1 as potentially reversible dementias cause delirium. Moreover, it is not uncommon for patients with dementia to experience development of delirium. For example, a person might be admitted to the hospital to have surgery or to be treated for an acute medical condition. Perhaps an already reduced cognitive capacity causes vulnerability to the cognitive effects of general metabolic dysfunction. People who become delirious for short periods and then recover should not be diagnosed with dementia, even a reversible one. One difference in presentation is that people with dementia, other than in the late stages, are alert and can respond to what is going on around them. People with delirium are grossly confused and disoriented to their surroundings. A true "reversible dementia" should meet the behavioral criteria for dementia discussed earlier; that is, the individual must show dementia in the absence of a delusional state.

Research continues on the question of reversibility. Several possibilities exist. For example, anticholinergic drugs impair memory functioning. Perhaps, reduced cognitive functioning caused by large doses of a medication can, indeed, permanently reverse when the person stops taking the medication. Or perhaps, dementia symptoms stemming from overmedication indicate the early stages of dementia in an already compromised brain, so that discontinuing the drug only temporarily increases cognitive functioning.

The remainder of this chapter focuses on AD. This represents the most scrutinized and researched dementia. We focus on the epidemiology of AD, diagnostic issues, clinical presentation, and neuropsychological profile and treatment.

Alzheimer's Disease

Alzheimer's disease (AD), named after its discoverer, Alois Alzheimer (Neuropsychology in Action 14.1), is a progressive cortical dementia that is irreversible and thus results in an inevitable decline. It is the most devastating and prevalent of the dementias, representing the eighth leading cause of death overall for people older than 65 (Hoyert & Rosenberg, 1997) and more than 50% of diagnosed dementia cases (Kay, 1995). The number of new cases of AD increases with age from 1% of the population aged 65 to 75 years to 6% to 8% of adults older than 85. The rate of survival varies widely between 2 and 20 years with a median survival rate of between 3 and 4 years after diagnosis (Helmer et al., 2001; Wolfson et al., 2001). The prevalence, or number of people living with AD at any one time, increases with age and survival rate. It is estimated that between 10% and 30% of people around the world older than 85 have AD (for example, Bowirrat, Treves, Friedland, & Korczyn, 2001; Gurland et al., 1999; Stevens et al., 2002; Wang et al., 2000). Based on the 2000 census, it is estimated that between 3 and 4 million people older than 65 have AD (Mayeux, 2003).

There appears to be no single cause for AD, and in most cases, the causative factor remains unknown. AD is linked to increased age, which has led some to speculate that it is a disease of "accelerated aging"—implying that if we all lived long enough, AD would be inevitable. Over a lifetime, women are about twice as likely to experience development of dementia or AD as men (Seshadri et al., 1997), but this may be partly accounted for by that women have a longer life expectancy (Mayeux, 2003). People with more education appear less likely to experience development of AD, but again, this is probably a marker of larger cognitive reserves acting as a buffer between neuropathology and disease manifestation.

AD does not have a clearly identified genetic component in most cases. A variation exists that is autosomal dominant, meaning the family pedigree shows about 50% of the family members as having AD, but this type probably affects less than 150 families worldwide. The most likely chromosomal culprits in genetically established AD appear to be chromosomes, 1, 14, and 21. Interestingly, people born with Down's syndrome, or trisomy 21 (named because the disorder results from an abnormality on chromosome 21), inevitably develop a dementia, usually by age 40. The associated brain changes corresponding to AD (neurofibrillary tangles and senile plaques) appear years before clinical diagnosis. In summary, although the biomedical research searching for causes and markers of the disease appears promising, scientists still know little about the actual causes of AD.

DIAGNOSTIC PROBLEM OF ALZHEIMER'S DISEASE

A definitive diagnosis of AD requires the behavioral presence of dementia and the identification of neuropathologic markers of AD. No single medical test, imaging procedure, or behavioral test can positively identify AD (for example, Mayeux, 2003), short of a brain biopsy showing the characteristic neurofibrillary tangles and neuritic plaques, which are most predominant in the hippocampus and cortical association areas. Because biopsy is not a procedure to which most people would submit, a definitive diagnosis cannot be made until autopsy. AD is difficult to diagnosis because there are other dementias that have may have similar symptoms, especially in the later stages of the disease. In diagnostic accuracy studies, where physicians have to choose the correct diagnosis among several types of dementias, AD disease tends to be overdiagnosed, meaning that other progressive dementias may be misdiagnosed as AD (Lopez et al., 1999). A recent Chinese study that analyzed both the clinical features and brain markers of various dementias at autopsy found that the agreement rate between clinical diagnosis of dementia and pathologic findings was 64.5% of cases (Wang, Zhu, Gui & Li, 2003). Concordance between clinical and biological findings was strongest for vascular dementias (66.7%) and less strong for degenerative dementias (40%).

The clinical diagnosis of AD depends largely on evidence related to behavioral and neuropsychological profiles

Neuropsychology in Action 14.1

The Discovery of Alzheimer's Disease

by Mary V. Spiers

A piece of neuropsychology history puts to rest doubts about Auguste D., the first case of Alzheimer's disease (AD) ever described. After having gone missing for nearly 90 years, Alois Alzheimer's blue cardboard file was found by psychiatrists in the archives of the University of Frankfurt, Germany, in 1996. Among the 32 sheets were Alzheimer's handwritten interview notes, samples of Auguste D.'s "amnestic writing disorder," and a report of the course of the disease. Alzheimer's first notes are as follows:

> Nov. 26, 1901
>
> She sits on the bed with a helpless expression. What is your name? *Auguste.* Last name? *Auguste.* What is your husband's name? *Auguste, I think.* Your husband? *Ah, my husband.* She looks as if she didn't understand the question. . . .
>
> What is this? I show her a pencil. *A pen.* A purse and a key, diary, cigar are identified correctly. At lunch she eats cauliflower and pork. Asked what she is eating, she answers *spinach. . . .*
>
> When objects are shown to her, she does not remember after a short time which objects have been shown. In between she always speaks about twins. When she is asked to write, she holds the book in such a way that one has the impression that she has a loss in the right visual field. Asked to write *Auguste D,* she tries to write *Mrs.* and forgets the rest. It is necessary to repeat every word. (Maurer, Volk, & Gerbaldo, 1997, p. 1547)

Dementia had been described before, with terms such as *paralytic dementia, atherosclerotic dementia,* and *senile dementia.* What made Auguste so unusual was that she was so young, only 51. After 4 1/2 years, Auguste died. When Alzheimer published his description of this case (1907, 1987), he had examined her brain and could describe the unique histologic findings of neurofibrillary tangles: "The nucleus and the cell have fallen apart and only a tangled bundle of fibrils points to the place in which there was once a ganglion cell" (Alzheimer, 1907, 1987). He had even drawn pictures of Auguste D.'s neurofibrillary tangles (Figure 14.3). To Alzheimer, this represented a new entity of "presenile dementia." In 1910, Kraepelin included the new syndrome of *Alzheimerische Krankheit* (Alzheimer's disease) in his famous textbook of psychiatry.

A controversy erupted after their discovery of Alzheimer's file because the original autopsy findings also indicated that Auguste D. had arteriosclerosis in smaller blood vessels, a fact that today is a criterion excluding pure AD. Other scientists argued that she may have had a metabolic disorder. Finding Auguste D.'s brain would be the only way to resolve whether she had what we now recognize as AD. After a 2-year search, yet another group of German researchers found more than 250 slides of Auguste's brain in the basement of the University of Munich. German researchers have been able to confirm the two classic signs of AD in the brain of Auguste D.: neurofibrillary tangles and amyloid, or senile, plaques. This puts to rest the notion that Auguste D. might have had a disease process other than AD. However, whether she had a coexisting vascular problem is likely to fuel debates for some time.

Figure 14.3 Alzheimer's drawings of neurofibrillary tangles from the brain of Auguste D. (From K. Maurer, S. Volk, & H. Gerbaldo, "August D. and Alzheimer's Disease," *The Lancet,* 1997, 349, Figure 5, p. 1549. Reprinted by permission of Elsevier.)

and on ruling out all other identifiable causes of dementia, such as those listed in Table 14.1. The clinical diagnoses of "probable" and "possible" AD reflect, in large measure, the certainty with which other causes of dementia can be excluded. This chapter also refers to probable AD as "senile dementia of the Alzheimer's type" (SDAT), to reflect the probable nature of the diagnosis.

NEUROPATHOLOGY OF ALZHEIMER'S DISEASE

Major Brain Structures Affected by Alzheimer's Disease

Two interesting facts exist regarding the neuropathology and pathophysiology of AD. First, the disease targets specific regions of the brain. Second, disease-targeted structures sustain neuronal loss and atrophy. Although AD is a "cortical dementia," because major areas of the cerebral cortex show brain shrinkage, this disease does not respect cortical boundaries. It greatly affects major subcortical limbic system structures such as the hippocampus and amygdala. Most pathologic changes occur in the cortical temporoparietal association areas and the *subcortical limbic cortexes.* Specifically, the disease destroys the major pathways to and from the hippocampus, cutting off direct connections to association cortices.

Gross postmortem inspection of the brain often finds cortical atrophy. In Figure 14.4, the most marked atrophy is in the frontal, temporal, and parietal areas. The gyri are thinned, and the sulci are noticeably widened. Researchers estimate that in AD about half of the large neurons deteriorate (Terry, Peck, deTeresa, Schecter, & Horoupian, 1981), resulting in a loss of volume. Specifically, these neurons lose dendritic arborization, or branching. The ventricles also enlarge, because of cortical thinning (Figure 14.5). Although dementia severity increases with increased cell death, longitudinal comparisons of global cerebral atrophy with dementia severity do not reliably indicate dementia (Bigler, 1987; Johansson, 1991).

A closer look at specific structures reveals that they sustain massive cell loss. In fact, SDAT appears to follow structural borders. Chief among these are the parietal and temporal cortices, the hippocampus and the structures leading to it (entorhinal cortex and the perforant neural path), the amygdala, and specific nuclei of the thalamus (Van Hoesn & Damasio, 1987). In addition, certain subcortical frontal areas are implicated, such as the nucleus basalis of Meynert and the olfactory areas. Noticeably spared are the primary motor and sensory areas (tactile, auditory, visual) and the basal ganglia. The affected structures correspond to areas of higher cognitive functioning and memory, leaving relatively untouched more basic sensory and motor abilities.

Image not available due to copyright restrictions

Images not available due to copyright restrictions

HISTOLOGIC MARKERS

The two neuropathologic findings that Alzheimer (1907, 1987) identified, still considered the primary markers of the disease, are neurofibrillary tangles and neuritic, or senile, plaques. These are evident by microscopic inspection of brain tissue obtained at autopsy. Neurofibrillary tangles resemble entwined and twisted pairs of rope within the cytoplasm of swollen cell bodies (see Figures 14.3 and 14.6). Tangles consist of proteins, termed tau proteins, that are believed to accumulate as a result of abnormal phosphorylation. The excessive collection creates tangles that are dispersed throughout the brain but disproportionately in the areas just listed, including the temporoparietal areas and the hippocampal complex. The specificity of structural deterioration in AD extends to the cellular layers of the cortex. For example, within the six-layered isocortex of the cortical association areas, tangles and plaques devastate layers 3 and 5, whereas other layers are relatively spared (Van Hoesn & Damasio, 1987).

Alzheimer described neuritic plaques as "clump-like deposits in the neuropil." They are round aggregates of "cellular trash" that have a particular affinity for the regions where the majority of synapses lie (the neuropil).

Image not available due to copyright restrictions

The synapses eventually disintegrate, leaving holes and neurites (that is, pieces of axons and dendrites) where there were once active connections (Figure 14.7). Plaques are likely to concentrate in the frontal and temporal regions (Zubenko, Moossy, Martinez, Rao, Kopp, & Hanin, 1989) and are numerous around the hippocampal formation. As we discussed earlier, tangles and plaques are not specific to AD. They also appear in normally aging individuals without evidence of dementia, as well as in other degenerative diseases. It is the pattern and quantity of these markers that defines AD.

An exciting recent discovery is that the substance of neuritic plaques and tangles may lead to hypotheses regarding possible causes of and treatments for AD. The neuritic plaques found in AD contain an amino acid peptide protein core termed **beta-amyloid (β-amyloid).** As a result, these neuritic plaques are also called *amyloid plaques.* Bradshaw and Mattingly (1995) review several possibilities for how β-amyloid may operate. First, it is coded on chromosome 21, the same chromosome responsible for Down's syndrome. The behavioral significance of this is that if they live past 30 years, people with Down's syndrome often show AD-like dementia symptoms. Therefore, chromosome 21 may be responsible for both problems. Second, there is debate on the function of β-amyloid. Is it a cause of the disease, a by-product of the disease, a "protective reactant," or an autoimmune response?

Image not available due to copyright restrictions

As we discussed earlier in this chapter, genetic research has focused on the protein ApoE4, which may be associated with both WM aging and AD. This additional protein in plaques and tangles has been studied for its importance in AD. ApoE4 is one of four possible variants, or alleles, of the protein ApoE. Seventy-five percent of people in the population have the ApoE3 variant (Corder et al., 1993), but risk for development of AD increases to 90% if a person inherits the ApoE4 variant from both parents. In addition, a double set of ApoE4 alleles also reduces the mean age of onset. ApoE4 is responsible for ferrying cholesterol into the brain; however, researchers are currently investigating how this protein may operate in AD. It appears on yet another chromosome, chromosome 19, which binds with β-amyloid in cerebrospinal fluid. The exact mechanism for this binding process is not yet known; however, researchers hypothesize that ApoE4 may not be the direct or sole cause of the disease (see Bradshaw & Mattingly, 1995); rather, the protective factors that ApoE2 or ApoE3 provide may be lost. However, there is not yet consensus whether it can serve as a specific or sensitive marker of the disease (Mayeux et al., 1998), and there are no genetic markers of AD that have yet been established for diagnostic purposes (Knopman et al., 2001). Researchers have also examined the CSF of patients with potential AD to examine potential β-amyloid deficiencies or the presence of tau proteins in cerebrospinal fluid. Although a combination of some of these biomarkers holds promise in aiding diagnosis, that some biomarkers are sensitive to more than one condition precludes their routine use in determining the diagnosis of AD (Knopman et al., 2001).

Neurotransmitter Systems Altered by Alzheimer's Disease

AD may impact multiple neurotransmitter systems. However, the most consistent evidence of a neurotransmitter with a direct effect on memory processes in AD is **acetylcholine (ACh).**

In the brain, ACh is synthesized in a group of neurons called the *basal forebrain cholinergic complex (BFCC).* The cell bodies of these neurons lie in the basal forebrain structures of the nucleus basalis of Meynert, the diagonal band of Broca's area, and the globus pallidus. These axons project to the hippocampus and the cerebral cortex, primarily the frontal and temporal cortexes. The BFCC is a subcortical component of the limbic system and the major source of choline for the hippocampus and cortex (Coyle, 1985). Researchers have long known that ACh plays a role in memory. Drachman (1977) demonstrated that blockage of receptors causes memory loss even in young adults. In AD, the devastation of the BFCC neurons profoundly depresses brain levels of ACh, perhaps as much as 60% to 90% (Terry & Davies, 1980; Bowen, Benton, Spillane, Smith, & Allen, 1982).

Some of the other neurotransmitters implicated in AD are the catecholamines, the amino acid glutamate, and the neuropeptides somatostatin and corticotrophin. However, at this juncture, none of these neurotransmitters appears to play a clear role in AD. Researchers have reported that all are reduced in AD, but their reduction may be secondary to the disease process. For example, general stress also reduces somatostatin. As you might imagine, research in this area is progressing quickly because of the push to find appropriate pharmacologic treatments.

Neuroimaging in Alzheimer's Disease

Gross neuroimaging of the brain in patients with AD may indicate cerebral atrophy on CT or magnetic resonance imaging (MRI). The electroencephalograms of patients with AD are likely to show generalized slowing (LaRue, 1992). Degree of atrophy or slowing taken in isolation is not reliably associated with degree of neuropsychological impairment (for example, see Bigler, 1987), but the degree of ventricular enlargement seen over time as the cortex atrophies accompanies increasing cognitive impairment (Burns, Jacoby, & Levy, 1991) but is only a gross index of general brain health. Special imaging procedures demonstrate the enlarged hippocampal fissure that results from neuronal loss, tangles, and plaques that begin early in the disease process. Also characteristic of AD is a pattern of metabolic or vascular insufficiency, or both, seen in the temporoparietal area, which shows up on positron emission tomography (PET) and single-photon emission computed tomography (SPECT) scans. This hypometabolism can be either unilateral or bilateral and depends on factors such as severity of illness, sex, and age at onset (for review, see Forstl & Hentschel, 1994).

CTs and MRIs are primarily useful, not to confirm a diagnosis of AD, but to rule out other conditions such as tumor or vascular causes of dementia seen as multiple small strokes or ischemic attacks. However, promising new methods of analyzing volume and ratio of specific structures through structural imaging may help confirm diagnosis of AD. PET and SPECT scans appear most sensitive for detecting the characteristic patterns of SDAT. These imaging measures are then correlated with neuropsychological measures to provide a dynamic picture of the disease process.

CLINICAL PRESENTATION AND NEUROPSYCHOLOGICAL PROFILE OF ALZHEIMER'S DISEASE

The clinical presentation of patients with AD can vary, but many share characteristic patterns (Neuropsychology in Action 14.2). The most consistent deficits across patients with autopsy-documented AD are memory and fluent anomic aphasia (for example, see Price et al., 1993). Visuospatial difficulties are also characteristic. These deficits correspond with neuroimaging studies showing patterns of hypometabolism in limbic and association areas in early stages of the disease. In this classic presentation, some frontal areas of the brain appear relatively spared. This also corresponds with neuropsychological testing and clinical observation indicating that, despite severe memory impairment, many patients with AD retain an appropriate "social facade," do not have a Broca-type (nonfluent) aphasia, and retain normal strength and simple motor speed until the end stages of the disease. However, the impairments progress over time, gradually affecting all higher mental functions of the brain. What follows is a description of the neuropsychological and behavioral performance, according to functional area, typical of those with the SDAT variant. Because memory dysfunction is the hallmark of AD, we devote more discussion to this problem than to the other functional areas.

Memory

AD globally and profoundly impairs memory. New declarative learning problems at all levels (encoding, storage, and retrieval) and retention over time are usually noticed first. In addition, structures of the brain that hold previously well-learned semantic knowledge information in organized associational frameworks begin to deteriorate. Finally, short-term memory span, names of family members, and familiar stories fragment. The only type of learning that appears to persist lies outside the corticolimbic system, with certain types of nondeclarative learning.

Neuropsychology in Action 14.2

Differentiating between Symptoms of Alzheimer's Disease and Normal Aging

by Mary V. Spiers

Although memory impairment is the hallmark of Alzheimer's disease (AD), those older than 65 (the time of life when AD is most likely to manifest) often decline in memory ability. The key is to differentiate between general complaints of forgetfulness and lowered cognitive functioning that accompany normal aging and cognitive indicators of incipient dementia. Consider the following two scenarios, which are compilations of cases seen by the authors.

Case 1: Mrs. C

Mrs. C is a 90-year-old woman from a small midwestern town who has lived by herself for the past 10 years since her husband died. She is active in her church and volunteers at a local thrift shop. At home she spends most of her time reading, keeping up with correspondence to family and friends, and talking with neighbors on the phone. She drove her car until a year ago, when after increasing restrictions on night driving due to failing eyesight, she agreed with her physician that she should give it up. She tells her family that her memory is quite poor. She can read through a whole book, but says if she picked it up again it would be "just like reading a new book." She watches the news daily and is interested in following the elections and candidates for office. Mrs. C has a definite opinion regarding who she likes, although she does not remember many of the details of current events and says the news "goes in one ear and out the other." However, she does remember major life events, if asked about them by her children. She can recount episodes from her teens and 20s quite well and tells old family stories from her childhood with incredible detail and animation. For the first time in her life she has had to start taking several prescription medicines for heart problems. At first she needed nearly constant prompting to remember to take her three daily doses at the right times. However, over the course of 2 to 3 months, she learned her medication routine. She always remembered to take her pills when she got up and before bed, but frequently forgot the 11 A.M. pill.

Case 2: Mrs. R

Mrs. R is a 75-year-old woman who is married and lives with her husband. Mr. and Mrs. R have always had an active social life, getting together with friends quite often to go dancing or play bridge in their retirement community. Within the past several years, Mr. R has noticed that his wife does not seem to be paying attention when they play bridge anymore. She has made wrong bids and makes mistakes keeping score. She usually makes a joke about these things, saying to her friend, "Lucy, you're just trying to distract me so you'll win." Everyone has a big laugh, which seems to just egg her on. Mrs. R particularly likes to tell stories of when she was young, and she has a lot of them to entertain everyone. When the conversation turns to the day's news, Mrs. R seems to have little comment on current events, although she and her husband have always watched the news together every night. She seems to get news stories mixed up. Mrs. R says she just does not have too much use for the news and that "it goes in one ear and out the other." A new couple has joined their dancing club, and much to Mr. R's embarrassment, Mrs. R keeps reintroducing herself to them even after 4 months. After a while it became comical, and Mrs. R says she does it on purpose for a joke. Mrs. R has taken medication for the past 15 years and has always managed well. But now her husband feels like he must remind her to take her pills because he noticed she often does not put it out by her plate as she used to do. She resents being reminded and says accusingly, "I put it out. Are you sure you didn't just take it and put it away when you cleared the table?" This behavior is upsetting to Mr. R, but the thing that bothers him most is that his wife, who had been a good cook, is now very disorganized in the kitchen. After he noticed that a cake tasted salty, he watched her as she prepared other things. She often added ingredients twice or totally left out essentials of her recipes.

Both Mrs. C and Mrs. R have trouble remembering in areas in which they were previously more able, and they appear to have declined from their own former levels of ability. In some respects, both show a similar pattern of memory loss in that remote memory, or information learned many years ago, such as stories from childhood or facts related to work or home persist remarkably well in comparison with new learning. Difficulty remembering what the news commentator said or learning a new medication routine or a new name presents more of a problem in both cases. These similarities between normal aging and dementia can prompt dread in people who see themselves as less able to rely on their powers of memory. However, these two cases have several notable differences. First, Mrs. C appears to have some insight into her memory difficulties, whereas Mrs. R rationalizes, jokes, and blames others for her poor memory. Second, Mrs. C learns and retains some new things, even though the learning may take longer.

Mrs. R, in contrast, not only is showing difficulty learning new things but appears to be losing her ability to perform previously well-learned tasks, such as cueing herself to take her own medication or to cook. Finally, there is a suggestion that Mrs. R's problems seem more pervasive, in that she may also have problems in concentration, attention, calculation skills, and name finding. Mrs. R's memory difficulties are characteristic of dementia, possibly AD, and may appear paradoxic to patients' families, who can see that their family member is socially appropriate and retains remote and overlearned information quite well. It is easy to discount the importance of cognitive problems.

Long-Term Declarative Memory—As in other conditions that produce "amnesia," SDAT results in profound difficulties in learning new declarative information. As discussed in Chapter 9, declarative memory can be loosely divided into episodic and semantic memory; people with SDAT have deficits in both. One of the first and most prominent symptoms of AD is a deficit in new declarative learning (sometimes termed *anterograde amnesia* to differentiate it from retrograde amnesia [deficit in remote recall]). On neuropsychological testing, patients with SDAT in the mild to moderate stages of the disease typically show marked impairment on both verbal and visual learning tasks, although the progression may begin with one area being of greater deficit. Performance on list learning over trials usually does not progress much beyond an immediate memory span length. That is, if a person has a memory span of four or five items, five attempts to learn a nine-word list often reveals a flat learning curve beginning with recall of four to five items and ending with recall of four to five items. Verbal recall of stories and word lists shows a large number of perseveration and intrusion errors (among others, see Butters et al., 1988). For example, the person may repeat words from the same list as if recalling them for the first time or may recall one aspect of a design that is presented, such as a dot in a box as five or six dots in a box. The person may recall specific events or stimuli across situations, intruding elements from one story into another story or remembering elements of one design as part of another. Although all people with classical amnesia show profound difficulties in new learning, this repeating and confusion of memory differs from most other amnestic dysfunctions that the corticolimbic circuit causes. Intrusions and perseverations are most common in two conditions, AD and Korsakoff's amnesia, which also involve similar patterns of frontal lobe involvement. Butters (for example, see Butters et al., 1988) hypothesizes that the similar pattern of intrusion and perseveration errors in SDAT and alcoholic Korsakoff's amnesia may be caused by a significant loss of cholinergic neurons in the basal forebrain area.

Although many healthy elderly people may forget, they can often remember lost thoughts with the help of retrieval cues. This facilitation of memory by retrieval cues also characterizes Huntington's disease, but the memory problem in AD is more global and profound. People with AD show impairment in encoding, consolidation, and retrieval. The constellation of memory deficits in AD greatly hinders retrieval because it depends on proper encoding, organization, and consolidation of material to be remembered. Thus, retrieval cues will not aid AD patients' recall of information, suggesting that encoding and consolidation have not occurred. Besides that patients with SDAT show flat learning curves (demonstrating little to no ability to profit from practice), any information that the patient may have remembered immediately after presentation quickly disappears. As the disease progresses, information is lost faster and faster. Although many people benefit from practice over days and weeks, patients with SDAT do not appear to show this consolidation of declarative learning.

Breakdown of Semantic Knowledge—People afflicted with AD have another fundamental problem of memory, which pervades the entire organization of knowledge. As discussed earlier in this book, the brain stores information at the site where it was first processed. That is, most visuospatial information is stored in the posterior areas of the cortex, primarily the parietal and posterior temporal lobes. Auditory information is stored in the temporal lobes, and so on. The dominant theory of memory consolidation, simply put, is that the hippocampus, which has afferent and efferent projections to most areas of the cortex receives to-be-remembered information, codes it for storage, and sends it back to the original processing site (Squire, 1987). Researchers believe memory for information and facts is not stored as separate and complete units (for example, all information about robins stored in one node). Rather, they hypothesize that the brain contains associations of meaning, "semantic networks," whose individual nodes may contain pieces of information or attributes, such as "bird," "wings," "small," and "red breast," which when activated as a pattern lead to the recognition of "robin."

Most amnestic patients, although they cannot encode new information, have an intact semantic organizational network for information. In AD, the memory disorder is much more pervasive, involving a progressive disintegration of this associational network, eventually even for old learned information. The evidence for this loss of knowledge through semantic degradation rests on several findings. First, neuropsychologists noticed that patients with AD do not organize new information semantically as they are attempting to learn it. Thus, if presented with word lists that have inherent semantic categories, such as fruits, vegetables, and items of clothing, most people learn and recall information within semantic categories, clustering the information together. This "semantic clustering" is deficient or nonexistent among patients with AD, who instead show a serial ordering or primacy/recency effect. Second, patients with AD appear to lose conceptual knowledge. Fluency tasks often reveal an interesting pattern. Asked to name as many animals as possible in

60 seconds, people with AD often can retrieve superordinate and high-frequency category exemplars such as cat or bird, but show difficulty retrieving subordinate category exemplars such as leopard or robin. This degradation appears to be more than just a problem in retrieving semantic information from long-term memory. This degradation has been shown to be consistent across tasks, so that the patient may also have difficulty in defining "robin" or naming a picture of a robin (Hodges, Salmon, & Butters, 1991). These difficulties represent neuropathologic changes of higher order intermodal association cortices strongly involved in semantic networking (for example, posterotemporal, inferior parietal), rather than classical language problems associated with the frontal operculum (Broca's area), superior temporal gyrus, or supramarginal gyrus. As the disease progresses, these connected memories or knowledge structures appear to break down to such a degree that even the identity and association of family members eventually become confused in the patient's mind.

In this discussion of memory in AD, we have focused primarily on the encoding, storage, and retrieval processes of declarative long-term memory. These are undoubtedly the areas of the most recognizable and profound memory difficulty. Two areas of memory that appear less affected by AD are short-term memory span and nondeclarative long-term memory.

Relatively Spared Memory Systems—On short-term memory tasks such as length of digit span forward, patients with AD perform relatively well in the early stages of the disease. In later stages, short-term memory retention declines. However, if the examiner looks closely at short-term memory capacity, or WM, it is typically compromised.

Patients with AD perform relatively well on some nondeclarative memory tasks. Separate nondeclarative memory systems exist outside of the subcortical limbic system. The workings of these systems for the most part appear implicit, or outside consciousness. Learning skills with a large motor and practice component, such as riding a bike or typing, or learning psychomotor tests, such as pursuit rotor or mirror tracing, appear to be part of a motor skills learning system. It is not yet clear whether other systems controlling classically conditioned responses and priming represent yet other nondeclarative memory networks, or if they are subcomponents of a single nondeclarative network.

People with AD show normal performance on some nondeclarative tasks and impairment on others. Soliveri (Soliveri, Brown, Jahanshahi, & Marsden, 1992) describes the pattern of nondeclarative memory performance in various neurologically impaired groups. Most people with AD perform well on motor learning tasks that researchers think represent an unimpaired striatal system. However, the picture is different with priming tasks. The methodology of priming, discussed in Chapter 9 with the discussion of memory, assumes that previous exposure to an item will facilitate its future processing. Word stem completion priming tasks typically first present a list of words, such as *there, church,* and *leaf.* Later, they present three-letter stems such as *the___, chu___* and *lea__*. Typically amnestics—even though they have not been able to demonstrate learning of the words through declarative means, namely, spontaneous recall—are likely to produce the targeted words on word stem completion tasks. People with AD usually cannot perform these tasks well. Interestingly, on perceptual priming tasks that present complete and incomplete figures, patients with AD appear to perform better in some instances. Because of this pattern, researchers suggest that patients with AD confront a specific difficulty in implicit verbal priming whereas maintaining nondeclarative learning abilities in perceptual priming and in attaining motor skills. Why would this be so? Verbal implicit priming tasks are probably another pointer to the AD breakdown of the semantic network. Motor skill learning is intact because it is controlled by the striatum, which is relatively unaffected in AD. Perceptual priming appears to point to a relatively more intact visual object recognition system, which may not be affected until late in the disease process.

Language/Speech

Patients with AD do show language problems, but these cannot be neatly characterized with other classic aphasias. In fact, the aphasia progressively worsens both in degree and type. Early in the disease process, AD patients show an anomic aphasia, characterized chiefly by word-finding and naming difficulties (Cummings, Benson, Hill, & Read, 1985). A confrontation naming test (such as the Boston Naming Test), in which the person must retrieve the exact name of an item from line drawings, often results in semantic and circumlocution (talking around) errors. A patient with AD is more likely to say "tool" for "hammer" or "some type of musical instrument" for "harmonica," indicating that he or she recognizes the semantic category but can retrieve only the general category or the wrong exemplar from the same category (for example, see Hodges, Salmon, & Butters, 1991). This type of anomia, together with the difficulty in semantic fluency tasks discussed earlier, suggests a semantic anomic aphasia. As the dementia progresses, language problems become more profound. Comprehension problems begin to

appear, followed by problems in repeating information, and last, declines in fluent conversational output may appear that resemble a global aphasia (Zec, 1993; Cummings et al., 1985).

Visuospatial Functioning

Visuospatial problems crop up by the middle stages of AD, if not before. Mr. T, a 70-year-old retired salesman and a patient of ours, came in for neuropsychological evaluation at the request of his wife and neurologist. When they moved to a new retirement community in Florida, Mr. T's wife noticed a change. He started getting lost while driving in the neighborhood, sometimes ending up at the other end of town; embarrassed and angry, he would have to call his wife. Even though they had been there for nearly a month, he kept losing his way and blamed it on that "all those tract houses built in the 60s look alike." Accompanied by his wife, Mr. T could follow the correct route; however, Mrs. T was a bit nervous about riding with her husband. She reported he had a tendency to drift to the left, and on several occasions she had to shout at him to avoid hitting another car. What was most disconcerting to Mrs. T, however, was that Mr. T seemed disoriented in his own home, often heading out to the kitchen to use the bathroom.

The problems Mr. T is showing demonstrate two things. First, he has marked visuospatial impairments in his daily life. Most obviously, he cannot orient himself in his environment, either in the neighborhood or at home. He does not have good spatial sense when he is driving. He veers to the left and appears to have lost his "inner compass." Second, moving to a new residence may unmask a condition that was not evident in a more familiar environment. Mr. T did not have a stroke or some other neurologic event that occurred suddenly. His wife discovered his spatial problems when they moved. Although Mr. T would still have been able to function in his old home, as his dementia progressed, it would have been only a matter of time before he was getting lost in his old, familiar neighborhood and becoming disoriented in his home of 15 years.

On neuropsychological examination, patients with AD usually show poor performance on a number of visuospatial measures. As in the other functional domains, the degree of impairment corresponds to the stage of dementia. Tests of line orientation (for example, the Benton Judgment of Line Orientation Test), spatial construction tasks (such as the WAIS-R Block Design), copying (such as the Rey–Osterreith Complex Figure Test, Bender Gestalt), drawing (such as the Clock Drawing Test), and visual integration (such as the Hooper Visual Organization Test)

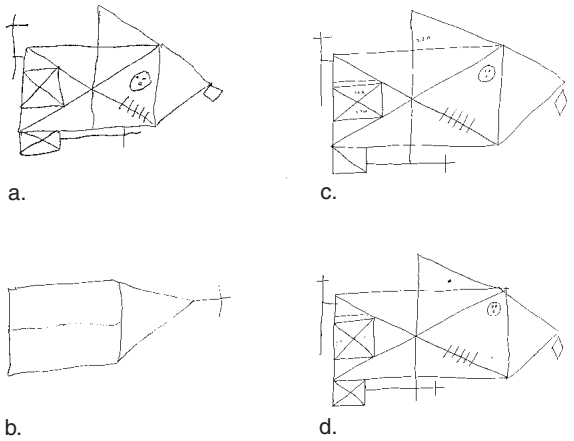

Figure 14.8 Drawing and memory performance on a modified Rey–Osterreith figure drawn by a patient with Alzheimer's disease (AD) and a normal elderly adult: (a) AD copy, (b) AD immediate recall, (c) normal control copy, and (d) normal control immediate recall. (Courtesy David Libon, Ph.D.)

are the most likely to be affected (for review, see Zec, 1993). Complex tasks such as the Rey–Osterreith appear more sensitive to impairment in the early stages of the disease than are simple drawing tasks. Figure 14.8 shows drawing performance in a patient with autopsy-confirmed AD. The patient made these drawings in the early stages of the disease. The more complex Rey figure is somewhat impaired even on the copy. As the dementia progresses, copying designs also becomes distorted.

General Intellectual Functioning

Experts often say that AD, like other dementias, results in a "decline in general cognitive functioning." However, as noted earlier, all functions do not decline at the same rate; thus, it is more useful to consider the subcomponents of measures of global intellectual functioning. We focus here on verbally mediated tasks of abstract reasoning, judgment, crystallized intelligence, and speed of cognitive processing.

The ability to abstract a higher order construct is often impaired in even mild SDAT (Zec, 1993). Verbally, the patient may be unable to say how two objects or concepts are alike, such as a phone and a radio (for example, on the WAIS-R Similarities Test). Visually, the person may be unable to state a common principle that relates multiple figures (for example, on the Category Test or the Ravens Progressive Matrices). This deficit is a problem in conceptualization and abstract reasoning. Thus, people with AD do poorly on a number of tasks that require reasoning and problem solving.

Crystallized intelligence (see earlier discussion) refers to accumulated knowledge over the life span. Often, neuropsychologists measure this via tests of vocabulary knowledge (for example, WAIS-R Vocabulary) or overlearned information. For example, someone who has lived in the United States for several years should know in what month Memorial Day falls. However, few formal tests measure specific areas of expertise that may accumulate from a person's line of employment. This knowledge store is one of the few areas that remain preserved until the later stages of the disease.

Although patients with SDAT are slower on speeded complex tasks (for review, see Zec, 1993), they do not exhibit the **bradyphrenia,** or extremely slow information processing speed characteristic of patients with subcortical dementias.

Executive Functioning

Although deficits are subtle early on, difficulties in executive control are evident to caregivers. For example, in an attempt to compensate for memory loss, a person may keep notes. But without an adequate executive strategy, increased disorganization may show up in notes found in various places around the house and in tasks started but left unfinished. Family members often notice perseveration of thought because the person tells stories over and over or asks questions repeatedly. The person may be less flexible than before. Many apparent "personality" changes may actually stem from frontal impairment. Repeated behaviors, such as checking and rechecking, may emerge from the combined effect of a poor memory and increased perseveration.

An interesting aspect of dysfunctional executive ability is that many patients with AD appear to lose **metacognitive awareness,** or the inability to self-monitor their own behavior and performance. Many clinicians describe patients with AD as having little insight into their own deficits. Often, they appear generally unaware or unconcerned about the magnitude or consequences of their deficits. Is this psychological response understandable as a defense mechanism against the devastating effects of the disease? Not in the typical sense. Many patients with AD appear truly unaware of their difficulties, and consistently overestimate their abilities to accomplish things.

Problems in the ability to organize, plan, and use appropriate strategies for problem solving in patients with AD often appear on tests designed for evaluating strategic processing (such as Tower of London or Tower of Hanoi) and qualitatively on tests designed for other purposes such as visuospatial problem solving (such as the Block Design Test of WAIS-R). Intrusions and perseverations often show up on memory tests. Perseveration is evident as an inability to shift sets on tests that require flexible problem solving (for example, Wisconsin Card Sorting Test or Trails Making Test B).

Orientation, Attention, and Level of Consciousness

AD is not an altered state of consciousness, such as delirium. General orientation and selective attention persist until late in the course of the disease. However, more complex forms of attention such as divided and alternating attention decline from the early stages. Orientation for person, time, and place is generally intact until the moderate to severe stages of AD.

Motor and Sensory Function

In relation to other areas of functioning, motor and sensory abilities are relatively preserved throughout the course of AD. Simple motor speed and strength persist until late in the course of the dementia. However, more complex motor behavior, which may involve coordination or skilled movement, declines earlier.

The disease process appears to spare sensory functioning—that is, visual, auditory, and tactile acuity. Olfaction is the only primary sensory area affected; sense of smell is compromised even in the mild stages of the disease (Jones & Richardson, 1990). Many patients with AD report visual disturbances such as difficulty in reading, interpreting pictures, and recognizing familiar people. Although ophthalmologists often find good acuity and full visual fields, neuropsychological testing often reveals visual-perceptual and visuospatial deficits, which may cause the self-reported visual disturbances.

Mood, Emotion, Personality, and Insight

As with Alzheimer's (1907, 1987) famous patient, clinicians may first refer people for psychiatric symptoms. In some cases, these symptoms stem from the cognitive difficulties that accompany AD, but in other cases, the symptoms, such as depression, may represent an additional disorder. Suspiciousness of others and frank paranoid delusions can manifest memory dysfunction. One 70-year-old woman tearfully related that her husband had begun accusing her of stealing his glasses and other personal items. After 50 years of marriage, he also accused her of having an affair. On questioning, it became apparent that he was accusing her of taking things he was misplacing. Because of his impaired time estimation, not uncommon in AD, 5 minutes could seem like an hour, or an hour like 5 minutes. So when she went to the grocery store on a quick errand, it seemed like an eternity to him.

He had little insight into his memory difficulties, and in trying to make sense of a frustrating situation, he externalized the problem and blamed his wife.

Symptoms that herald a significant about-face in personality usually raise a red flag for family members. Such patients are most likely to be seen by mental health professionals. However, psychiatric symptoms that are exacerbations of premorbid personality styles make recognizing change extremely difficult. A woman always considered impulsive and distractible, flighty or disorganized, may at first appear simply eccentric when she begins to lose track of daily memories. When attempting to deal with memory loss, the person is likely to carry on with coping styles and defense mechanisms characteristic of earlier times. As memory becomes less reliable, a person concerned with order, timeliness, or organization may obsessively check dates, doctor's appointments, medications, memos, and lists.

Depression and Dementia—A common problem in making a differential diagnosis of behavioral disturbances among the elderly is to distinguish psychological depression from global loss of intellectual function. The most effective way to make these diagnostic determinations is to obtain formal psychometric testing from a neuropsychologist, who can describe the patient's cognitive functioning in detail, recognize normal and abnormal patterns of performance, and establish a baseline of performance against which to measure any changes over time. In addition, more subjective guidelines may include the depressed patient's tendency to exaggerate memory problems when compared with the demented patient's tendency to deny or minimize them. It is important to query for information regarding any situational/environmental life crisis that might have precipitated a depressive reaction, but that would not be expected to trigger a dementia process. Because some elderly patients are heavily medicated, it is also important to review all prescriptions to determine whether any, alone or in combination, interfere with optimal cognitive functioning. Of course, depression may also coexist with a cognitive disorder. Approximately 40% of people with AD may also suffer from depression or symptoms of depression, although major depressive episodes are relatively rare (Cummings, 1994).

A common differential diagnostic issue with which consulting neuropsychologists deal is the referral to distinguish between depression and dementia in elderly patients. Following is a possible scenario:

When asked about her husband's behavior during an initial interview, Mrs. S related that her husband no longer appears interested in his daily activities and hobbies. He used to tinker with their cars and had a hobby of building wooden clocks. He has gradually given both of these up over the past year and a half and says he is no longer interested in them. He spends much more of his day sleeping than he used to, although he is up a lot at night. He has also lost weight and doesn't seem to have a strong interest in eating. In fact, says his wife, Mr. S doesn't seem to have a strong interest in anything. "If it wasn't for me," she says, "he'd probably spend his whole day sitting in his chair. I try to give him things to do, like crossword puzzles or little things to fix, but when I come back, he hasn't gotten anywhere. We don't see our friends anymore because he just doesn't seem to have much to say." Mr. S agreed that he had given up most of his former hobbies, saying he just wasn't interested in them anymore, although he wasn't sure why. He didn't admit to feeling particularly sad or discouraged about these or any other events. Largely, he appeared to be apathetic, not particularly moved in any direction either to be excited and motivated to accomplish things, or to be despondent about his situation. Although he didn't seem to display internal motivation, Mrs. S did say that her husband would accompany her on outings when she planned them. Recently, they had gone to New England on a four-day chartered bus trip with members of their church. Mr. S went along on all the activities and did not spend time sleeping during the day.

At first glance, Mr. S appears to suffer from symptoms suggestive of depression: He has lost interest in previously enjoyable hobbies and activities, and his eating and sleeping habits have changed. Curiously, however, he does not admit to depressed mood or show other subjective or affective signs of depression. He also will become involved in some activities. At this point, three possibilities need to be considered: (1) Mr. S may have primary depression, (2) a dementing process may explain Mr. S's depressive symptoms, or (3) Mr. S may have both progressive dementia and depression. Further discussion of depressive symptoms and testing for depression may show motivational and affective difficulties, perhaps a reaction to a more sedentary lifestyle after retirement, or problems related to his current life situation over the past several years. Chronic medical problems, if they exist, are likely to result in decreased energy, a loss of vitality, and depressed mood. However, it is also possible that these symptoms may be largely explained by dementia. Mr. S may have given up former hobbies such as clock building because he no longer has adequate visuospatial functioning or the organizational and planning abilities to successfully approach novel or complex problems. He also may suffer from "cognitive inertia." If this is the case, what appears to be poor motivation may be an inability to structure

and organize in such a manner as to accomplish tasks. Although at first only complex projects may be affected, later in the disease, even straightforward tasks such as washing dishes or taking out the garbage may be difficult to begin, because the affected person does not know where to start. Other possibilities to consider, consistent with AD, are that he may have little insight into his difficulties and thus may appear vague and somewhat detached when speaking about himself. Certainly, further interviewing and testing concerning memory and other cognitive problems are warranted. The primary objective here is not to differentiate between dementia and depression based on a brief description of Mr. S's difficulties. Rather, the point is to consider that, especially when psychiatric symptoms present themselves for the first time in older patients, these may signal underlying cognitive problems. Although changes in personality and mood occur with some frequency in AD, they are not necessary or particular to this disease.

Treatment

No currently available treatments can reverse, halt, or slow the progression of AD. We simply do not yet know enough about the neurophysiology and causes of the disease to develop medical treatments tailored to attack the underlying mechanisms. What, then, does treatment focus on? First, there is a big push for psychopharmacologic investigators to develop drugs that will enhance cognitive functioning. Many drugs are in the experimental stages, and a few have made it to market. Most target the cholinergic system, and therefore memory. Second, both pharmacologic and behavioral interventions are aimed at ameliorating psychiatric symptoms and excess disability (that is, additional cognitive and psychiatric impairment not directly attributable to the disease). With each of these treatments, the goal is to improve quality of life for both the AD sufferers and their caregivers. This section provides an overview of psychopharmacologic and behavioral approaches to intervention.

TREATMENTS FOR COGNITIVE ENHANCEMENT

As discussed earlier, ACh is the neurotransmitter system that holds the most promising physiological link to AD. Many drugs that target the cholinergic system seek to increase its production or action and, therefore, to compensate for the impaired cholinergic production in the basal forebrain, including the nucleus basalis. Researchers have tried varied approaches to augment levels of brain ACh. One approach is to increase the availability of ACh precursors such as choline. Because large quantities of choline are found in lecithin, a substance contained in foods such as egg whites and chocolate, researchers once thought that by increasing dietary choline, they might also elevate brain levels of ACh. However, no clear improvements in memory have materialized from this or other approaches. Other pharmacologic approaches have attempted to target the synaptic transmission itself. One method increases ACh by blocking its breakdown by inhibiting acetylcholinesterase. Other methods strive to directly increase the output of ACh or stimulate the postsynaptic cholinergic (muscarinic) receptors to increase firing. Physostigmine (Synapton) was one of the first cholinergic augmenting drugs that clinical trials tested with AD patients in the mid-1980s. Although some studies suggested improvement, this gain appeared minimal in light of overall declining functioning. But there is some indication that longer term use may result in more gain (for review, see Ashford & Zec, 1993). In the mid-1990s, tacrine (Cognex), which is a long-acting acetylcholinesterase inhibitor, received a flurry of attention. It appeared to show some positive effects, but also resulted in a side effect of liver toxicity. To date, no fewer than 10 drugs have been designed specifically to enhance cholinergic activity in the brain. At this point, however, the search is still on to find the right combination of noticeable memory enhancement coupled with tolerable side effects.

Alternative experimental approaches aimed at understanding the pathophysiology of AD hold the promise of future therapeutic benefit. Nerve growth factor (NGF) is a method being researched to increase cholinergic neuronal functioning. NGF is part of a family of **neurotrophins,** or neuron-feeding nutrients, that researchers have long known sustain neural viability in the autonomic nervous system. The cholinergic system neurons in the basal forebrain also have specific receptors for NGF. In animals, antibodies to NGF result in neuronal shriveling and death. Also in animals, introducing NGF appears to increase ACh functioning and learning and memory behavior in those with lesioned brains. NGF may prove therapeutic in AD if it can sustain life and promote growth of surviving cholinergic neurons. Methods suggested include intraventricular infusion of NGF through a pump (Olson, 1990), attachment of NGF to a gene that can specifically target the ACh system through a retrovirus, and direct neural implants of tissue with active NGF (Dunnet, 1991).

A pharmacologic treatment to halt or reverse the memory and cognitive loss suffered in AD is likely to emerge as our understanding of the underlying pathophysiology develops. Probably this will involve a multifaceted

approach to treatment, because large areas of the brain are affected. The treatments reviewed here primarily target the most common and prominent symptom of new learning. A truly effective solution will have to conquer the pervasive cognitive decline.

COGNITIVE, BEHAVIORAL, AND PSYCHIATRIC SYMPTOM CONTROL

The other avenue of treatment for AD aims at symptom control. Behavioral, psychiatric, and cognitive difficulties can emerge either associated with the progression of the disease itself or attributable to processes above and beyond those symptoms that can be explained by the disease itself—a condition termed *excess disability.* Attempts to manage these symptoms use either pharmacologic or behavioral tools.

Common behavioral and affective symptoms associated with dementia include depression, insomnia, persecutory ideation, hallucinations, apathy, agitation, irritability, and purposeless or inappropriate activity patterns. Minor tranquilizers or antidepressants may aid depression and insomnia, but pharmacologic treatment of psychotic symptoms such as delusions or hallucinations may cause serious unwanted side effects. Neuroleptics may further impair cognition, increase agitation, and cause other unwanted motor symptoms.

Patients with AD are also susceptible to illness and conditions associated with aging such as respiratory or urinary tract infections and hearing and vision problems. The associated behavioral problems associated with this "excess disability" can include decreased or increased activity levels, delirium, or hallucinations. In the case of illness, when the condition resolves the behavioral problem likewise should subside. Visual or hearing problems may also amplify hallucinations or sensory illusions.

Because of the severe memory deficit, behavioral management strategies based on learning and responding to reinforcement paradigms can easily prove futile. Instead, most management strategies seek to restructure the environment to ensure safety, provide appropriate stimulation, and redirect inappropriate behavior. As the disease progresses, the person needs more constant supervision. Many nursing homes have specially designated Alzheimer's units because of the difficulties of behavioral management. If a patient is living at home, the burden on caregivers can be enormous. Respite care in the form of dementia "day care" programs serves the purpose of providing appropriate activity and behavioral management, as well as a needed break for caregivers.

Summary

Psychological studies of the elderly have established that aging itself does not necessarily cause dementia. Instead, aging produces predictable changes in patterns of abilities in crystallized and fluid intelligence. Healthy and active individuals in their 60s, 70s, and 80s do not necessarily differ substantially from their past level of functioning in the level of their crystallized cognitive skills or abilities. Relatively stable skills include well-learned verbal abilities such as reading, writing, and speaking; simple arithmetic ability; and immediate and long-term memory. In contrast, fluid intelligence, including short-term memory, abstract and novel problem solving, and behavioral slowing are examples of types of functioning that normal aging may compromise. Health care costs, the aging of the U.S. population, and a renewed concern for well-being of older people have hastened inquiries and interest in this area. Although elderly people are at high risk for diseases that impair cognitive functioning (such as AD), cognitive impairment is potentially reversible in 5% to 20% of dementia cases (for example, in nutritional deficiencies). An understanding of precise neuropsychological deficits can improve the medical management even of patients with irreversible dementia. Neuropsychologists play an important role in comprehensive medical, functional, psychosocial, and neuropsychological assessment. Assessment of mental status and cognitive abilities yields valuable information about prognosis, and it is important in monitoring a patient's health or illness and helping the patient make further life plans (Zillmer & Passuth, 1989; Zillmer, Fowler, Gutnick, & Becker, 1990).

Critical Thinking Questions

- Will exercising one's mind help ward off dementia? Must one "use it or lose it"?
- How is Alzheimer's disease best identified in life?
- How can a neuropsychological profile aid dementia sufferers and their families?
- How does the concept of self of the patient with Alzheimer's disease change with the progression of the disease?

Key Terms

Dementia
Crystallized intelligence
Fluid intelligence
Neurofibrillary tangles
Senile plaques
Atrophy
Mild cognitive impairment (MCI)
Cortical dementia
Subcortical dementia
Multiple infarcts (multi-infarct dementia)
Delirium
Alzheimer's disease (AD)
Beta-amyloid (β-amyloid)
Acetylcholine (ACh)
Bradyphrenia
Metacognitive awareness
Neurotrophins

Web Connections

http://www.mc.uky.edu/nunnet
Official site of the "Nun Study," a longitudinal study of aging and AD funded by the National Institute on Aging.

http://www.agelessdesign.com
Ageless Design: Smarter, Safer Living for Seniors—Site of the first organization to dedicate its resources, imagination, and heart to creating smarter, safer living for seniors. By recommending logical, cost-effective home modifications, unique ideas, and products, homes can accommodate those dealing with age-related conditions and embrace the special needs of people as they age.

http://www.un.org/esa/socdev/ageing
The United Nations Program on aging around the world.

http://www.alzforum.org
Alzheimer's Forum—a nonprofit foundation that has established this site to serve the scientific and clinical research community.

http://www.informatik.fh-luebeck.de/icd/icdchVF-D-Index.html
ICD-10 Codes for Dementing Disorders—provides a classification system (the ICD-10) of mental and physical disorders used by the World Health Organization. This site includes a brief description and diagnostic criteria for most major brain diseases.

http://pni.med.jhu.edu
Johns Hopkins University Division of Psychiatric Neuro-Imaging—these pages describe quantitative brain analyses of neuropsychiatric disorders such as AD, using MRI, functional MRI, and SPECT imaging.

http://dementia.ion.ucl.ac.uk
Dementia Web—site is based at the National Hospital for Neurology and is supported by The Institute of Neurology and the Division Imperial College School of Medicine. This site provides updates on dementia research, a virtual chat room, a dementia support group, and other links.

http://www.neurologychannel.com/dementia
Neurology Channel—has information about dementia and other neurologic disorders.

http://www.mentalhealth.com/dis/p20-or05.html
Internet Mental Health: Dementia—provides diagnosis, treatment, and research reports for caregivers and specialists.

http://tv.cbc.ca/national/pgminfo/memory/index.html
The National Online: In Search of Memory—provides information on three forms of memory: semantic, procedural, and episodic memory. It relates these memory forms to different dementia disorders.

Chapter 15

SUBCORTICAL DEMENTIAS

Age is not determined by years, but by trouble and infirmities of mind and body.

—*Mark Twain*

Keep in Mind

- How do the cortical and subcortical dementias differ from each other?
- How do behavioral motor presentations differ among subcortical disorders?
- What are the symptoms and progression of Huntington's and Parkinson's diseases?
- How is Creutzfeldt–Jakob disease acquired?

Overview

Subcortical dementias are so named because, although these conditions often affect cortical areas and functioning, the structures that are prominently damaged are subcortical. Parkinson's disease (PD) and Huntington's disease (HD) attack the basal ganglia; PD targets the substantia nigra, and HD targets the caudate nucleus. Creutzfeldt–Jakob disease (CJD) affects yet another noncortical structure, the cerebellum. The common behavioral feature characterizing these and most subcortical dementias is slowed cognitive and motor dysfunction (Neuropsychology in Action 15.1: Understanding Subcortical Dementia). What is interesting is the manner in which each disease affects the motor system in a different way. You can truly appreciate the complexities of the motor system by examining these diseases. Motor problems present great physical limitations and hardship. These dementias, however, do not represent only motor system dysfunction. The dementias we present in this chapter are progressive and involve multiple functional systems. We present PD in greater detail than the other disorders because it is more common, and these patients are more likely to be seen by clinical neuropsychologists.

Parkinson's Disease

Parkinson's disease (PD) is a slowly progressive disease of the dopaminergic system that, like Alzheimer's disease (AD), largely affects older adults. Later stages of the disease are associated with dementia. PD, or idiopathic parkinsonism as it is also known, is the most common manifestation of parkinsonism. **Parkinsonism,** like *dementia,* does not refer to a particular disease, but rather to a behavioral syndrome marked by the motor symptoms of tremor, **rigidity,** and slowness of movement. This cluster of motor symptoms may be caused by PD but also by drugs, encephalitis, toxins such as carbon monoxide and manganese, and injury. Mohammed Ali, the famous boxer, experienced parkinsonian symptoms (called *dementia pugilistica*) after repeated blows to the head (Figure 15.1). Parkinsonism occurring in the absence of PD can be a static condition. Although the cause of PD is unknown, and the disease is therefore called idiopathic, it is known to selectively affect the substantia nigra and the dopaminergic systems of the brain.

PD affects an estimated 1% of the population of the United States that is older than 50 years, with the incidence of new cases increasing with age (Bennett et al., 1999; Checkoway & Nelson, 1999). PD rarely occurs before age 40, and the public case of actor Michael J. Fox, who developed PD at age 29, is highly unusual. PD appears more common in men than women, although no differences in risk factors have been identified. Dementia in PD, however, does appear to be age related. Between 24% and 31% of those with PD meet the criteria for dementia (for review, see Aarsland, Zaccai, & Brayne, 2005). However, only about 12% of patients with PD who are in their 50s have dementia, compared with about 70% of those older than 80 (Mayeux et al., 1992). Younger patients with PD are likely to function well, but dementia is more likely with increased age and disease severity. People most likely to have dementia appear to be those who have either had the disease for a longer period or are older at the time of diagnosis (Kay, 1995).

NEUROPATHOLOGY OF PARKINSON'S DISEASE

PD is marked by a degeneration of dopaminergic cells and pigmentation in the substantia nigra (black substance) (Figure 15.2). It is also characterized by **Lewy bodies,** which are small, tightly packed granular structures with

Image not available due to copyright restrictions

Figure 15.1 Mohammed Ali, who experienced development of Parkinsonian symptoms from injuries that occurred during his boxing career, lit the flame in the 1996 Summer Olympics. (© AP/Wide World Photos.)

ringlike filaments found within dying cells. Although neurodegeneration and Lewy bodies are pathognomonic markers in cells of the substantia nigra, patients with PD may also have concentrations of them in other pigmented subcortical areas such as the locus ceruleus or unpigmented areas such as the nucleus basalis of Meynert, hypothalamus, cerebral cortex, cranial nerve motor nuclei, and components of the autonomic nervous system (for review, see Olanow & Tatton, 1999). Although the pattern of concentration of Lewy bodies in the substantia nigra indicates PD, the presence of Lewy bodies in the brain is not specific to PD. They may also appear in normally aging people, individuals with AD, and those with other progressive neurodegenerative conditions. This leads to speculation that Lewy bodies are either (1) indicators of a general disease process or (2) markers of cell death.

The darkly pigmented, or melanized, substantia nigra is a midbrain structure that is part of a group of subcortical structures that collectively make up the basal ganglia. The basal ganglia, which reciprocally connect to the premotor cortex and the supplementary motor areas via the thalamus, largely function to control the fluidity of overlearned and "semiautomatic" motor programs (Bradshaw & Mattingly, 1995). The loss of dopamine from the substantia nigra is directly related to the problems of movement initiation and motor rigidity in PD (Bradshaw & Mattingly, 1995). Aging itself takes a toll on the dopamine system, and some cell loss is expected. But the dopaminergic degeneration in PD is several times that of normal aging. Perhaps the reason that noticeable parkinsonian symptoms do not appear in older adults is because there is a "dopamine threshold," estimated to be breached at between 50% and 80% cell loss (Bradshaw & Mattingly, 1995), before symptoms appear.

CLINICAL PRESENTATION AND NEUROPSYCHOLOGICAL PROFILE OF PARKINSON'S DISEASE

When a physician refers patients with PD to a consulting neuropsychologist, the diagnosis has usually been well established from the characteristic **resting tremor** and allied motor symptoms. In this case, the referral is usually to help determine the presence or extent of cognitive decline. However, physicians may refer patients to either a psychotherapist or a neuropsychologist to aid in diagnosis before the "classic" symptoms appear. Unlike stroke, which presents with sudden motor weakness, PD is insidious, slowly sneaking up on its victim. The patient may first sense vague aches and pains and wonder whether arthritis is developing. A general feeling of tiredness or malaise may come first, which could easily be attributed to overwork or "burnout." Other patients with PD may first report feeling irritable or depressed. These symptoms may be met with assurances, a suggestion to undertake medical tests, or a referral to a psychologist to investigate possible psychosomatic problems or depression. As the disease continues to progress, subtle motor

Neuropsychology in Action 15.1

Understanding Subcortical Dementia

by Jeffrey L. Cummings M.D., Professor of Neurology and Psychiatry, UCLA School of Medicine, Los Angeles, CA

Subcortical dementia is a clinical syndrome characterized by slowness of cognitive processing, executive dysfunction, difficulty retrieving learned information, and abnormalities of mood and motivation. The syndrome is produced by disorders affecting frontal-subcortical circuits, including lesions of the striatum, globus pallidus, and thalamus.

Kinnier Wilson (1912), in his original description of Wilson's disease, recognized the clinical features of subcortical dementia, which von Stockert (1932) described again in the context of discussing postencephalitic Parkinson's disease (PD). Martin Albert and colleagues (Albert, Feldman, & Willis, 1974) reintroduced the syndrome into clinical neurology in descriptions of the subcortical dementia of progressive supranuclear palsy at Boston University in 1975. Substantial controversy centered on this syndrome when researchers first introduced it. Critics of the concept suggested that most dementia syndromes include both cortical and subcortical abnormalities, and that the clinical phenomenology was not distinctive enough to guide differential diagnosis. Subsequent experiences have helped to remold the concept and to account for these criticisms. For example, the subcortical changes in AD in the nucleus basalis of Meynert lead to a cholinergic deficiency that manifests at the cortical level. Thus, although the pathology is subcortical in location, the dysfunction primarily affects the cerebral cortex. Likewise, although there are cortical changes in Huntington's disease, they are minor compared with the marked subcortical abnormalities, and the mental status changes correlate with the subcortical rather than the cortical abnormalities. Thus, even within these mixed syndromes, it is possible to identify cortical and subcortical patterns of dysfunction.

Researchers have increasingly documented the clinical features of subcortical dementia (Cummings, 1986). Slowing of cognition stems from the increased central processing time imposed by subcortical disorders. Patients have prolonged response latencies and slowed complex reaction times. They show executive dysfunction, including difficulty with set shifting, as measured by tests such as the Wisconsin Card Sorting Test or Trails B of the Trail Making Test; reduced verbal fluency on tests of word list generation, such as the number of animals that can be named in 1 minute; impoverished motor programming, as measured by tests such as execution of serial hand sequences; and poor abstracting abilities when asked to interpret proverbs or to distinguish among similar concepts. Memory abnormalities are primarily of a retrieval deficit type. Patients store information at nearly normal rates but have difficulty retrieving the information in a timely way. Thus, on tests of recall they perform poorly, but on tests of recognition memory they may perform in the normal range. This recall deficit includes both recent and remote information. Patients with subcortical dementia show neuropsychiatric and neuropsychological abnormalities. Apathy and depression are particularly prominent. Less common are irritability, disinhibition, mania, and psychosis. Motor abnormalities also accompany most subcortical dementias when the disease involves striatal structures, the substantia nigra, or globus pallidus. Parkinsonism and chorea are the predominant motor manifestations in patients with subcortical dementia.

Recent advances in neuroanatomy contribute to neuropsychological understanding of subcortical dementia syndromes. Five frontal subcortical circuits link regions of the premotor cortex to areas of the striatum, globus pallidus, and thalamus. The dorsolateral prefrontal subcortical circuit mediates executive function and projects from dorsolateral prefrontal regions to the head of the caudate nucleus, globus pallidus, dorsomedial thalamus, and back to the prefrontal cortex. The anterior cingulate region in the medial prefrontal region mediates motivated behavior via a frontal subcortical circuit including the nucleus accumbens, globus pallidus, dorsomedial thalamus, and anterior cingulate. An orbitofrontal subcortical circuit mediates the social governance of behavior and includes orbitofrontal cortex, inferior caudate nucleus, globus pallidus, and dorsomedial thalamus. Dysfunction in the lateral prefrontal-subcortical circuit produces executive dysfunction; abnormalities of the anterior cingulate-subcortical circuit result in apathy; and abnormalities of the orbitofrontal-subcortical circuit produce disinhibited, tactless behavior (Cummings, 1993).

Treatment of patients with subcortical dementia depends on the specific cause of their syndrome. Parkinsonian disorders and PD are treated with levodopa and other dopaminergic agents. The depression syndrome in many patients with subcortical dementia typically responds to antidepressant agents such as selective serotonin reuptake inhibitors. The apathetic syndrome may respond to dopaminergic agonists or psychostimulants such as methylphenidate. Cognitive dysfunction in patients who have a cholinergic disturbance, such as those with PD, may respond to cholinergic therapies such as cholinesterase inhibitors.

symptoms begin to appear. Perhaps the person notices weakness in an arm or leg, including problems in writing, holding a pen, or typing. Voice quality becomes softer and more monotone, and facial expression appears flat to others. If the symptoms are limited to one side of the body, it may appear that the person has suffered a

mild stroke. It is nearly impossible to diagnose PD at this stage because the classic motor symptoms have not yet emerged. It would also be rare to even suspect PD, because these initial symptoms could herald a multitude of different problems.

The cognitive profile of those diagnosed with PD is somewhat heterogeneous depending on the presence of dementia and the stage of the disease. Raskin and colleagues (Raskin, Borod, & Tweedy, 1990) suggest two possibilities for the occurrence of dementia in patients with PD. First, demented PD patients may represent a qualitatively different subgroup, experiencing a later onset of symptoms and showing more subcortical and frontal atrophy. The second explanation is that this group may differ only in degree, with a more pronounced progression of cognitive decline. Dementia in patients with PD has been contrasted and compared with both AD and Lewy body dementia (LBD). In LBD, Lewy bodies are prominent throughout the cortex and present a pattern similar to that seen in AD. A magnetic resonance imaging (MRI) study comparing patients with PD with and without dementia with patients with LBD showed that patients with PD with dementia and patients with LBD had widespread cortical atrophy, but patients with PD without frank dementia had atrophy primarily in the frontal lobes (Burton et al., 2004).

This section examines the cognitive profile of nondemented patients with PD. Some authors suggest that the cognitive profile is heterogeneous; that is, there may be several subgroups of PD, possibly pointing to subgroups of neuropathology (Dubois, Boller, Pillon, & Agid, 1991). Others have also raised questions about lateralization of cognitive deficits. Do cognitive deficits in any way parallel the type and degree of motor symptomatology?

Just as memory dysfunction is the hallmark of AD, motor dysfunction is characteristic of PD. Our review of functional systems begins with the clinical presentation and neuropsychological dysfunction of the motor system.

Table 15.1 *Motor Symptoms of Parkinson's Disease*

Positive Symptoms
Resting tremor
Rigidity (cogwheel)
Stooped posture
Impaired righting reflex/poor balance
Negative Symptoms
Bradykinesia: slowness of movement
Hypokinesia: reduced motor initiation
Gait disturbance
Slow
Festinating (rapid small steps)
Freezing
Masked facies: reduced facial expression
Slowed speech
Decreased voice amplitude
Ocular disturbances
Decreased blink rate
Decreased light accommodation
Slowed saccades

Motor Symptoms

The motor symptoms of PD generally fall into groups of positive and negative symptoms (Table 15.1). Positive symptoms indicate an excess of motor behavior, or abnormal motor reactivity, whereas negative symptoms indicate a diminution or loss of motor functioning. Some experts believe that negative symptoms may manifest before the positive symptoms, although they may be frequently missed. You can think of **bradykinesia** as a poverty of movement that is not only slowed but reduced in magnitude. Semiautomatic movements such as walking, arm swinging, blinking, swallowing, and facial expressiveness may appear almost frozen, as if the person is robot-like and must consciously think to move. The description of a patient with PD as having **"masked facies"**—denoting a masklike face—captures the essence of an emotionless face. The person's demeanor may seem depressed; a vacant stare may be produced by the combination of reduced facial emotion, slow speech, and decreased eye blinking. In addition to slowness, many movements decline in magnitude. Patients with PD do not take long steps and swing their arms high in the air, but rather exhibit a rapid, small, shuffling, **festinating gait.** Handwriting also gets slower and smaller **(micrographia),** and the voice becomes softer as the ability to project the sound of one's voice becomes increasingly difficult. Patients with PD also describe difficulty in initiating movement, or **hypokinesia,** and may have to consciously think to begin walking, to turn around, or to lift a fork. During the movement, the person may also freeze and may need to

"will" the action to continue. Ironically, it may also be difficult to stop an action such as walking or writing, which has led to the suggestion that PD results in a fundamental deficit in initiating and terminating semiautomatic motor programs (for example, see Bradshaw & Mattingly, 1995).

Despite the debilitating effect of the negative symptoms of PD, the positive symptoms of PD are perhaps more noticeable, and most people recognize them as the hallmarks of the disease. Chief among these are a resting tremor and rigidity. Resting tremor, as opposed to a cerebellar intention tremor, is often characterized as "pill rolling." This rhythmic shaking, often first occurring in one hand or the other, looks as if the person might be rubbing or rolling a coin or pill between thumb and forefinger. The tremor stops or lessens with voluntary movements such as reaching, swinging the arm, grasping, or manipulating objects. When the person is sleeping, the tremor usually disappears.

However, with heightened states of alertness, concentration, or nervousness, the tremor is likely to increase. The degree of tremor at any one time is partly due to the voluntary–involuntary nature of the movement, the level of alertness, and the level of stress. It is not always predictable, coming in bursts, but it does increase in speed and may become more violent as the disease progresses. In the early stages of PD, it is not uncommon for the tremor to influence only one side of the body, affecting the hand and foot first and maybe one side of the face. Eventually, it moves to the contralateral side and affects all extremities.

Rigidity, the other major positive symptom, occurs as a tightening of muscles and joints. When a neurologist tries to move the person's wrist, elbow, or knee, there is persistent resistance to this passive movement. Sometimes this resistance appears as a ratcheting movement, as if the person's joint were a cogwheel (cogwheel rigidity). Muscles may appear tense and feel contracted to touch, even when the person is relaxing. This increasing rigidity may result in the characteristic stooped or hunched posture of PD. In addition to a more rigid posture, poor balance and the inability to adjust posture may be evident. The inability to catch oneself quickly, or impaired righting reflex, may appear if the person is pushed or missteps.

On neuropsychological testing of the motor system, patients with PD are extremely slow, with poor reaction times. This is certainly evident on basic tasks that may require simple speeded movement, such as finger tapping. Poor motor performance is also evident on many other tasks that have a speeded motor component such as copying geometric designs with blocks within a specified time limit (such as WAIS-R, Wechsler Adult Intelligence Scale, Revised [WAIS-R] Block Design).

Because PD usually begins as a lateralized motor disorder, some investigators have speculated that the cognitive profile may also show lateralized impairment. Indeed, this may be the case. People with hemiparkinsonism often do show a neuropsychological profile consistent with what would be expected from lateralized cortical damage (Raskin et al., 1990). Exclusively left-sided motor symptoms link to more right hemisphere deficits. Raskin also suggests that this profile may reflect unilateral damage to basal-cortical pathways, resulting in disconnection, rather than unilateral lesions of the basal ganglia.

Motor symptoms may result in lateralized neuropsychological profiles—but is there a relation between the degree of motor impairment and the severity of cognitive dysfunction? Patients with PD followed for up to 10 years did not show evidence of such correspondence (Portin & Rinne, 1986). Although drugs that targeted the motor symptoms, such as levodopa (L-dopa), had great impact on motor performance, they had little effect on cognitive performance.

Visuospatial Deficits

Of nonmotor, higher cognitive functions, visuospatial deficits in nondemented PD are among the most commonly reported in the literature and among the most controversial. Many studies have found that patients with PD perform poorly on spatial tasks that have a motor component. This is not surprising because evidence exists for impairment on visuospatial tasks regardless of whether there is a motor component (for review, see Raskin et al., 1990). However, enough studies show mixed results, or no impairment on visuospatial tasks, to throw the issue of spatial impairment into doubt (for review, see Dubois et al., 1991). To what can we attribute this discrepancy? It may be caused, in part, by the heterogeneity of presentation in patients with PD. Different patients may have somewhat different pathology, and thus different clinical presentations. As discussed earlier, those with more left-sided motor impairment may show more right hemisphere damage (visuospatial deficits). Some studies include patients in more advanced stages of the disease. Some patients with PD may have a comorbid dementia. In any case, factors having to do with possible subgroups of patients with PD continue to cloud the picture of visuospatial functioning.

In nondemented PD sufferers who have visuospatial dysfunction, does such dysfunction point to parietal impairment or some other mechanism? First, patients with PD may report having difficulty orienting themselves in space. For example, when having to walk around the

house in the dark without the aid of visible landmarks or outside in a fog, one person relates, "I used to walk alone in the wood, fog or no fog, but when the symptoms of PD appeared, I noticed that I could not orient myself any more, and in case of fog, I got lost" (Dubois et al., 1991, p. 203). Spatial abilities require the person to visualize the relative position of objects in three-dimensional space, and to make a motor response to orient himself or herself or other objects in that space. Therefore, the visual-spatial-motor aspects link in an overall spatial framework. Disease could theoretically disrupt this network in the parietal lobes or anywhere along the visuomotor system. Some investigators have suggested that the basal ganglia play a role in the visuomotor aspects of visuospatial problems in patients with PD (Danta & Hilton, 1975; Dubois et al., 1991). But what about patients who have visual-perceptive difficulty, but no visuomotor problems? For example, a popular test used by neuropsychologists, Benton's Judgment of Line Orientation Test (Benton et al., 1983), requires matching drawings of lines in various orientations to a template (Figure 15.3). It does not require drawing or movement of the body. Yet, many nondemented PD patients have difficulty with this task (Goldenberg, Wimmer, Auff, & Schnaberth, 1986). One explanation is that any disruption in the visual-spatial-motor circuit may impair performance. Another suggestion is that even in tasks in which a person does not use a motor response, he or she still has an internal representation of a perceptual-motor response (Villardita, Smirni, LaPira, Zappala, & Nicoletti, 1982).

In summary, although it is not clear whether all patients with PD experience visuospatial dysfunction, a sizable proportion does. Certain subgroups of patients, or those in more advanced stages of the disease, for example, may show the most difficulty. The parietal lobes per se do not appear chiefly responsible for the problem. Rather, the basal ganglia are implicated in a larger visuospatial network.

Executive Functioning

Many patients with PD have executive functioning difficulties. Difficulties with specific executive functions can be evident, although most do not have difficulty with abstract thinking (Raskin et al., 1990). These deficits show up early in the disease process, and thus appear to result directly from the disease (for review, see Dubois et al., 1991).

Among executive dysfunctions reported in the literature are difficulties with changing mental sets, maintaining mental sets, and temporal structuring. The inability to switch mental set in response to environmental demands, or perseveration, shows most clearly on neuropsychological testing through measures that require strategy shifts to solve problems (such as the Wisconsin Card Sorting Test) or an alternating response between two different types of stimuli (such as the Trail Making Test B or the Stroop Test). Someone who has set-shifting problems repeatedly tries to use the same strategy, even if it is not working. Investigators have found that patients with PD do not make more total errors on these types of tasks, but the errors they do make are perseverative (Raskin et al., 1990; Dubois et al., 1991). The perseverative problem in maintaining set occurs after the patient tries a new or different strategy. It is a tendency to revert back to a previous strategy after switching "mental set." Some authors have also explained the verbal fluency difficulties of this group as a problem of set maintenance (Dubois et al., 1991). Verbal fluency tasks typically require the person to list as many words as possible that begin with a specified letter or belong to a specified category. The problem appears most evident when the person uses several different letters. First, the task is to name as many words, within a 1-minute time period, that start with the letter *F,* then to name all the possibilities that begin with *A,* then with *S.* In such tasks, during the middle of the *S* sequence, patients with PD may revert to words that begin with *F* or *A* (Lees & Smith, 1983).

A difficulty in "time tagging" events is a problem in temporal structuring. Researchers have reported patients with

PD may have memory for news events without associated memory for the event order (Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988). In daily life this can translate into problems remembering "when" medications have been taken or learning the sequence of new tasks. Temporal ordering is an executive problem that interacts with memory.

Not all of the frontal lobe is involved in the dysexecutive problems of PD; rather, the premotor area and the basal ganglia with its associated projections to the frontal lobes are implicated.

Language/Speech

PD typically does not produce classical aphasia. Also, few, if any, linguistic impairments appear involving grammar and sentence structure (Dubois et al., 1991). Thus, general language processing and comprehension are intact. Some researchers indicate that more subtle problems in understanding grammatic complexity may be evident on more sophisticated neuropsychological tests (Levin, Tomer, & Rey, 1992). However, close to 70% of patients with PD have difficulties with articulation and the neuromechanical aspects of speech production (Levin et al., 1992). We have mentioned that patients with PD lose voice amplitude and vocal emotional expression **(dysphonia),** which results in monotonous voice. Other speech irregularities may include segmented accelerated bursts of speech **(tachyphemia)** and compulsive word or phrase repetition **(palilalia).**

Tests that measure aspects of expressive or receptive aphasia show little impairment in patients with PD. However, patients may perform poorly on semantic fluency and word-finding tasks (such as the Boston Naming Test). However, as discussed earlier, these tasks are better conceptualized as belonging in another domain (executive functioning). Behavioral assessment of speech is the method that will demonstrate the characteristic disarticulation problems.

Memory

Compared with AD, memory functioning is relatively spared in PD, even in patients with PD with dementia (Sagar et al., 1988). Digit repetition and block-tapping repetition are usually preserved (for review, see Dubois et al., 1991). On tests involving episodic memory, paired associate learning, auditory verbal learning, and visual reproduction of geometric designs, patients with PD do show a recall deficit but demonstrate encoding and registration of declarative material through recognition tasks (for reviews, see Dubois et al., 1991; Levin et al., 1992). The implication of this pattern is that strategic memory processes for organization and retrieval of declarative information are defective.

Nondeclarative learning presents a mixed bag in PD. Verbal priming and perceptual-motor adaptation are largely unimpaired in patients with PD without dementia (Crosson, 1992; Heindel, Salmon, Shults, Wallcke, & Butters, 1989). However, nondeclarative learning, which relies on intact motor or executive functioning, is often deficient. The ability to learn new motor skills declines as the disease progresses (Crosson, 1992). This is not surprising, considering the general dysregulation of the motor system. Procedural learning, measured by rule-learning tasks, such as the Tower of London, may be deficient, but results are mixed. At times, patients with PD perform poorly because of a problem in maintaining mental set for the rule, again pointing more to a problem in executive functioning than to a memory registration problem.

Most of the apparent memory difficulties experienced by patients with PD stem from interactions among the executive, the memory registration, and the motor systems. Patients with PD may show difficulty in motor skill acquisition. Patients with PD without dementia can passively register declarative information in short- and long-term memory. However, many have trouble using this information effectively. This includes effectively organizing information to be recalled, maintaining a consistent mental set when trying to learn or retrieve information, and time tagging or knowing not only that something has occurred but "knowing when" it happened.

Mood, Emotion, Personality, and Insight

A large proportion of patients with PD suffer from depression. Debate continues whether the mood disorder is a primary dysfunction of the disease or a secondary result of the medications used to treat the disease. To those suffering from depression, the debate may seem academic. Some researchers also suggest that depression may be a natural reaction to realizing that the patient has PD. Although this probably occurs to some degree, it does not seem to adequately explain the occurrence of depression. Patients with PD appear to be more depressed than patients with many other chronic diseases (Raskin et al., 1990).

Although few standardized neuropsychological tests measure expression of emotion, researchers have studied this in patients with PD. The findings are somewhat equivocal, but some suggest that patients with PD have a dysfunction in emotional expression associated with a

right-frontal focus (for example, see Ross, 1985). These patients may have difficulty in showing an angry face or a surprised face but may be able to recognize emotional expression. Does this finding suggest a cortical deficit in emotional expression? Or rather, a problem in the more mechanical aspects of emotional expression? Because of the "masked facies," it is difficult to determine whether emotional expression is lost or just diminished in frequency and intensity. Future research may help answer this question.

TREATMENTS FOR PARKINSON'S DISEASE

Without treatment, patients with PD are souls trapped in the cages of their bodies, unable to command or coax their mutinous muscles into action. Out of the tragedy of this disease, however, has emerged a palette of treatments that are worth examining, not only for addressing PD but because they represent creative and forward-thinking approaches to the treatment of aging-related brain disorders in general. Interestingly, the treatment for PD appears to be traveling full circle from surgery to drugs to surgery. In addition, gene therapies, tissue implants, and various approaches to prevention are on the horizon.

The first surgical approaches to PD in the late 1950s were based on the idea of alleviating symptoms by interfering with what was thought to be "malfunctioning circuitry" in the basal ganglia through heat-induced surgical lesioning of the global pallidus. By 1960, a group of Swedish researchers could demonstrate motor improvement in a significant number of their patients. However, this treatment preceded the advent of computed transaxial tomography (CT) scans, MRIs, and the precision stereotaxic and electrode recording tools needed to locate specific neurons. The imprecision of this surgery made negative side effects likely.

The discovery of L-dopa as a possible treatment for PD in 1961 (Birkmayer & Hornykiewicz, 1961) was revolutionary and heralded a new approach to the treatment of neurodegenerative diseases. With the advent of a seeming miracle drug, surgical approaches fell by the wayside by the late 1960s. Today, there exists a menu of drugs that act not only on the dopaminergic system but also on related neurotransmitter systems.

In Paris in the 1860s, **anticholinergics** extracted from plant sources (such as scopolamine from jimsonweed, black henbane, or deadly nightshade) were the first treatments used for PD. Although the mechanism of action was not known initially, these solanaceous alkaloids acted by blocking the action of acetylcholine, offering some symptomatic control of motor systems for tremor and rigidity. However, the side effects of "anticholinergic intoxication" limit their usefulness. Possible systemic effects, including dry mouth, blurred vision, constipation, weak bladder, and cognitive effects such as memory problems, confusion, slurred speech, and visual hallucinations, can create more than a small nuisance for patients. Physicians now prescribe synthetic anticholinergics of different types, if at all, during the early stages of the disease, and usually in combination with levodopa.

L-Dopa is the left (levo) form of the dopa molecule, a simple amino acid. Prepared as a drug, it is called *levodopa.* Plants and animals manufacture it, and it appears naturally in fava beans and other legumes. Levodopa, being a dopamine precursor, directly metabolizes into dopamine. Cousins of levodopa include dopamine agonists and analogs that mimic the action of dopamine by stimulating its release, whereas reuptake blockers work by preventing reuptake at the synapse to retard metabolic removal. Drugs acting on the dopaminergic neurotransmitter system are still the best family of drugs found to alleviate tremor, bradykinesia, and rigidity. The difficulty with these orally ingested drugs, however, is that they convert to dopamine in the body and do not easily penetrate the blood–brain barrier. Probably less than 1% actually crosses over to be useful to the striatum, causing systemic buildup of dopamine in organs such as the liver and kidneys. Therefore, medications usually combine L-dopa with a decarboxylase inhibitor (such as carbidopa) to prevent the conversion to dopamine until it crosses the blood–brain barrier. Because carbidopa cannot cross the blood–brain barrier, it acts as a protector against conversion in the body until it releases the levodopa into the brain. This arrangement delivers about five times the dopamine to the targeted area, greatly enhancing the effectiveness of the drug.

Physicians may also use other drugs to treat PD, either as adjuncts or to counteract side effects of long-term dopaminergic drug usage. Doctors may add monoamine oxidase B (MAO-B) inhibitors, antidepressants, and agents to counteract the effect of **dyskinesia** to the complex menu, which must be taken at intervals as frequently as every 4 hours. These drugs are extending the survival of patients with PD, but not without a price. The side effects of dopaminergic drugs, including vivid nightmares, disturbed sleep, perceptual illusions, and hypomania can be very disturbing. Also, after a long course of treatment, usually 10 years or so, the drugs lose effectiveness, dopaminergic neurons become hypersensitive, and the therapeutic window becomes shorter in duration, resulting in a severe on/off syndrome. During the "on" phase, the drug exerts its action but may overshoot, resulting in

Neuropsychology in Action 15.2

Pallidotomy Surgery: A Case Report

by Barbara L. Malamut Ph.D.

The following case report profiles one "typical" patient who underwent right pallidotomy in an attempt to alleviate some of his adverse motor fluctuations. M.J. is a 56-year-old, right-handed man with a 16-year history of Parkinson's disease (PD). His symptoms first began on the left side of his body with abnormal spontaneous movements of his foot, including a rhythmic tapping and an involuntary curling up of his toes. After about 10 years, his motor deficits worsened and he suffered from significant bilateral symptoms including bradykinesia, rigidity, and motor fluctuations. He had dyskinesias when his medication was "on" and freezing when "off." Other than PD, M.J. had no other major medical or psychiatric problems. He was forced to go on medical disability 3 years ago. He has few hobbies, spending his days maintaining the house, walking the dog, doing yard work, and some cooking. M.J. acknowledges a feeling of depression, which increases when he does not feel well.

When he arrived for his presurgical neuropsychological assessment, M.J. presented as an alert, oriented, pleasant, and cooperative man with a stiff, slow gait. Dystonic posturing of his head and upper torso was evident when sitting. Although his facial expression was fixed, he displayed a range of affect. A moderate tremor, which was greater on the left, was also evident. His spontaneous speech was soft in volume, with a choppy cadence, but his language was intact.

No disturbance in thinking was noted during the interview. Results of neuropsychological testing indicated a few areas of mild impairment that were consistent with PD. These included problems with speed of mental processing, working memory for both auditory-verbal and visuospatial information, visual scanning, graphomotor control, and retrieval of verbal and visuospatial material. Recognition memory was intact. Consistent with his self-reported history, M.J. was depressed, socially isolated, and withdrawn.

Figure 15.4 In the pallidotomy surgery for Parkinson's disease, the surgeon is using the triangulation of three coordinates of the frame to pinpoint the patient's globus pallidus. (Reproduced from Ueckert, S. [1996, January 22]. In R. SoRelle, "New procedure slows effects of Parkinsons: Surgery can restore balance to system." *Houston Chronicle,* 4a, by permission.)

(*continued*)

M.J. was a good candidate for pallidotomy because he was generally in good physical and mental health, his neuropsychological profile did not indicate cognitive decline or dementia, and his medications had lost much of their effectiveness. The day of M.J.'s surgery, he was injected with a local anesthetic and fitted with a stereotactic frame necessary to locate the area to be lesioned (Figure 15.4). With the frame in place, a computed transaxial tomography scan was done and compared with his previous magnetic resonance image, to identify the precise placement of critical brain structures. After drilling a tiny hole through M.J.'s skull, the surgeon inserted a small canula, or tube, through the dura mater and snaked a microelectric probe through his brain toward his right pallidum. As the probe approached the area of neuronal hyperactivity, sound bursts became more frequent. The surgeon first stimulated the area to observe motor response. (M.J. was conscious so his responses to stimulation could be tested and any adverse affects on vision or speech could be noted before actual lesions were made.) Being careful not to affect the nearby optic tract, the surgeon then made a small heat-induced lesion to permanently destroy the overactive neurons of the pallidum. After this surgery, M.J. needed a few stitches and was released within 24 hours. M.J. experienced no surgical complications.

Six months later, M.J. returned for a neuropsychological re-evaluation to monitor his cognitive status. He reported that since surgery, his left-sided rigidity had disappeared and he no longer had pain or involuntary movements when walking. On observation, he no longer had dystonic posturing but did continue to walk with a slow, shuffling gait. In addition, his speech was now normal in volume, but he had developed a mild stammer. Overall, M.J. was pleased with the results of his surgery, although he realized this was not a cure. Improvement relative to his preoperative neuropsychological evaluation was noted in speed of mental processing, working memory for both auditory-verbal and visuospatial information, and graphomotor control. M.J.'s problems with depression remained, and he began taking antidepressant medication and agreed to begin psychotherapy.

This case raises several critical and common issues regarding pallidotomy surgery. Although pallidotomy effectively alleviates many motor symptoms and pain associated with later stages of PD, it does not cure the disease or return the patient to preinjury functioning. The long-term benefits and risks of pallidotomy are unknown. Studies currently under way are examining the cognitive sequelae of the pallidotomy procedure in comparison with the natural progression of the disease. The newest procedure, approved by the U.S. Food and Drug Administration in July 1997, is deep thalamic stimulation, which works as a type of electronic pacemaker interfering with the ventral intermediate thalamic nucleus. The surgery, performed like pallidotomy, primarily reduces tremor but may have little effect on the other PD symptoms. This surgery, unlike pallidotomy, does not result in permanent lesions. Other treatment modalities currently being explored, such as gene therapy and fetal implant surgery, may be promising avenues for the future. These procedures may actually arrest or reverse PD, rather than just ameliorate some of its motor symptoms.

an effect akin to an overdose. In this phase, severe dyskinesia resembling choreic movements and dystonia involving muscular posturing may result. This may cycle quickly to "off" symptoms, which include the disease symptoms, particularly freezing, severe tremor, and panic.

L-Dopa could not live up to the hopes that pharmacologic substitution of missing dopamine would be sufficient treatment. The debilitating "on/off" drug phenomena led to the return of surgical techniques. These operations currently are intended for those for whom the drug treatments are no longer effective. Now, however, high-tech precision imaging of the brain results in a greater chance of locating the offending neurons. Currently, two types of operations are being conducted. The first operations focus on surgical lesioning of offending neurons. The second wave of surgeries, deep brain stimulation operations, involves nondestructive electrical interference.

Pallidotomy, the PD surgery of the late 1950s, was revived in the early 1990s. Surgeons use it in an attempt to alleviate the abnormal uncontrolled movement of dyskinesia and the frequent on/off symptoms. In pallidotomy, surgeons lesion the ventral (that is, the internal portion) of the globus pallidus by heat-coagulating the neurons. Studies have shown that the decreased dopamine in the basal ganglia causes the motor portions of the pallidum to become overactive. This hyperfiring, in turn, inhibits the thalamus and portions of the brainstem (which causes bradykinesia and dyskinesia). Lesioning the posteroventral portion of the pallidum arrests this excessive output to the thalamus and brainstem (Neuropsychology in Action 15.2). Surgeons use a second lesioning procedure on a portion of the thalamus, **thalotomy,** to attack tremor. Interestingly, they also use this procedure for patients with tremor caused by multiple sclerosis, essential tremor of old age, cerebellar tremor, and poststroke tremor. These two operations are typically unilateral and not done in combination. In fact, the lesion sites for the two operations are only millimeters apart. Bilateral lesions done at the same time appear to greatly increase the risk for cognitive deficits. In pallidotomy, the risk may be greatest for memory difficulty and confusion. For thalotomy, speech dysfunction appears to be the greatest risk.

Deep brain stimulation procedures represent the newest variation of these surgeries. The target site is the same as in thalotomy, except that instead of a destructive lesion, surgeons transmit electrical interference to the neurons via a

permanently implanted lead. An implanted adjustable neurostimulator operates somewhat like a pacemaker and can be turned on and off by the patient.

Although these surgeries represent new hope for patients for whom drugs are no longer effective, they are palliative, not curative. Patients experience relief of symptoms, and about 80% may improve, but they must still take medication. The progression of the disease continues.

Huntington's Disease

Huntington's disease (HD), although rare, has been well studied in the last quarter of the 20th century. Why the resurgent interest in a disease that physicians described more than a century ago and then seemingly left to languish until the 1960s? From 1872, when George Huntington described this "hereditary chorea," until the 1960s, researchers paid little attention to this neurologic disease, which causes adults in the prime of their lives to seemingly "go insane," develop a tendency toward suicide, and suffer devastating motor impairment in the form of chorea. Families of HD sufferers have spearheaded the search for the gene that controls the disease. For neuropsychology, the specificity of this disease offers a window to learn about the widespread behavioral effects of caudate nucleus deterioration.

George Huntington was not the first to describe the twisting, writhing, grimacing choreic movements, which are reminiscent of a puppet at the hands of a sinister master. In the 16th century, "peculiar" families were described, but the hereditary nature of the disease did not appear to come into the medical consciousness until evolutionary theory emerged in the mid-1800s (Wexler, 1995). Other physicians before Huntington hypothesized about the hereditary nature of the disease, but it was young George Huntington, just 22 years old, who in his 1872 article described the disorder most clearly and most completely. He emphasized the emotional and psychological aspects of the disease, describing "the tendency to insanity, and sometimes that form of insanity that leads to suicide." This became the classic account of the disorder, forever after associated with the name Huntington.

The story of the search for the "Huntington's gene" begins in the late 1960s. After years of relatively little scientific interest in this apparently incurable disorder, two families picked up the torch. Marjorie Guthrie, ex-wife of the singer Woody Guthrie, who had HD, founded an organization of HD families to raise money for research. The Wexlers, whose story is told in the book *Mapping Fate* (Neuropsychology in Action 15.3) were instrumental in pushing basic scientific research toward the search for the gene. Nancy Wexler, at risk for HD herself, was active in the study of colonies of HD families in Venezuela. Largely through the energy generated by these and other at-risk families, researchers pinpointed the offending gene in 1993. This discovery does not translate into an immediate cure or treatment. However, it does provide the first hopeful step in that direction.

HD is a progressive subcortical dementia. This rare disease, which affects about 5 to 10 in 100,000 people, is linked to the gene *IT15* on chromosome 4 and is passed on by one parent in an autosomal dominant inheritance pattern. As far as genes go, *IT15* is a big one, with more than 300,000 base pairs, and it is evident in all tissues of the body. People with normal versions of the gene have between 11 and 34 repeats of the trinucleotide CAG (cytosine, adenine, guanine), which codes the gene. However, those with the HD-positive gene have 37 to as many as 100 or more repeats. More repeats entail earlier onset and greater severity of symptoms. Some overlap exists between normal and abnormal functioning, making 35 to 40 a borderline range. When operating normally, *IT15* produces the amino acid glutamine. It is not clear how the body uses glutamine, or the exact function of *IT15,* but researchers do know that expanded gene sequence repeats on other genes characterize inherited diseases such as myotonic dystrophy and spinobulbar muscular dystrophy, which affected President Kennedy.

Autosomal dominance translates into a 50% chance of acquiring the disease. Because this disorder runs in families, HD is not suspect unless there is a family history. In those with a family history, a simple genetic test can determine the presence of the disease, but much to the surprise of many scientists, most people at risk have chosen not to be tested (see Neuropsychology in Action 15.3).

NEUROPATHOLOGY OF HUNTINGTON'S DISEASE

Deterioration of the caudate nucleus bilaterally plays a primary role in the neuropathology of HD, although ultimately, HD affects multiple brain systems. The caudate nucleus is one of the structures that comprise the striatum, together with the globus pallidus and putamen. The striatum is part of the basal ganglia, which is responsible for modulating motor activity. However, the role of the striatum is somewhat different from that of the substantia nigra, which is primarily affected in PD. Although the substantia nigra is responsible for the proper initiation and termination of movements, the

Neuropsychology in Action 15.3

Testing Fate: Would You Want to Know If You Were Going to Get Huntington's Disease?

by Mary V. Spiers

Would you take a test to determine whether you would develop an inherited brain disease in the future? This is the question facing family members of people with Huntington's disease (HD), a subcortical dementia with devastating motor and cognitive consequences. Fortunately, the disease is rare, but if it runs in your family, you have a 50% chance of acquiring this autosomal dominant genetic disease. There is no cure and there is no treatment, and if you do have it, you may pass it on to your children. You are also likely to die while in your 50s. Would knowing this help you to plan? Plan not to have children, perhaps plan not to even marry, or perhaps try to pack a lot of living into a short time? Would knowing lessen your worry? Or would knowing be a traumatic experience? Would you consider suicide? Would you always be on guard watching and waiting for the first symptoms to appear?

These questions face the 125,000 people at risk for the disease in the United States. In 1983, researchers discovered a genetic marker that paved the way for the first testing for HD. Then 10 years later, in 1993, researchers located the gene *IT15* (named "Interesting Transcript") on the short arm of chromosome 4, and the test became much more accurate. Only a simple blood test is required. Scientists predicted a flood at testing centers, but there has been only a trickle of people, about 6% of those at risk. Why is this? The answers come from those at risk. Alice Wexler, author of the book *Mapping Fate,* describes the story of her own family, and of her mother, who died of HD. After her mother's diagnosis in 1968, the Wexler family, led by her father and sister, spearheaded one of the most innovative approaches to scientific investigation, bringing scientists and families together in collaborative efforts to search for the HD gene. The book chronicles the scientific and personal odyssey of the discovery of the gene. Alice Wexler describes her own ambivalence and the feelings of others who have struggled with the idea of getting tested. Some have taken the test, mentioning control and relief from uncertainty as major reasons. Others are concerned about confidentiality of their medical records and possible denial of insurance coverage. For those who have tested positive, the experience is often traumatic and, surprisingly, may not alleviate the anxiety because there is no certainty as to when the symptoms may develop. Even for those who test negative, the result may come as a shock as they realize they have built their lives around the possibility that they might acquire a fatal disease. Alice Wexler, like so many others, has decided against being tested. If you were at risk, you could test your fate. But would you want to?

striatum controls the proper timing, ordering, and sequencing of movement patterns (Bradshaw & Mattingly, 1995). The caudate nucleus has reciprocal projections (afferent and efferent neurons) to a number of limbic and prefrontal areas. Although HD primarily affects the caudate, it may also affect the putamen, other areas of the striatum, and possibly other limbic system structures such as the hippocampus. By the end stages of the disease, the frontal lobes may also shrink by 20% to 30% (Vonsattel, 1992).

In patients with HD who are showing the symptoms of the disease, structural neuroimaging techniques such as CT or MRI clearly reveal the loss of cell mass in the caudate and a widening of the ventricles. On MRI, the volume of the caudate and other basal ganglia structures is clearly reduced. The apparent structural deterioration of the caudate corresponds to a downward progression of behavioral functioning. Functional neuroimaging via positron emission tomography scan is more sensitive to early changes and can show hypometabolism in the frontal and striatal regions before deterioration is evident structurally (Hasselbalch et al., 1992) and before a clinical diagnosis (Penny & Young, 1993).

CLINICAL PRESENTATION AND NEUROPSYCHOLOGICAL PROFILE OF HUNTINGTON'S DISEASE

How do the symptomatology and neuropsychological functioning of the HD sufferers differ from profiles of AD or PD? HD results in a unique pattern of impairment in which difficulties associated with frontal lobe functioning and motor functioning are prominent. Although PD also results in frontal executive system and motor impairment, the presentation differs in some ways. The caudate nucleus, rather than the substantia nigra, is the main culprit in HD.

Many of the cognitive difficulties of patients with HD likely stem from a breakdown in premotor frontal lobe functioning and the connectivity of the caudate-frontal system. Early in the disease process, patients with HD show characteristic frontal signs of rigidity, perseveration,

and difficulty switching mental set in daily life, as well as on neuropsychological testing. Some dysfunctions stem from the impacts that poor executive organizational abilities and attention/concentration problems have on cognitive functioning. For example, the memory difficulties of patients with HD appear largely attributable to poor executive functioning. Capacity for learning new information declines in HD, but the picture differs from the AD profile. Patients with HD demonstrate low levels of free recall but improve greatly if given a recognition test. Why? Apparently they encode new information, or multiple-choice recognition tests would not aid performance. Patients with HD appear to suffer primarily from a retrieval problem caused by ineffective memory search operations. They may have a poor ability to differentiate what they know from what they do not know (for review, see Brandt & Bylsma, 1993). This problem in strategic memory processing and metamemory (knowledge of one's own memory) appears attributable largely to frontal lobe and executive functioning difficulties rather than to hippocampal involvement, although both may interact to some degree. Executive difficulties probably also interact with other cognitive processes such as verbal and spatial conceptualization and processing.

The final manner by which the striatofrontal lobe complex may exert its effects on cognitive functioning is through multiple connections to other areas of the brain. Patients with HD appear to have difficulty orienting themselves in space, which may be a parietal dysfunction. For example, the old-time child's game of blind man's bluff, in which one child is spun around blindfolded and then required to tag others by sound alone as they call out, would be difficult for patients with HD. Potegal (1971) has explained this egocentric spatial disorder as a problem in readjusting, or the ineffectiveness of the caudate in modulating changes in spatial position. Although research has not yet confirmed this interpretation, it appears reasonable, given the role of the striatum in modulating other motor activity.

The emotional difficulties experienced by many patients with HD likely result from prefrontal and limbic system interactions. Patients with HD exhibit a disproportionately high degree of affective disturbance, in the form of depression and manic depression. The suicide rate of 6% (Farrer, 1986) in HD is greater than in other degenerative disorders. Are these emotional disturbances a response to a desperate situation, or perhaps a symptom of frontal-subcortical impairment? Suicide may be an understandable response, given the severe cognitive devastation that people in the early stages of the disease can anticipate. HD sufferers are no strangers to what will befall them. They have seen a parent, a grandparent, aunts, and uncles succumb to the same horrible disease. However, the rate of emotional disturbance in HD is greater than expected. Depression is the most common affective disturbance (Brandt & Bylsma, 1993), but the literature reports a wide range of affective and psychiatric disturbances in patients with HD. These include anxiety, apathy, irritability, impulsivity, aggression, sexual disturbance, schizophreniform thought disorder, and psychosis involving hallucinations and delusions (for reviews, see Brandt & Bylsma, 1993; Bradshaw & Mattingly, 1995). Interestingly, the emotional disturbances often precede motor symptoms. At this point, the affected individual may not even be aware of his or her diagnosis. These emotional symptoms can be best conceptualized as a symptom of the disease, or a predisposition toward symptoms such as depression. However, this is not to say that reactions to the illness do not contribute to the picture of emotional disturbance. A reaction to the severity of the disease can compound a predisposition to depression.

The motor difficulties of HD are characterized by **chorea:** twisting, writhing, undulating, grimacing movements of the face and body. Interestingly, overmedicated PD patients also show choreic movements. This has led to the hypothesis that the dopamine system lies at the root of both these problems. Obviously, this gross-motor dysfunction seriously hinders everyday activity. Like patients with PD, patients with HD are slow motorically (bradykinesia). Also, as in PD, the chorea tends to disappear with sleep and increase with stress. Unlike PD, patients with HD walk with a wide-based gait. Their speech is dysarthric, becoming increasingly erratic in its rate of production and staccato with intermittent pauses. They become clumsy and uncoordinated, unable to do fine-grained work. In testing patients with HD, these severe motor difficulties disrupt performance on other tests that have a motor component, even if the test is designed to measure other functions such as visual problem solving. In assessing the cognitive performance of patients with HD, motor-free tests provide the clearest picture. Currently, no cure exists for HD, and the treatments that exist focus primarily on the relief of emotional symptoms such as depression and hallucinations.

Creutzfeldt–Jakob Disease

Creutzfeldt–Jakob Disease (CJD), a dementia long hidden in obscurity because of its rarity (one that most neuropsychologists have never seen personally in one of their patients), has suddenly leaped into the limelight because of its connection to "mad cow disease" and

because of the fear that its incidence is increasing. CJD is a compelling disease, unlike the other dementias we have considered, because of both its speed of progression and mode of transmission. With a malignantly cascading decline over 3 to 4 months, it is the most quickly progressing dementia. Scientists have long known that humans can transmit this disease via transplants of affected neural tissue, cornea transplants, or contamination via medical procedures, but it is now also becoming clear that CJD and its variants can cross species through the consumption of tainted meat containing neural tissue. Extensive spongelike holes appear in the brains of its victims, giving it the fitting name "spongiform encephalopathy" (SE). The mechanism by which the brain becomes infected has eluded scientists for decades because CJD does not manifest the symptoms of typical acute infections. Virologists, biologists, and chemists are joining clinicians to unravel the mysteries of this disease.

In the early 1900s, Bertha, a 23-year-old German woman, was a patient of Hans Gerhard Creutzfeldt. Creutzfeldt, an assistant of Alois Alzheimer at the Munich Psychiatric Clinic, was, like Alzheimer, trying to clarify the differences and similarities between behaviors understood as "psychiatric" and "neurologic." Creutzfeldt noticed that Bertha showed many behaviors typical of other mental illnesses, such as believing she was possessed by the devil, neglecting her hygiene, and posturing strangely. However, other symptoms suggested frank brain impairment. Bertha also had an unsteady gait, twitchy eyes, a voluntary tremor, and a tendency to giggle inappropriately. These latter symptoms, which we now recognize as indicating subcortical motor and emotional dysfunction, were Creutzfeldt's clues. After Bertha died, Creutzfeldt examined her brain tissue under the microscope. What he saw were the little "stars" of astrogliosis (Figure 15.5) dotting her brain. In 1920, he published his article that describes Bertha. With the synchronicity that often occurs in science, Dr. Jakob reported a similar case in 1921. Creutzfeldt and Jakob thus share the distinction of discovery.

CJD is a quickly progressive subcortical dementia estimated to affect only 1 person in 1 million people per year. This is extremely rare even in comparison with HD, which affects 5 to 10 per 100,000 people. CJD appears around the world with the same prevalence and does not appear to vary across groups or cultures. Although Creutzfeldt's patient was young, most cases have been in their 50s or 60s. For the most part, researchers have hypothesized that CJD spontaneously arises as a random mutation. As long as it is not passed on to others, the disease dies out with its victim. Some variants of CJD may manifest themselves differently in the behavior of those it afflicts. For example, the extremely rare familial CJD variant termed **Gerstmann-Straussler-Scheinker syndrome (GSS),** reported in only a handful of families, results in a "fatal insomnia." This is the only reported incidence of transmission other than through external infection. Researchers believe that in older people CJD incubates for years before manifesting.

Figure 15.5 The dark stars of astrogliosis. (Courtesy D. Carlton Gajdusek.)

One of the most alarming aspects of this disease, and the reason it has been catapulted out of obscurity, is its relation to other SEs. Variations of SE, as mentioned earlier, are aptly named: Portions of the brain actually resemble a sponge, because of the microscopic pattern of holes. Researchers have identified SEs in species from minks to sheep (scrapie) to cows (bovine spongiform encephalopathy [BSE] or "mad cow disease") to humans (CJD and kuru). In his book *Deadly Feasts,* Richard Rhodes chronicles the history of the SEs. He describes the history and current status of research into CJD and kuru. **Kuru** is a SE that the Fore people of Papua New Guinea contract, which presented itself when they began ritually cannibalizing their dead at the beginning of the 1900s. Rhodes (1997) also describes the history of the research, which suggests that SEs can easily leap across species, and that they are probably variations of the same disease process.

Neuropsychology in Action 15.4

Creutzfeldt–Jakob Disease and Mad Cow Disease: What's the Connection?

by Mary V. Spiers

In his book *Deadly Feasts* (1997), Richard Rhodes traces the history of spongiform encephalopathies (SEs) in humans and other species. He reflects scientists' views that these diseases are variations of the same infectious process, and that the ingestion or injection of diseased neural tissue can spread many SEs within or across species. He also forecasts an alarming increase in human encephalopathies over the next few years if people do not contain and eliminate the disease in the animal food supply.

How exactly did mad cow disease (bovine spongiform encephalopathy [BSE]) arise and become a threat to humans? Farmers routinely give cattle protein supplements: dairy cows all through their life, and beef cattle for end-stage fattening. As long as farmers fed cattle largely vegetable protein (such as soy) or fish protein together with their diet of grass or hay, and no transmission from randomly affected cattle occurred, BSE did not arise. However, during the 1980s, a series of events in Great Britain triggered a BSE epidemic. One factor was that, because the pound was devalued, the price of soy and fish meal increased, so the agricultural industry began to rely more heavily on animal sources of protein. Animal protein typically comes from the by-products of slaughterhouses—bones and offal (guts, heads, tails, and blood) are processed into bonemeal pellets or powder and fed to other cattle. As long as the rendering process killed any disease, bonemeal was a good source of protein. During the 1980s in Britain, changes in the rendering process decreased the bonemeal processing temperature and abandoned fat removal, no longer destroying BSE in tissue. By the late 1980s, BSE had spread throughout Great Britain and had infected more than 2000 cattle. Farmers noticed that their cattle were "becoming aggressive, rather nervous, knocking other cows. . . . and becoming dangerous to handle. . . . If you shooed her, she would stumble, particularly on the back legs, and go down, and then scrabble along" (p. 172). In 1988, the British government ordered milk from affected cows destroyed. However, not until an outbreak in humans occurred in 1996 were massive amounts of beef cattle destroyed. The base rate for CJD is 1 in 1 million people older than 50. CJD cases developing under that age are extremely rare. In the world, there had been only 10 known adolescent cases. Only with kuru-associated cannibalism did researchers notice that young people acquired spongiform encephalopathy with a shortened incubation period. Between 1991 and 1996, 10 cases of a CJD variant of people younger than 40 emerged in Great Britain. According to statistical probability, this is an epidemic. Only time will tell whether awareness has stopped the spread of this disease.

In his book he predicts an alarming increase in the incidence of CJD (Neuropsychology in Action 15.4).

NEUROPATHOLOGY OF CREUTZFELDT–JAKOB DISEASE

The cause of CJD has eluded scientists until recently because it is a transmissible or infectious agent with none of the usual symptoms of acute infection. In fact, scientists first thought that kuru could be genetic, because it occurred primarily among the women and children of the Fore people. However, only the women and children were eating the dead in a mortuary love feast. Men believed contact with women weakened them, and they did not partake in the ritual. Acute infections are easily identified by noticing the body's defensive immune system response. Inflammation, increased numbers of lymph cells in cerebrospinal fluid, and fever are typical, yet none of these symptoms occurs in CJD or any of the SEs.

No one knows from where this infectious agent originally arose. Perhaps it originated from a randomly occurring mutation. This might account for the rarity in the population at large and that CJD occurs with equal frequency throughout the world. However, in the last century, SE has also been transmitted by eating infected neural tissue. This has happened both within species such as cows (BSE or mad cow disease) and across species. SE has developed in mice, hamsters, and even primates injected with kuru. CJD has developed in humans who have eaten infected meat (see Neuropsychology in Action 15.4). Many scientists now believe CJD to be a slow virus that incubates over years, perhaps in the spleen, and is camouflaged in cells so as not to be recognized as an invader. Some have also hypothesized that slow viruses are responsible for AD, PD, and amyotrophic lateral sclerosis (ALS).

What exactly do SEs, specifically CJD, do to the brain? Certain areas of the brain look spongy, taking on a characteristic spongiform pattern. CJD, like kuru, attacks the cerebellum, but it also damages the cerebrum. Microscopically, the "stars" of astrogliosis that Creutzfeldt found were the result of the glial cells, or the "cleanup machines" of the brain, filling in after neuronal tissue had died. Astrogliosis is the

aftereffect, not the cause of the disease. Amyloid plaques are also numerous, but as discussed earlier, these are not specific to CJD but are also found in other diseases such as AD.

Patricia Merz, with the aid of her electron microscope, first found small, twisted, sticklike fibers in the cells of tissue samples of sheep with the sheep version of SE, called "scrapie" (Merz, Somerville, Wisneiwski, & Iqbal, 1981). Interestingly, she could then correctly distinguish between healthy control subjects and affected victims with CJD from these scrapie-associated fibrils (SAFs) in spleen and neural tissue samples. Merz hypothesizes that SAFs may be the disease agent, which incubates in the spleen over years before affecting the brain. SAFs have been found in kuru and CJD brains, but not in AD, PD, or ALS brains. This was the first indication of a disease agent specific to SEs such as CJD.

The name that has become popular in referring to SAFs is *prions* (Pruisiner, 1982). Currently, several different variations or strains have been identified. Prion proteins (PrPs), the protein components of prions, which are present in both normal and afflicted individuals, have been the target of research interest in CJD. However, infected PrP resists normal protein digestion via enzymes. Interestingly, both diseased and normal PrP have the same DNA specifications. This helps explain the riddle of why the body's immune system does not attack the infected protein. It does not recognize the protein as foreign! However, one of the unsolved mysteries of this disease is to understand how a normal protein changes to an abnormal protein with the same structural DNA. Several hypotheses exist to explain the mechanism of action. One is that there may be a small virus, termed a *virion,* that has not yet been identified. Proteins are not known to mutate on their own, but perhaps small bits of "naked" nucleic acid infected with the virion, divorced from their cells, attach themselves to proteins and force the mutation. Another explanation involves an interesting nonbiological form of replication. Carleton Gajdusek (1988), who won the Nobel Prize in Medicine, has postulated that something else must be transporting the infectious agent, because even when the nucleic acid is destroyed by radiation, the "infection" persists. He explains this as a crystal nucleation process. Similar to how crystals such as diamonds form in nature, the infection provides the pattern that is the nucleus, or catalyst, for the reaction. Successive proteins then mutate by patterning themselves after the original. If this sounds like science fiction, scientists have already dubbed this the "Ice-9" metaphor after a Kurt Vonnegut novel in which all the water on earth turns to ice, in a crystallization process.

Whether a yet undiscovered virion, nuclear crystallization, or some other process is causing CJD, scientists are pursuing this disease with renewed vigor because of its unfortunate recent resurgence. We now turn to the clinical aspects of CJD.

CLINICAL PRESENTATION AND NEUROPSYCHOLOGICAL PROFILE OF CREUTZFELDT–JAKOB DISEASE

Even though emotional symptoms may be first evident, the hallmark of CJD, as well as other SEs such as kuru, is motor symptomatology. The motor symptoms are those expected of cerebellar and subcortical dysfunction. Movements become uncoordinated, walking resembles a drunken stagger, and speech is slurred and inarticulate. Involuntary tremors and choreiform grimaces emerge, and finally victims cannot swallow and thus may die of starvation. Visual function alters, eventually leading to blindness in some people. These cerebellar and subcortical motor problems may follow initial, emotionally related complaints of mood disorders such as anxiety, depression or hypomania, fatigue, difficulty sleeping, and attention/concentration problems. As with the confusion over Creutzfeldt's patient Bertha, these symptoms may lead one to first believe that a pure mood disorder is present, or in Bertha's case, which was more advanced, a delusional or psychotic disorder. However, the classic motor symptoms quickly reveal themselves.

The dementia of CJD and its variants has a rapid progression, typically less than a year and usually within 3 to 4 months. Kuru has a similar progression. The Fore people of Papua New Guinea categorized the disease (using pidgin) in five stages: (1) *kuru laik i-kamap now* ("kuru like he come up now"), the first stage before motor symptoms are present; (2) *wokabout yet* ("walk-about yet"), motor and gait problems apparent; (3) *sindaun pinis* ("sit down finish"), inability to walk; (4) *slip pinis* ("sleep finish"), stuporous state; and (5) *klostu dai nau* ("close to die now"), final stage during which swallowing is lost (Rhodes, 1997). Some have likened the progression to classical advanced parkinsonism, but it certainly has features of HD as well.

Neuropsychological testing of patients with CJD is rarely done, not only because of the rarity of the disease, but also because of its circumstances. By the time the disorder is identified, patients are untestable. Unfortunately, at this time, there are no treatments and no cure. Perhaps the only fortunate aspect is that the disease dies out if it is not passed along. The level of kuru in the Fore people has decreased dramatically since they have stopped eating infected tissue.