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Cognitive Trajectories in Midlife and Cognitive Functioning in Old Age

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A major distinction among lifespan psychological theories is their differing position on stability versus change in middle age. Theories focusing on aspects of ego development or the self have suggested that major intrapsychic changes occur in midlife (Erikson, 1980; Levinson, 1978; Whitbourne, 1986). These theories focus on qualitative change and vary in the extent to which change is considered normative or universal. The midlife crisis first described by Jaques (1965) and expanded on by Levinson (1978) represents the most dramatic example of intrapsychic change said to occur in middle age.

Trait theories, in contrast, such as those concerned with personality (Costa & McCrae, 1980; McCrae & Costa, 1984) or intelligence (Schaie, 1996, 2005), have depicted midlife as a period of considerable stability with relatively little intraindividual change occurring, at least when studied at the aggregate level (see also Martin & Zimprich, Chapter 6, this volume). Costa and McCrae (1993) and Costa et al. (1999) have written extensively on interindividual stability in personality traits; individuals maintain the same

rank ordering on a personality trait in comparison to others in the group across adulthood. Similarly, ability performance has been reported in longitudinal studies of mental abilities as representing a flat plateau with little change in slope in midlife; these findings have been interpreted to indicate that there is considerable intraindividual stability in the middle years (Dixon, de Frias, & Maitland, 2001; Schaie, 1984, 1996; Willis & Schaie, 1999). The study of stability in personality or ability traits has focused primarily on possible change in the *level* of functioning, with less examination or concern regarding *slope*. Recently, however, there has been increasing interest in studying individual differences in both level and slope. An aggregate or mean level approach to the study of cognition is likely to mask the subgroups of individuals that exhibit either positive or negative slope trajectories in midlife. In this chapter, we utilize data from the Seattle Longitudinal Study (SLS) to explore individual differences in trajectories of cognitive change during midlife and discuss possible factors associated with variability in change trajectories.

We begin by briefly reviewing some of the major propositions of lifespan development theory as they may apply to study of cognition in midlife (Baltes, 1987; Baltes & Baltes, 1990; Baltes, Staudinger, & Lindenberger, 1999). We then discuss some of the limitations in the design of prior research on cognitive functioning in midlife and consider how these limitations may have contributed to a stability view of adult cognition in middle age. We present two types of data on ability performance in midlife from the SLS: (a) normative performance data indicating considerable stability in cognitive functioning in midlife and (b) cognitive change trajectories. The latter suggest that for subgroups of individuals, change in both level and slope does occur in the middle years. We then consider whether cognitive change in midlife may be predictive of cognitive functioning in old age, and we provide illustrative data from the SLS showing that for some individuals, midlife change trajectories are related to long-term outcomes, such as cognitive impairment in old age. We next briefly review current research on select factors (e.g., chronic disease, biomarkers, and the work environment) that have been reported to be associated with differential cognitive change trajectories in middle age. Structural changes in the brain that occur in midlife or early old age in healthy adults are considered. We conclude that there is growing evidence of considerable individual differences in cognitive functioning in midlife, and variability in cognitive trajectories in midlife may predict clinically meaningful outcomes in old age.

Midlife Development From Lifespan Theory

Lifespan theory focuses on the salience of balancing contrary forces in midlife (Baltes et al., 1999; Staudinger & Bluck, 2001). Indeed, the relative stability that appears to characterize midlife may be a reflection of this "balance" of contrary forces in development. A major proposition of lifespan theory is that development at all life stages involves both gains (growth) and losses (decrement). A unique feature of midlife may be that it is the developmental period characterized by a "tie" in the relation of gains and losses; some domains of functioning are still increasing, many domains are being maintained, and others are beginning to decline. This tie in gains and losses in midlife is said to be associated with a balance in midlife in the impact of biology and culture. While age-related decline in biological functioning may begin to occur in midlife, the complexity and sophistication of cultural structures to support development may peak in middle age. Early midlife may be the peak time to reap the cultural assets of education, career, relationships, and family. Indeed, culture and environment are believed to play an increasingly important role in adult development, as compared with early development. Related to the gain-loss ratio and to the biology-culture dynamics is the proposition dealing with allocation of resources across the life span. In early life, resources are allocated to growth, whereas in old age, resources are allocated to regulation of loss. Staudinger and Bluck (2001) have suggested that in midlife, resources may be primarily allocated to maintenance and recovery; however, some resources are still allocated to growth or regulation of loss. Thus, again midlife is a unique developmental phase in which allocation of resources may be balanced between growth, maintenance, and regulation of loss.

Limitations of Prior Research on Midlife

It is ironic that currently there may be a greater variety of theories of midlife development than there are longitudinal data sets against which to evaluate such theories. The paucity of literature on midlife cognition, for example, was illustrated by a literature search for studies of memory in middle age, conducted by Dixon and colleagues (Dixon et al., 2001) for the first handbook on midlife development (Lachman, 2001). The authors

reported that an average of five articles containing midlife participants were published annually during the past 20 years. However, virtually none of these studies was focused primarily on midlife; the articles were identified only because they included a middle age group. Moreover, the vast majority of studies were cross-sectional in design (Bäckman & Nilsson, 1996). Dixon et al. (2001) concluded that there is little evidence of programmatic research on memory in midlife with different authors employing alternative sets of tasks as well as utilizing diverse definitions of middle age.

The paucity of longitudinal data specifically targeting middle age is due, in part, to limitations in the design of many past aging studies (Dixon et al., 2001). The traditional extreme age group comparative design (young adults compared with old adults) of many cognitive aging studies in the past few decades has resulted in serious design limitations for building a lifespan perspective of adult cognitive development. Comparison of only two age groups implies the assumption of a linear trajectory of change, with performance in midlife assumed to fall midway between young and old age. Given only two data points, nonlinear forms of developmental trajectories could not be tested. Moreover, the assumption that the extreme groups differed primarily as a function of age was problematic because the old and young also differed on other variables related to cognition, such as health, job status, sensory deficits, and educational attainment.

More recent studies have involved research designs that included a group in middle age. However, often the age range for the midlife group has been considerably larger than the age ranges for the young or older groups, as later adulthood is now segmented into young-old, old-old, and very old age. Moreover, cohort comparisons of midlife adults, when at the same chronological age, may be particularly important. A number of lifespan developmentalists (Baltes, 1987; Schaie, 1984; Staudinger & Bluck, 2001) have proposed that midlife is the period most heavily impacted by sociocultural events, rather than biological events, given that puberty is past and the biological decline of old age is only at an early stage.

Cognitive Functioning in Midlife: Findings From the Seattle Longitudinal Study

In our prior research on midlife cognition within the SLS, we have focused on normative change in ability performance in middle age (Schaie, 2005; Willis, 1987; Willis & Schaie, 1999). That is, we have presented *average*

estimates of cognitive change for all SLS participants studied over a given age range. We have reported cohort differences in level of ability performance in midlife (e.g., baby boomers vs. parents of baby boomers; Willis & Schaie, 1999). However, even in cohort-related analyses, the focus was comparison of cohort differences, *averaged* across all members of a cohort at a given age period (Willis, 1989).

Figure 8.1 presents the typical finding of stability in cognitive performance in midlife (age range 39–60 years) when data are aggregated across all SLS participants studied longitudinally over this age range. Performance is shown for six abilities: verbal meaning, spatial orientation, inductive reasoning, number, word fluency, and delayed recall (Schaie, 1996, 2005). For these six mental abilities, the magnitude of change across the 21-year period is less than 0.2 standard deviation (*SD*) units. No statistically reliable age-related change is shown for any ability. Cognitive functioning at the aggregate level thus supports the position of lifespan developmental theory that

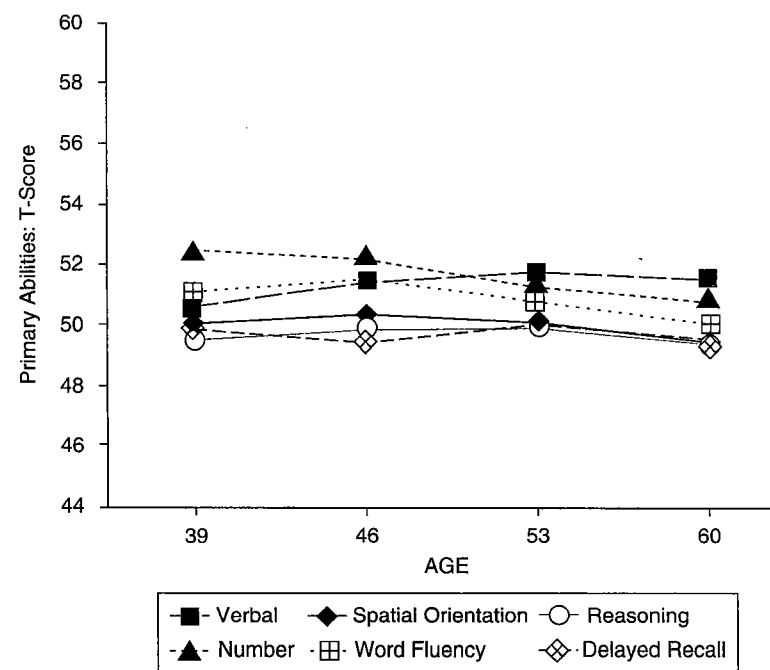


Figure 8.1 Primary Mental Abilities: Longitudinal Change in Midlife

because both gains and losses occur in midlife, the relative balance of gains and losses in middle age may create the illusion of stability.

Different Trajectories of Cognitive Change in Midlife

Lifespan developmental theory, however, also maintains that there are individual differences in the experience of middle age (Schaie, 1989a, 1989b). Individuals vary in the relative amount of gains and losses experienced in midlife. Variability in patterns of gains and losses becomes evident when subgroups of individuals varying in cognitive change trajectories are studied, rather than focusing on the mean or aggregate level (Schaie & Willis, 1993).

In this section, we present new findings related to different patterns or trajectories of cognitive change across midlife for abilities studied in the SLS. We focus on three cognitive abilities studied in the SLS: number, delayed recall, and word fluency (Thurstone & Thurstone, 1949). As shown in Figure 8.1, all three abilities exhibit patterns of stability in midlife when examined at the aggregate or mean level. These abilities represent distinct domains of cognition. Number ability represents the crystallized intelligence domain, which in cross-sectional studies appears to be maintained into old age because of negative cohort differences, but which in longitudinal studies shows decline beginning in early old age (Schaie, 2005). Episodic memory, as represented by delayed memory recall, is one of the most widely studied abilities in cognitive aging (Hultsch, Hertzog, Dixon, & Small, 1998); showing age-related decline in the 60s, it is the ability most commonly associated with early stages of cognitive impairment and dementia (Albert & Killiany, 2001; Petersen, 2003). Word fluency is a measure of executive functioning representing higher-order cognitive skills required for executing complex tasks of daily living (Lezak, 1995; Willis, Allen-Burge, et al., 1998). In the SLS, we have found midlife performance on both delayed recall and word fluency to be predictive of neuropsychologists' ratings of cognitive impairment in old age, as discussed in a later section of this chapter.

Development of Cognitive Change Trajectories

Midlife change in these abilities was studied over a 14-year interval, involving two 7-year intervals and three data points (age 46, 53, and 60 years). Ability change was examined at the individual level ($N = 433$). Defining cognitive change trajectories required consideration of both

level of performance at baseline (age 46; intercept) and rate of change over the 14-year period (slope). For each of the three abilities, participants were classified as having reliably declined (decliners), improved (gainers), or remained stable (stable) over the 14-year interval. The statistical criterion for the definition of individual decline or gain was one standard error of measurement or greater over the 14-year period. Subjects were classified by defining a one standard error of measurement confidence interval about their baseline score (age 46; Dudek, 1979; Schaie & Willis, 1986; Willis & Schaie, 1986). If their score at age 60 fell below or above this interval, they were classified as having declined or gained, respectively. Standard errors of measurement (T -score units) for the three abilities were number = 6; delayed recall = 6; word fluency = 6. The proportions of participants classified as stable for number, delayed recall, word fluency were 79%, 53%, 69%, respectively. The proportions classified as having declined were 15%, 31%, and 20%, respectively; those having gained were 6%, 16%, and 11%, respectively. Thus, although Figure 8.1 presents a normative pattern of stability across midlife, the above procedure indicates that 15% to 31% of individuals have declined on at least one of the three abilities, whereas 6% to 16% have gained on at least one of the abilities. However, the nature of cognitive change trajectories for a given individual varies by ability. Only 2% of the sample had gained on at least two of the three abilities, and only 13% had declined on at least two of the three abilities. Delayed recall was the ability exhibiting the greatest proportion of individuals showing either decline (31%) or gain (16%).

In the second step of the analysis of change trajectories, the distribution of scores at baseline (age 46) for each of the three abilities was examined and divided into tertiles. Each participant was classified in terms of intercept at age 46 (i.e., tertile) and slope across the 14-year interval (decline, stable, gain). Repeated measures analyses of variance indicated a significant interaction between slope status and age for each of the three abilities. However, the triple interaction between slope status, tertile (intercept), and age was not significant for any ability, indicating that the interaction of age and slope did not vary by intercept. Hence, Figures 8.2, 8.3, and 8.4 present the interaction of slope status and age averaged across tertiles at baseline.

Number Ability: Cognitive Change Trajectories

Figure 8.2 presents age-related change in number ability for individuals classified as having remained stable, declined, or increased over the

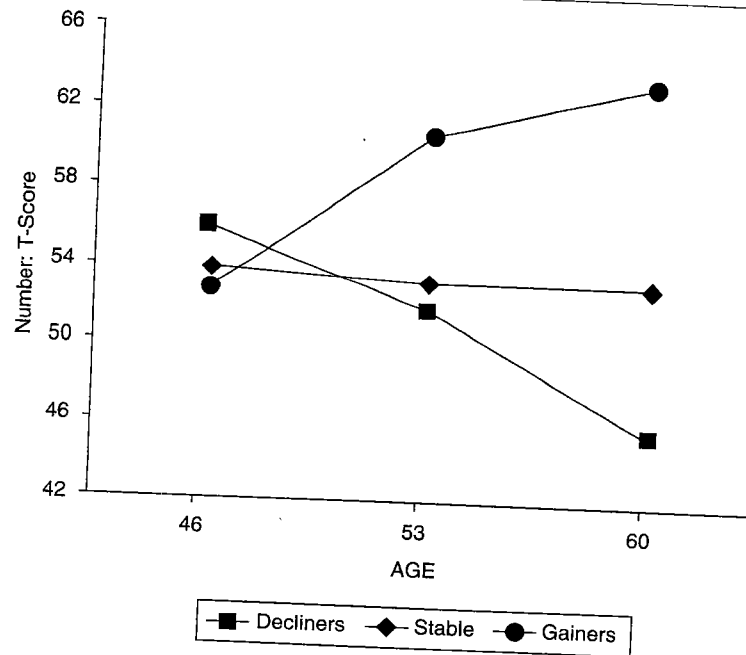


Figure 8.2 Age-Related Change in Number Ability for Individuals Classified as Remaining Stable, Declined, or Increased

14-year interval. At age 46, performance levels of the three groups were roughly comparable: The difference between the decline group and the other two groups was approximately 0.2 *SD* units. However, by age 53, the gainers diverged significantly from the stables and decliners, and by age 60, the gainers were performing more than 1 *SD* unit above the stable group. In contrast, although stables and decliners did not differ in performance level at age 46, by age 60, the decline group performed almost 0.8 *SD* units below the stable group.

Delayed Recall: Cognitive Change Trajectories

Figure 8.3 presents age-related change for the delayed recall ability for the three groups. At age 46, the group of decliners did not differ in performance level from the stable group but did differ from the performance of gainers (0.2 *SD* units). By age 53, all three groups differed significantly in level of performance. By age 60, the decline group was performing more

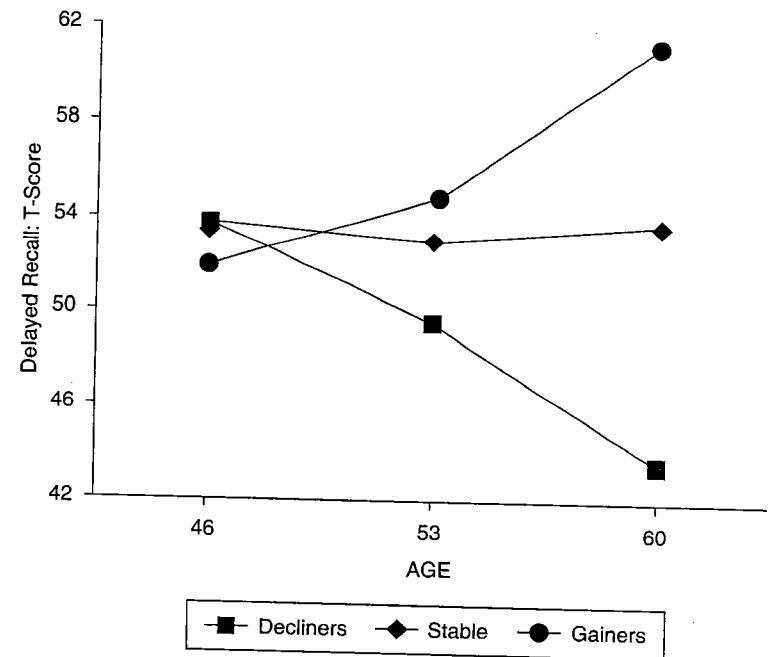


Figure 8.3 Age-Related Change for the Delayed Recall Ability for Individuals Classified as Remaining Stable, Declined, or Increased

than 1 *SD* unit below stables, whereas the gainer group was performing approximately 0.8 *SD* units above the stable group.

Word Fluency: Cognitive Change Trajectories

Figure 8.4 presents age-related change for the word fluency ability for the three groups. The stable, decline, and gain groups did not differ significantly at age 46. However, at age 53 and age 60, the decline group was performing at a level significantly below both the stable and gain groups. The gain group at age 53 and age 60 was performing at a significantly higher level than the stable group. The decline group had dropped over the 14-year period by 1 *SD* unit, whereas the gain group had increased by almost 1 *SD* unit.

In summary, these data indicate that although there is considerable stability in cognitive functioning when studied at the aggregate level,

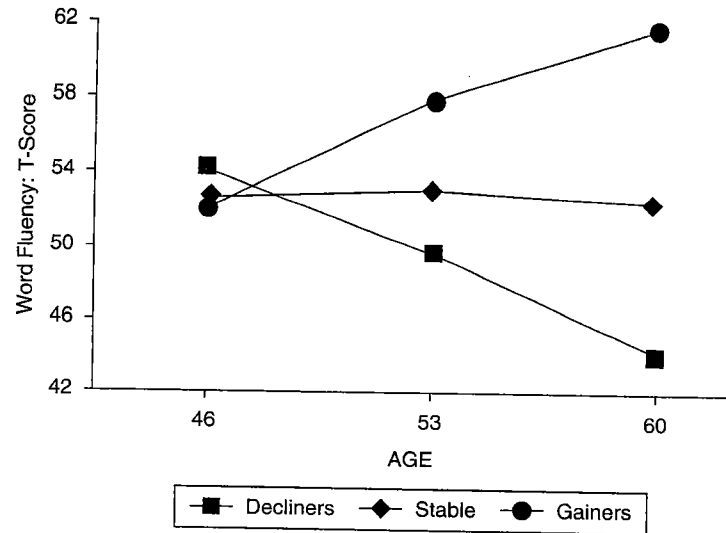


Figure 8.4 Age-Related Change for the Word Fluency Ability for Individuals Classified as Remaining Stable, Declined, or Increased

there are wide individual differences in patterns of cognitive change for subgroups of individuals in midlife. Individuals included in these analyses were functioning at quite comparable performance levels at age 46. By age 60, however, performance of the subgroups had diverged dramatically, with group differences on the order of 1 *SD* unit.

Association of Midlife Cognitive Change and Cognitive Impairment in Old Age

Given the wide individual differences in cognitive change trajectories in midlife, the question arises whether there is an association between cognition in middle age and subsequent functioning in old age (Schaie, 1984). Of particular concern is the question whether there is an association between negative cognitive trajectories in midlife and cognitive impairment in later adulthood.

Findings from a limited number of prospective studies indicate a lengthy preclinical phase of cognitive impairment that may extend up to several decades preceding the diagnosis of onset of Alzheimer's disease

(AD). In a study on normal aging in twins, LaRue and Jarvik (1987) noted deficits on multiple cognitive measures for those diagnosed as having dementia 20 years later. Snowdon and colleagues (1996) found that impoverished linguistic ability, when the participants were in their 20s, was associated with the clinical expression of AD almost 60 years later (Snowdon et al., 1997). In the Framingham study cohort, presence or absence of probable AD during a 22-year surveillance period was related to initial test performance (M. F. Elias et al., 2000; M. F. Elias & Robbins, 1991; Linn et al., 1995). In a prospective study over 15 years, healthy adults who eventually developed dementia performed less well on psychometric testing at initial assessment (Rubin et al., 1998).

Most current prospective studies of the preclinical phase, however, may have begun too late. While the length of the preclinical phase shown in prospective studies is impressive, participants at initial assessment were typically already in old age (Petersen, 2003). Most current short-term longitudinal prospective studies of cognitive risk for dementia originate in young-old age, or even in old-old age, but not in middle age. Entry age for the Framingham study was 65 years (M. F. Elias, Robbins, Elias, & Streeten, 1998; M. F. Elias & Elias, 1997) and 64 years for the Rubin et al. (1998) study. In the very well-characterized Kungsholmen study (Fratiglioni et al., 1991) entry age was 75 years. As initial assessment of individuals in their early 60s has been found to be predictive, the question arises whether cognitive status or change even earlier in midlife may provide important information about the preclinical phase. Current prospective studies on adults in their mid-60s and older must meet the challenge of differentiating older adults experiencing normative age-related change from adults experiencing preclinical decline, given the onset of normative age-related decline for fluid-type abilities is in the 60s (Hultsch et al., 1998; Schaie, 2005). However, cognitive decline in midlife is clearly non-normative, and hence, prospective studies beginning in midlife may have particular merit.

While significant age-related decline is not normative until after age 60 on most ability measures, there are wide individual differences in rate of change as shown in Figures 8.2, 8.3, and 8.4. Having demonstrated different trajectories of cognitive change in midlife for the SLS cohorts (birth years 1907–1941), we then compared the magnitude of change in midlife for two subgroups from these cohorts: participants rated in old age as *normal* versus *cognitively impaired* by two neuropsychologists based on performance on a neuropsychological test battery.

Figure 8.5 presents the magnitude of decline in midlife for those rated as normal as compared with those who were cognitively impaired in old age. Significant group differences in midlife were found for four SLS measures (immediate and delayed recall, fluency, speed)—all of these measures map on the cognitive domains of interest as precursors of impairment (Figure 8.5, top graph). For the group subsequently rated as impaired in old age, magnitude of decline over the 46 to 60 age interval was on the order of 0.30 to 0.40 *SD* units for the SLS memory and fluency measures and on the order of 0.20 *SD* units for SLS speed.

The magnitude of midlife decline for the impaired-in-old-age group was on the order of the magnitude of decline shown from age 60 to 74 in normative aging samples (Schaie, 2005). Specifically, average decline from age 60 to 74 was 0.36 *SD* units on delayed recall, whereas the to-be-impaired group showed this level of impairment (0.38 *SD* units) from age 46 to 60. Equally important is that normal and impaired in old age did not differ in midlife performance on ability measures of verbal, spatial orientation, or number (Figure 8.5, bottom graph)—thus, group differences in decline in midlife did not occur for all abilities. Rate of decline in midlife differed only on memory, fluency, and speed—cognitive domains of interest as precursors of impairment.

Age of onset of decline and rate of decline varies by ability, and there are wide individual differences in rate and onset of decline. Rabbit (1993) posed the question, "Does it all go together, when it goes?" SLS findings and findings from other longitudinal studies (e.g., Hultsch et al., 1998) do not support the perspective of global decline.

Potential Factors Associated With Differential Cognitive Trajectories in Midlife

Within the study of cognitive aging, relatively limited attention has been given to factors associated with level and rate of change in abilities in midlife. However, in related fields such as neuropsychology, neurology, health psychology, and behavioral genetics, there is growing evidence for the impact of disease, biomarkers, and life experiences on cognition in middle age. In a recent review of factors associated with cognitive change in 34 longitudinal studies, Anstey and Christensen (2000) concluded that education, hypertension, objective health status, cardiovascular disease, and the APO-E gene are the factors most consistently related to cognitive

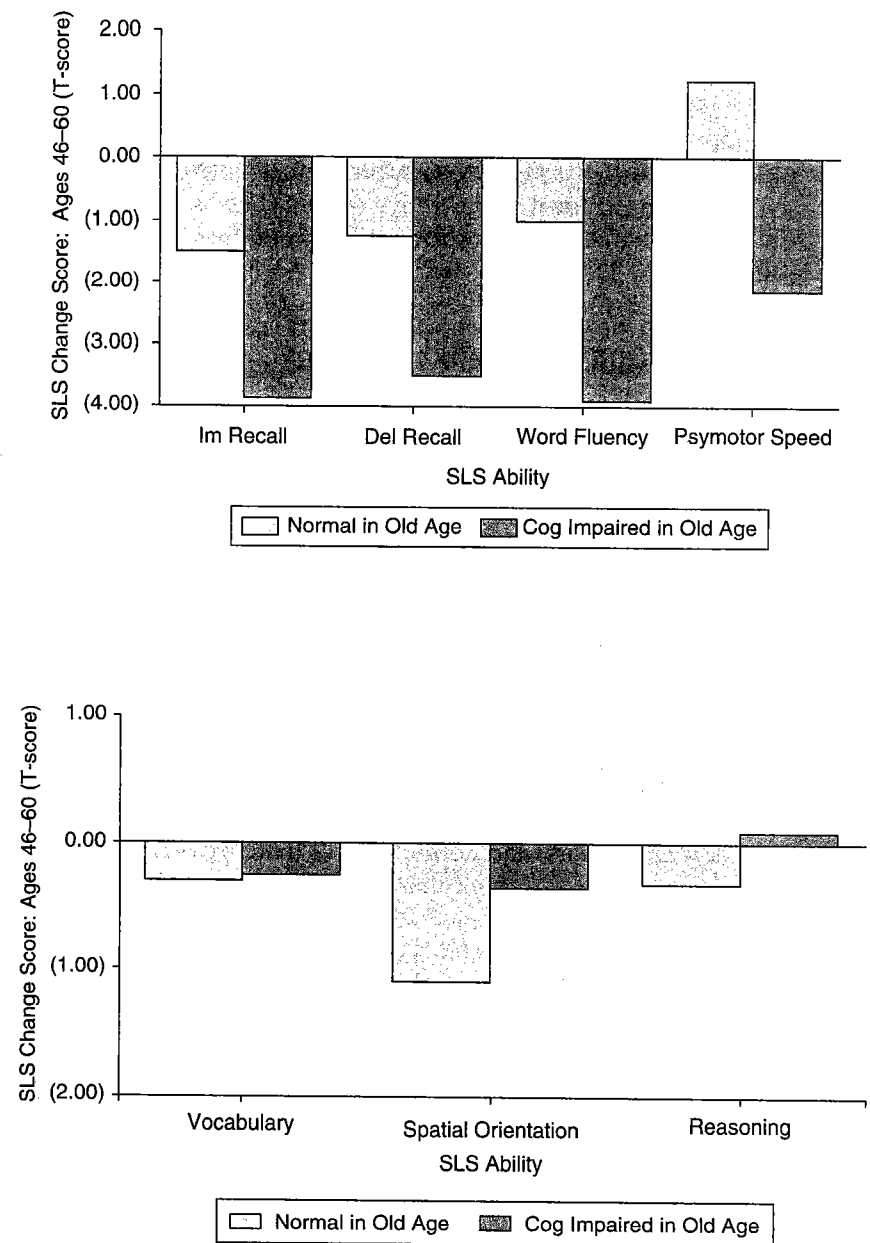


Figure 8.5 Magnitude of Decline in Midlife for Those Rated as Normal Compared With Those Cognitively Impaired in Old Age

change across adulthood. Although risk factors for cognitive decline have received far greater attention, there is growing recognition of the role of protective factors in cognitive maintenance and plasticity. Protective factors are important as possible mechanisms to be targeted in preventive interventions. In addition, protective factors are of interest due to the dramatic increase in the level of protective factors such as education and occupational status that have occurred for recent-born, compared to early-born, cohorts.

Risk Factors for Midlife Cognitive Decline

Hypertension

Hypertension is one of the earliest manifestations of cardiovascular disease and has been one of the most extensively investigated diseases with respect to cognitive functioning (M. F. Elias, Elias, & Elias, 1990; Waldstein & Elias, 2001). There is now evidence indicating that hypertension is associated with poorer cognitive performance among adults not only in old age but at all adult ages. While the impact of hypertension on cognition in old age is well established, recent findings by P. K. Elias and colleagues have further established the role of hypertension on cognitive functioning in young and middle adulthood (M. F. Elias, Elias, Robbins, Wolf, & D'Agostino, 2001; P. K. Elias, Elias, Robbins, & Budge, 2004). Indeed, several studies suggest that cognitive performance differences are greater between young hypertensives (younger than 50 years) and normotensives than between late midlife hypertensives (50–70 years) and normotensives (M. F. Elias, Schultz, et al., 1990; Waldstein et al., 1996). Hypertension in early midlife is of particular concern, given that duration or lifetime exposure to elevated blood pressure may be a particularly important predictor of cognitive outcomes in old age (Knopman et al., 2000; Swan, Carmelli, & LaRue, 1996). Several epidemiological studies have found that higher blood pressure levels during middle age predict poorer cognitive outcomes in old age (Launer, Masaki, Petrovitch, Foley, & Havlik, 1995; Swan et al., 1996). In a 20-year longitudinal study, the magnitude of cognitive decline was 12.1% greater for persons who were hypertensive than for those who were never hypertensive. Thus, chronic hypertension is associated not only with level of performance but also with accelerated longitudinal decline in cognition (M. F. Elias, Robbins, & Elias, 1996; M. F. Elias et al., 1998; Knopman et al., 2000).

Hypertension has been associated with lower performance levels on tests of attention, learning and memory, executive functions, and

visuospatial, psychomotor, and perceptual abilities (M. F. Elias & Robbins, 1991; M. F. Elias et al., 1987; P. K. Elias et al., 1995; Waldstein & Elias, 2001). Crystallized verbal abilities appear to be less affected.

Hypertension and Multiple Risk Factors

A limitation of many studies examining the impact of hypertension on cognition has been lack of consideration of multiple risk factors (e.g., gender, education, smoking, obesity, diabetes), as comorbidities are common among hypertensives. The number of risk factors has been significantly related to lower cognitive functioning. For each increase in the number of risk factors, the risk of performing in the lower quartile of distribution of cognitive scores for Learning and Memory increased by 39%. Moreover, studies assessing the long-term duration of risk factors showed a much stronger relationship with cognition (M. F. Elias et al., 1998).

Diabetes

In 20 case control studies of the association between cognitive function and Type 2 diabetes in older adults, almost all found cognitive impairment, with learning and memory abilities showing the most pronounced deficits, but also evidence for effects on attention, psychomotor speed, and problem solving (Strachan, Deary, Ewing, & Frier, 1997). Virtually all these studies have been cross-sectional with small sample sizes; thus, the long-term relationship between cognition and diabetes has not been examined. In addition, these studies have not taken into account common disorders that accompany diabetes and normal aging, such as cerebrovascular disease, hypertension, and impaired vision. Large-scale epidemiological studies support the findings of case control studies, but most epidemiological studies have been cross-sectional with the exception of the Framingham Health Study, which showed strong evidence of a causal relationship between diabetes and cognitive dysfunction (P. K. Elias et al., 1997); duration of diabetes was associated with poorer performance on verbal memory and abstract reasoning tests.

Biomarkers

Cholesterol and Cognition

The existing literature suggests that complex relationships exist between serum lipids and cognitive function (Muldoon, Flory, & Ryan, 2001). In healthy samples, certain abilities may be inversely associated with serum

cholesterol level, whereas other aptitudes appear to be positively correlated with cholesterol concentration. Low serum cholesterol has been found to be associated with better memory and crystallized intelligence performance (Muldoon, Ryan, Matthews, & Manuck, 1997). On the other hand, studies also show that high serum cholesterol may be associated with optimal mental speed and mental flexibility. For example, high serum cholesterol was associated with less decline in digit-symbol substitution test performance over 5 years in middle-aged twins (Swan, LaRue, Carmelli, Reed, & Fabsitz, 1992).

What might explain these seemingly conflicting findings regarding the association of cholesterol and cognition? Muldoon et al. (1997) found that compared with people with high cholesterol, those with relatively low cholesterol (hypocholesterolemia) have more education, have a lower body mass index, have lower blood pressure, and are less likely to smoke. One possibility is that people with a wide range of crystallized knowledge are most aware of the health risks of certain behaviors and, thus, are more likely to adopt lifestyles that maintain lower cholesterol levels (Muldoon et al., 2001). According to this hypothesis, causality is in the direction of crystallized intelligence affecting health-related behaviors, resulting in reduced serum cholesterol concentrations. These questions can only be addressed in longitudinal studies in which the reciprocal associations between longitudinal trajectories of cognition and health outcomes can be examined.

APO-E

The $\epsilon 4$ allele of the APO-E gene is associated with an increased risk for AD and may modify the age of onset of AD (Saunders et al., 1993). An individual with no copies of the $\epsilon 4$ allele has a lifetime risk of developing AD of 9%, whereas the presence of one $\epsilon 4$ allele increases lifetime risk for AD to 29% (Swartz, Black, & St. George-Hyslop, 1999). However, there is accumulating evidence that the greater significance of APO-E $\epsilon 4$ may be in its association with age-related decline in cognitive performance rather than for the risk of developing AD (Carmelli et al., 1998; Hyman et al., 1996; Riley et al., 2000). In a study of adults with an average age of 45 (age range 24–60 years), individuals with an $\epsilon 4$ allele had lower scores on learning and memory tasks than did individuals with no $\epsilon 4$ allele (Flory, Manuck, Ferrell, Ryan, & Muldoon, 1999); no effect of the $\epsilon 4$ allele was found on measures of psychomotor speed or attention.

APO-E $\epsilon 4$ may be associated with earlier brain volumetric change, possibly evident in midlife. Nondemented $\epsilon 4$ carriers aged 45 to 70 years

have been found to have smaller hippocampal volumes (Plassman et al., 1997), a faster rate of atrophy in the hippocampus (Moffat, Szekely, Zonderman, Kabani, & Resnick, 2000), and decreased blood flow in the temporal and parietal lobes (Reiman et al., 1996; Small et al., 1995). The presence of a single $\epsilon 4$ allele was also found to be associated with increased rate of hippocampal volume loss ($p < .03$) in healthy women in their 60s (Cohen, Small, Lalonde, Friz, & Sunderland, 2001). However, hippocampal volume loss was not correlated with changes in any of the cognitive measures.

APO-E $\epsilon 4$ genotype may play a modifier role with respect to other risk factors and cognition (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999). The APO-E $\epsilon 4$ genotype is a risk factor for atherosclerosis (Hofman et al., 1997), coronary heart disease (Davignon et al., 1988; Mahley, 1988; P. Wilson et al., 1994), and hypertension (Metter & Wilson, 1993; Warden & Thompson, 1994). After adjusting for lipids and other risk factors, the APO-E $\epsilon 4$ genotype is the strongest genetic determinant for coronary heart disease in both men and women (P. Wilson et al., 1994). It promotes increased levels of circulating cholesterol (Escargueil-Blanc, Salvayre, & Negre-Salvayre, 1994). Larson et al. (1990; see also Jarvik et al., 1995) have reported that APO-E $\epsilon 4$ may moderate the relationship between cholesterol and dementia; effects of $\epsilon 4$ on cholesterol metabolism were not independent of its effects on dementia. Only longitudinal studies have the long-term multiability data sets capable of examining these alternative explanations for the role of APO-E $\epsilon 4$ across the adult life span.

Protective Factors

Education

Education has proven to be the most consistent nonbiological correlate of both cognitive level and rate of change (Anstey & Christensen, 2000). Moreover, educational level is associated with cognitive change not only in old age but also throughout adulthood (Farmer, Kittner, Rae, Barko, & Regier, 1995; Lyketsos, Chen, & Anthony, 1999). Education most often predicts change in crystallized abilities, memory, and mental status and is less consistently predictive of change in fluid abilities and speed. In the MacArthur Studies of Successful Aging, education was the best predictor of change in cognition (Albert et al., 1995). The effects of education on cognitive change remain when controlling for factors such as age, gender,

race, and health. However, among hypertensives, relatively lower levels of education were associated with poorer neuropsychological function, whereas more highly educated hypertensives and normotensives (more than 16 years education) showed comparable performance (M. F. Elias et al., 1987).

Educational level increased significantly across birth cohorts in the first half of the 20th century. Hauser and Featherman (1976) report a total increase of about 4 years of education from the cohort born in 1897 to the cohort born in 1951. Intergenerational differences in level of schooling peaked among men born just after World War I; a deceleration has occurred across more recent cohorts.

Several explanations for the effect of education on cognitive change have been proposed. One explanation maintains that education may serve as a proxy for factors such as health behavior, socioeconomic status, occupational hazards, or nutrition, which affect cognitive change and covary with education. Alternatively, education may produce direct effects on brain structure through an increase in number of synapses or vascularization (Greenough, Larson, & Withers, 1985).

It has also been hypothesized that education does not alter vulnerability to disease but rather delays the appearance of clinical symptoms by postponing the point at which a sufficient number of abnormalities have accumulated. Moreover, education's impact on brain structure may continue throughout life by instilling lifelong habits of mental stimulation that produce neurochemical or structural alternations in the brain that are themselves protective. Thus, although formal education is acquired early in life, the effects of education on brain function would be mediated by habits that are maintained throughout life. A third hypothesis is that education may protect and preserve learning acquired through schooling but not the rate of biological decline. Greater expertise in crystallized knowledge would compensate for, or disguise, the rate of biological aging in the well educated. Because crystallized intelligence increases through most of adulthood and declines only in late life, the positive effects of education would be expected to increase progressively into midlife and old age (Christensen et al., 1997).

Environmental Complexity and the Nature of Work

Schooler and colleagues have examined the effects of environmental demand, particularly in the work context, on adult cognition (Schooler,

1987, 1990, 1998). Recent findings are particularly relevant to midlife cognition (DeFrias & Schaie, 2001). The reciprocal relationship between substantively complex activities (work, leisure) and cognition has been examined longitudinally over three decades. Job conditions involving self-directed, substantively complex work increase intellectual flexibility and self-direction. Recent findings indicate that the reciprocal relationship between substantively complex work and cognition is even stronger for men in late midlife than was found previously in younger men (Schooler, Mulatu, & Oates, 1999, 2004). In addition, Schooler's work suggests that there are age-cohort differences in work complexity; older age-cohort workers were found to do less substantively complex work.

Schooler and colleagues (Schooler, 1998; Schooler et al., 2004) suggest that if technical and economic development in a society leads to more complex environments, including intellectually demanding work conditions, such increased environmental complexity should result in higher levels of intellectual functioning. Environmental complexity is defined by stimulus and demand characteristics; the more diverse the stimuli, the greater the number of decisions required, the greater the number of factors to be taken into account in making decisions, the more complex the environment. Cognitively demanding complex environments lead not only to higher intellectual functioning, but greater valuation of self-direction and autonomy (Schooler, 1990). A self-directed, substantively complex environment impacts cognitive functioning, not only in young adulthood, but also in midlife and old age (Attwell, 1987; Schooler et al., 2004). Cognitive variability may be due, in part, to variability in individuals' involvement in complex, self-directed activities.

In the SLS, we have examined the association of work variables to retirement status and cognitive functioning over a 7-year interval, with age and education as covariates. SLS participants who continued to work scored higher on immediate recall than those who retired during the 7-year interval (DeFrias & Schaie, 2001). Those participants reporting higher job complexity scored higher on immediate recall than those with low complexity. In addition, those reporting low complexity in their jobs declined on Fluency over the 7-year interval.

Cognitive Engagement

Recent research on cognitive engagement provides further support for the importance of environmental stimulation on cognition in middle and

later adulthood (Kramer & Willis, 2003; R. S. Wilson et al., 1999). Katzman (1993) has proposed that persons with higher educational levels are more resistant to the effects of dementia as a result of having greater cognitive reserve and increased complexity of neuronal synapses. Like education, participation in work or leisure activities may lower the risk of dementia by improving cognitive reserve (Scarmeas, Levy, Tang, Manly, & Stern, 2001; Wang, Karp, Winblad, & Fratiglioni, 2002).

Two recent studies examined prospectively the association of cognitive activities and risk of dementia. In the Religious Orders Study (R. S. Wilson et al., 2002), cognitive activity was assessed at baseline and members followed for approximately 5 years. A 1-point increase in cognitive activity score was associated with a 33% reduction in risk of AD. However, members were very highly educated and were aged 60 to 70 years on average at baseline. In the Bronx Aging Study (Verghese et al., 2003), similar findings were reported. Again, members were aged 75 to 85. Thus, longitudinal studies examining the impact of cognitive activity across the life span on subsequent cognitive decline are needed.

Although these results suggest that such activities have a protective role, there is an alternative explanation. In dementia, there is a long period of cognitive decline preceding diagnosis (M. F. Elias et al., 2000; Small, Fratiglioni, Viitanen, Winblad, & Bäckman, 2000). Reduced participation in activities during this preclinical phase of dementia may be the consequence, and not the cause, of cognitive decline. Resolution of this issue requires a long period of observation before diagnosis to disentangle the effects of preclinical dementia.

In an early study (Gribbin, Schaie, & Parham, 1980), four groups of SLS participants with distinctly different lifestyles were compared on magnitude of cognitive decline over 7- and 14-year intervals. Magnitude of cognitive decline varied by lifestyle group for verbal, spatial, reason, and fluency abilities. The lifestyle group most fully engaged in social and leisure activities and with high socioeconomic status showed greater maintenance of cognitive ability over 7- and 14-year intervals. The greatest cognitive decline occurred for those with the lowest activity engagement.

Exercise

In the Anstey and Christensen (2000) review of factors associated with cognitive change, findings were mixed on the effect of physical activity. However, in a recent meta-analysis of fitness intervention studies, Colcombe and Kramer (2002) found that fitness effects were selective and

that aerobic fitness training had a substantially larger positive impact on tasks with large executive control components. In the MacArthur Studies of Successful Aging (Albert et al., 1995), self-report of strenuous daily physical activity was one of four significant predictors of cognitive change. Carmelli et al. (1998) found that individuals (aged 65–86) who improved on a cognitive composite reported the highest physical activity; individuals who declined cognitively reported significantly lower exercise levels than those not declining. However, Hulstsch et al. (1999) found that physical activity did not affect memory over 6 years. In the Midlife in the United States study, Markus and colleagues (2004) found educational differences in health practices, with college-educated individuals reporting a higher rate of exercise and a lower rate of smoking. There have been several studies supporting the effects of physical activity on brain function and cognition. Active older adults have been shown to maintain more consistent cerebral perfusion (Rogers, Meyer, & Mortel, 1990), to have shorter event-related potential latencies, and to demonstrate higher cognitive scores (Dustman et al., 1990).

The Brain and Cognitive Performance in Midlife and Old Age

Although brain atrophy in patients with mild cognitive impairment and AD has been found, research on brain change in healthy adults experiencing normal aging is limited (Albert & Killiany, 2001). The majority of studies examining the association of age and brain volume have been cross-sectional. In aging healthy adults, brain regions are affected differentially. The prefrontal cortex (PFC) appears to be the most vulnerable, whereas the effect of aging on the hippocampus (HC) is moderate and on the entorhinal cortex (EC) is relatively spared (Du et al., 2003; Raz, 2000; Raz, Rodrigue, Head, Kennedy, & Acker, 2004). In contrast, in the course of AD, pathological changes in the EC and HC precede those in the PFC (Braak & Braak, 1991; Laakso, 2002; Thompson et al., 2003). Although shrinkage of both the HC (Xu et al., 2000) and EC (Dickerson et al., 2001) is associated with concurrent AD and predicts clinical deterioration (Jack et al., 2000), volume reduction in the EC is viewed as the earliest indicator of incipient conversion from preclinical cognitive impairment to dementia (Dickerson et al., 2001; Killiany et al., 2000).

A few longitudinal studies of volumetric change have been reported. Raz and colleagues (Raz, Rodrigue, Head, Kennedy, & Acker, 2004)

recently reported on change over a 5-year period in EC and HC volume assessed twice in healthy adults, mean age 57 years (range 26–82 years), educational level 16 years. It was hypothesized that the EC volume declines at a slower rate than the HC volume. HC volume exhibited significant age-related differences at baseline and at follow-up and shrunk at a faster pace (0.86% per annum) than the EC volume (0.33% per annum); no EC shrinkage was observed in adults under age 50. However, participants over age 50 showed increased annual shrinkage of the HC (1.18%) as well as EC shrinkage (0.53% per annum). Thus, there were markedly different age trends for the HC and EC. However, both regions showed increased shrinkage for older participants (50+ years). In a follow-up study, Rodrigue and Raz (2004) examined the association of memory performance with volumetric decline over 5 years in the HC, EC, and PFC regions. Longitudinal decline in the entorhinal region was associated with poorer performance on a composite declarative memory measure, including the Wechsler Memory Scale Logical Memory and California Verbal Learning Test. Decline in the HC and PFC regions, however, was not significantly associated with poorer memory performance. The correlation between EC decline and the memory composite was on the order of $r = .40$.

Cross-sectional studies have reported a significant relationship between volumetric measures of the frontal cortex and tasks of executive function. Raz, Gunning-Dixon, Head, Dupuis, and Acker (1998) reported that volume of the prefrontal cortex was inversely correlated with performance on the Wisconsin Card Sorting Test. In addition, at an early stage of learning to solve the Tower of Hanoi puzzle, speed and efficiency were associated with age, PFC volume, and working memory in healthy adults (Raz, Dixon, Head, Dupuis, & Acker, 1998). When hypertensive participants were excluded, the effect of prefrontal shrinkage on executive aspects of performance was no longer significant, but the effect of working memory remained. Moreover, in a study examining the neural substrates of age-related differences in mental imagery, it was suggested that age-related shrinkage of the PFC and age-related declines in working memory are associated with age deficits in visual-spatial imagery tasks (Raz, Briggs, Marks, & Acker, 1999).

Hypertension has been associated with smaller PFC and underlying white matter volumes and increased frontal white-matter hypertensities (WMH; Raz, Rodrigue, & Acker, 2003). Likewise, smaller PFC and WMH have been associated with age-related deficits in executive functioning (Gunning-Dixon & Raz, 2000; Raz et al., 1998). The effect of untreated

hypertension has also been found to affect a number of cognitive tasks, in particular, executive functions, speed of processing, and memory (Brady, Spiro, McGlinchey-Berroth, Milberg, & Gaziano, 2001; P. K. Elias et al., 1995; Waldstein, Manuck, Ryan, & Muldoon, 1991). Thus, PFC shrinkage and WMH may mediate the effects of hypertension on cognitive performance, including executive functioning and speed of processing. In support of this hypothesis, Raz and colleagues have found that hypertensives committed significantly more perseverative errors (an index of prefrontal dysfunction) while showing no differences on tests of working memory, fluid intelligence, and vocabulary.

Summary and Future Directions

We began this chapter by briefly reviewing some of the major propositions of lifespan development theory as they may apply to the study of cognition in midlife. That is, while trait theorists have argued for considerable intraindividual stability in midlife, ego psychologists have proposed that substantial qualitative changes such as the “midlife crisis” (Jaques, 1965) may prevail for many individuals during this life stage. We noted that this discrepancy may be attributable, in part, to the prevailing focus in studies of ability and personality development on changes in aggregate means (level) rather than on differences between individual change trajectories (slope).

Data from the SLS were then presented that show aggregate stability over the midlife period for selected abilities. However, when individual trajectories are disaggregated into subtypes of stables, decliners, and gainers (using a 1 standard error of measurement criterion), it is found that although the majority of individuals remain stable over the age range from 46 to 60 years, there are significant subsets of individuals that show significant gain or decline across midlife. The proportion of gainers and decliners differ by ability; the proportion of decliners is greatest for measures of immediate and delayed memory.

We next considered whether cognitive change in midlife predicted long-term outcomes, such as cognitive impairment in old age. Illustrative data from the SLS showed that for some individuals, midlife change trajectories could be related to cognitive impairment in old age. In particular, measures of immediate and delayed recall, fluency, and speed were identified as early predictors.

Cognitive psychologists have given only limited attention to risk factors associated with cognitive change in midlife. We therefore reviewed the literature in neuropsychology, health psychology, and behavioral genetics to identify risk factors that have been related to cognition and that deserve greater attention in studies of cognitive aging. These risk factors associated with lower performance on many cognitive functions include the early occurrence of hypertension, diabetes, serum cholesterol, and allele 4 of the APO-E gene.

But, while a number of physiological influences pose risks for the maintenance of optimal cognitive function, there are also a number of protective factors that have been identified in well-functioning, midlife individuals that predict better cognitive performance in old age. These protective factors include high levels of education, environmental complexity, the nature of work, cognitive engagement, and exercise. Here, we suggested a number of mechanisms that might explain the favorable effects attributed to these protective factors.

Finally, we reviewed evidence on the relation of changes in brain and cognitive performance in midlife and old age. As yet, there is a paucity of longitudinal evidence on structural changes in brain volume. However, it does appear that in normal individuals, the PFC is most vulnerable to aging, the HC is moderately affected, and the EC is relatively spared. By contrast, in the cognitively impaired, the EC is the first part of the brain likely to be affected.

We conclude then that many of the phenomena of cognitive aging, at least in those individuals who will eventually become cognitively impaired or those who represent the sparse group of the unusually well-functioning "super-aged," can be traced back to physiological and behavior changes that begin in midlife (or even earlier). Hence, attempts at long-term prediction of either cognitive impairment or successful aging must be based on studies that begin at much earlier ages than do most studies currently in progress.

There is a complex interaction between genetic predispositions, onset of chronic disease, and protective factors based on lifestyles often associated with the availability of economic resources that is likely to account for substantial proportions of variance associated with the individual differences in midlife cognitive functions we have described. Future cognitive aging studies will therefore require much better assessment of both risk factors and protective factors.

Finally, a better understanding of structural and functional changes in the brain will facilitate an understanding of how the risk and protective

factors identified—which we now know to be associated with cognitive aging—play out at the neurophysiological level. Not the least of such analyses, however, will require further inquiry into possible reciprocal relationships between changes in the brain and changes in behavior.

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