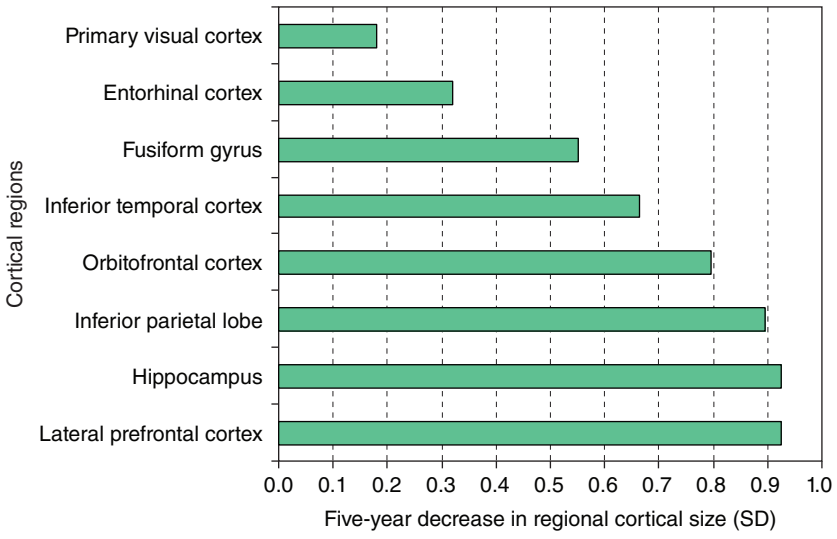

FIGURE 11-14 Five-year decline in mean volumes of different brain regions, measured in standard deviation (SD) units (Cohen's *d*). The primary visual cortex shows the least average shrinkage, and the prefrontal and inferior parietal cortex and hippocampus show the most average shrinkage. *(From N Raz et al: Ann N Y Acad Sci 1097:84, 2007.)*

but these findings are not specific and their diagnostic utility is unclear (Fig. 11-15). Other neurophysiologic changes in the brain frequently occur with aging and may contribute to cognitive decline. Functional imaging studies have shown that some older people have diminished coordination between the brain regions responsible for higher-order cognitive functions and that such diminished coordination is correlated with poor cognitive performance. In young healthy individuals, the brain activity associated with executive cognitive functions (e.g., problem-solving, decision-making) is very well localized; in contrast, in healthy older individuals, the pattern of cortical activation is more diffuse. Brain pathology has typically been associated with specific diseases; amyloid plaques and neurofibrillary tangles are considered the pathologic hallmarks of Alzheimer's disease. However, these pathologic markers have been found at autopsy in many older individuals who had normal cognition, as assessed by extensive testing in the year before death.

Taken together, trends in brain changes with aging suggest that some neurophysiologic manifestations are compensatory adaptations rather than primary contributors to age-related declines. Because the brain is capable of reorganization and compensation, extensive neurodegeneration may not be clinically evident. Therefore, early detection requires careful testing. Clinically, cortical and subcortical changes are reflected in the high prevalence of "soft," nonspecific neurologic signs, often reflected in slow and unstable gait, poor balance, and slow reaction times. These movement changes can be elicited more overtly with "dual tasks," in which a cognitive and a motor task are performed simultaneously. In a simple version of a dual task, when an older adult has to stop walking in order to talk, an increased risk of falls can be predicted. Poor dual-task performance has been interpreted as a marker of reduced overall capacity for central processing, so that simultaneous processing is more constrained. Beyond the brain, the spinal cord also experiences changes after the age of 60 years, including reduced numbers of motor neurons and damage to myelin. The motor neurons that survive compensate by increased branching complexity and by service to larger motor units. As motor units become larger, they decline in number at a rate of ~1% per year, starting after the third decade. These larger motor units contribute to reductions in fine-motor control and manual dexterity. Age-related changes also occur in the autonomic nervous system, affecting cardiovascular and splanchnic function.

Systemic Changes Coexisting with and Affecting One Another • ***THE PHENOTYPE OF AGING: THE FINAL COMMON PATHWAY OF SYSTEMIC INTERACTION*** While age-related system changes have been described individually, in reality, these changes develop in parallel and affect one another through many feed-forward and feedback loops. Some systemic interactions are well understood, while others are under investigation. For example, body composition interacts with energy balance and signaling. Higher lean body mass increases energy consumption and improves insulin sensitivity and carbohydrate metabolism. Higher fat mass, especially visceral fat mass, is the culprit in the metabolic syndrome and is associated with low testosterone levels, high sex hormone–binding globulin levels, and increased levels of proinflammatory markers such as CRP and IL-6. Altered signaling can affect neurodegeneration; insulin resistance and adipokines such as leptin and adiponectin are associated with declines in cognitive function. Combined with loss of motor neurons and dysfunction of the motor unit, a state of inflammation and reduced levels of testosterone and IGF-1 have been linked to accelerated decline of muscle mass and strength. Normal intersystem coordination is also affected by aging. The hypothalamus normally functions as a central regulator of metabolism and energy use and coordinates physiologic responses of the entire organism through hormonal signaling; aging-related changes in the hypothalamus alter this control. The central nervous system (CNS) also controls adaptive sympathetic/parasympathetic activity, so that age-related CNS degeneration may have implications for autonomic function.

The phenotype that results from the aging process is characterized by increased susceptibility to diseases, high risk of multiple coexisting diseases, impaired response to stress (including limited ability to heal or recover after an acute disease), emergence of "geriatric syndromes" (characterized by stereotyped clinical manifestations but multifactorial causes), altered response to treatment, high risk of disability, and loss of personal autonomy with all its psychological and social consequences. In addition, these key aging processes may interfere with the typical pathophysiology of specific diseases, thereby altering expected clinical manifestations and confounding diagnosis. Clinically, patients may present with obvious problems within only one of these domains, but, since systems interact, all four main domains should be evaluated

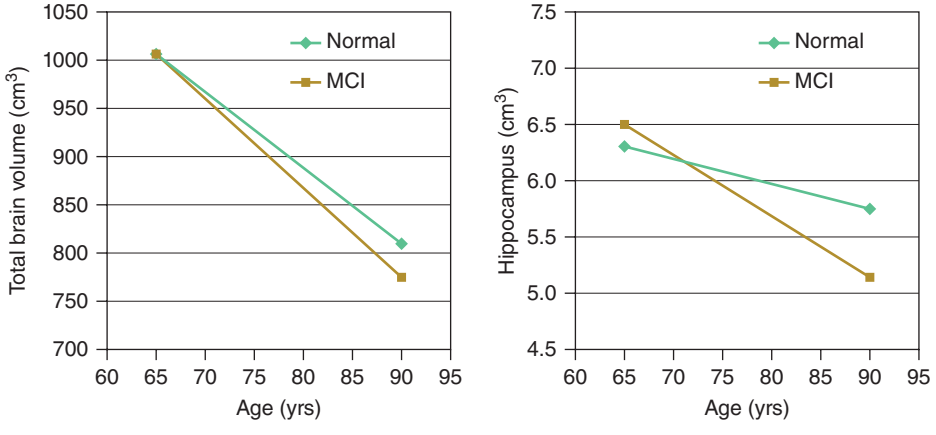

FIGURE 11-15 Longitudinal changes of regional brain volumes in normal aging and mild cognitive impairment (MCI). *(From I Driscoll et al: Neurology 72:1906, 2009.)*