Chapter 7

Behavioral Genetic Investigations of Cognitive Aging

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Introduction

One of the universal concerns of human beings is the issue of aging: How will I meet the changes and challenges that occur with age? What impact can I have on my own aging process? The first modern twin study designed to investigate genetic and environmental influences on the aging process was the New York State Psychiatric Study of Aging Twins begun in 1946. In the last two decades, there has been an upsurge in the number of behavioral genetic studies of the various facets of the aging process. A recent summary reports over two dozen twin studies investigating physical, psychological, and social aspects of aging (Bergeman, 2007). In this review, we focus on the three components of cognitive aging. Primary aging is the normal and pervasive changes in cognitive abilities that occur with age. In contrast, secondary aging is typified by changes in cognitive functioning that result from disease or pathological processes. The distinction between primary and secondary aging is of paramount importance; some changes that were once thought to be an inevitable part of aging (e.g., senile dementia) have been shown to be the outcome of disease processes that can be diagnosed and potentially treated. Finally, the acceleration in decline of cognitive functioning that occurs in the years immediately preceding death is termed tertiary aging or terminal decline. Distinguishing primary, secondary, and tertiary aging is paramount to understanding the nature of cognitive aging.

Behavioral genetic research on primary aging has focused both on general intelligence and specific cognitive abilities, as well as covariates of intellectual functioning that may be the sources of genetic and environmental contributions to cognitive aging. In investigations of secondary aging, the contributions of both measured genotypes and measured lifestyle variables to forms of dementia are discussed. Methods for investigating tertiary aging are presented, including estimating trajectories of change from age at death. The issues that will face future investigators and the quantitative methodologies that will be required to address these issues are also discussed.

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Primary Aging

Primary aging encompasses general age-related changes due to ontogenetic or inherent processes (Berger, 2005; Busse, 2002). Consistent findings of a loss (or gain) in cognitive ability systematic with chronological age in healthy adults would be a suggestive of primary aging effects where confounding factors such as education or socioeconomic background are ruled out. Systematic loss with age has been observed most prominently for perceptual speed and fluid abilities (Horn, 1988; Schaie, 1996) while relatively more conserved abilities tend to show losses later in the second half of the lifespan, e.g., memory loss (Horn, 1988; Schaie, 1996).

General Cognitive Ability

Original results from cross-sectional studies of cognitive aging suggested higher levels of heritability for general cognitive ability than is typically observed in young adulthood (cf. Chapter 6, this volume). As evidenced by the data summarized in Table 7.1, heritability estimates for general cognitive ability are about 0.80 in adulthood. The remaining variance is primarily nonshared environmental variance. The large age ranges (45–68 years) included in these studies, however, may be masking age changes in heritability as a result of successive phases of the aging process. Evidence from cohort sequential and longitudinal analyses, for example, provide a more complex image of the

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Table 7.1 Results from cross-sectional twin studies of primary cognitive aging

Variable	Study	Age range	Heritability
General cognitive ability	GOSAT	18–70	0.81
	MTSADA	27–95	0.75
	NTR	42–87	0.81
Verbal ability			
Information	MTSADA	27–95	0.77
Vocabulary	GOSAT	18–70	0.64–0.68
Verbal measures	NTR	42–87	0.59–0.86
Word fluency	GOSAT	18–70	0.53
Spatial ability			
Block design	MTSADA	27–95	0.73
Block design	OKUT	50–78	0.60
Spatial measures	GOSAT	18–70	0.39–0.57
Spatial measures	NTR	42–87	0.33–0.58
Memory			
Digit span	MTSADA	27–95	0.55
Figure memory	MTSADA	27–95	0.60
Memory factor	NHLBI	59–80	0.56
Memory	NTR	42–87	0.51
Text recall	MTSADA	27–95	0.53
Processing speed			
Digit symbol	MTSADA	27–95	0.62
Digit symbol	NHLBI	59–80	0.67
Digit symbol	OKUT	50–78	0.22
Perceptual speed	NTR	42–87	0.49–0.75

Note: GOSAT, German Observational Study of Adult Twins (Neubauer et al., 2000); MTSADA, Minnesota Twin Study of Adult Development and Aging (Finkel, Pedersen, & McGue, 1995a; Finkel, Pedersen, McGue, & McClearn, 1995b); NHLBI, National Heart Lung Blood Institute Twin Study (Swan et al., 1990, 1999); NTR, Norwegian Twin Register (Sundet, Tambs, Harris, Magnus, & Torjussen, 2005); OKUT, Osaka/Kinki University Twin Study (Hayakawa, Shimizu, Ohba, & Tomioka, 1992).

nature of genetic influences on cognitive abilities across the adult lifespan. Using latent growth curve analyses (McArdle, Prescott, Hamagami, & Horn, 1998; Chapter 2, this volume), genetic and environmental influences on static (intercept) and dynamic (rates of change) measures of cognitive aging can be investigated. In addition, changes with age in genetic and environmental components of variance can be calculated from the latent growth curve parameters. In other words, both the heritability of change and the change in heritability can be estimated.[1]

[1] It is important to note the challenges inherent in applying latent growth curve models to studies of aging twins. As with all studies of aging, attrition due to both nonresponse and death has a significant impact on sample size and assumptions about missing data. Furthermore, in studies of cognitive aging, the reasons for nonresponse (e.g., dementia or terminal decline) may be integrally related to the phenotype in question. In twin studies of aging we have the additional issue of twinness: in order for a twin pair to contribute fully to the investigation of genetic and environmental influences, both twins must participate. Finally, to ensure stability of parameter estimates in the latent growth curve model, at least three waves of measurement are necessary, and estimate stability increases with additional measurement occasions, see McArdle et al. (1998) for a more complete discussion of these issues.

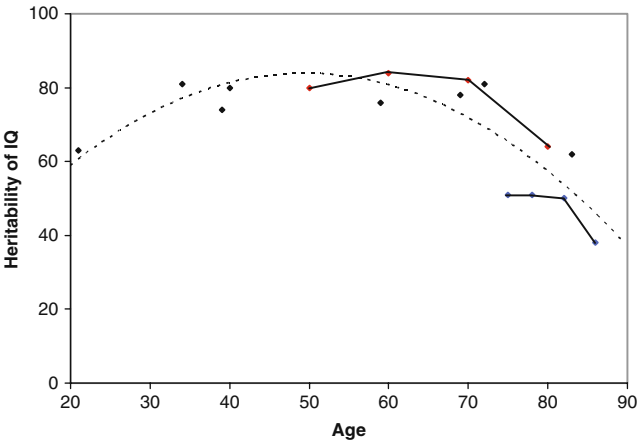

Fig. 7.1 Summary of heritability estimates for general cognitive ability across the adult lifespan. Single-point estimates are from the following cross-sectional studies: Bouchard, Lykken, McGue, Segal, and Tellegen (1990), Finkel et al. (1995b), McClearn et al. (1997), Neubauer et al. (2000), Sundet et al. (2005), Tambs, Sundet, and Magnus (1986) and Tambs et al. (1989). Longitudinal data are from McGue and Christensen (2002) and Reynolds et al. (2005). The *dotted line* is the polynomial regression line fitted to all the points ($R^2 = 0.71$)

A growing body of evidence from longitudinal investigations of cognitive aging indicates a decrease in heritability in late adulthood. A summary of the data on general cognitive ability is presented in Fig. 7.1: evidence from both cross-sectional and longitudinal studies converges on the conclusion that heritability for general cognitive ability increases from young adulthood, plateaus in adulthood, and decreases late in life. The dotted line represents the polynomial regression line fitted to all points, and even through the data come from eight different studies, the regression line explains 71% of the variability among the data points. When the data are considered in terms of raw variance, instead of proportion of variance, it becomes clear that the decrease in heritability results from fairly constant genetic variance and increasing nonshared environmental variance (e.g., Reynolds et al., 2005). Thus we can interpret the results as an indication of an accumulation of unique environmental influences that begin to have a greater impact on individual differences in cognitive ability in late life.

The implications of late life changes in heritability are supported by investigations of the heritability of change in general intelligence. It is possible that the genetic and environmental factors influencing *level* of cognitive functioning are not the same as the genetic and environmental factors that affect *change* with age. In fact, results from longitudinal twin studies indicate greater genetic influences on the intercept, or level of cognitive performance, than for either linear or quadratic components of cognitive decline (McGue & Christensen, 2002; Reynolds, Finkel, Gatz, & Pedersen, 2002; Reynolds et al., 2005). Results from several longitudinal twin studies of aging are summarized in

Table 7.2 Results from longitudinal twin studies of primary cognitive aging

			Change in heritability		Heritability of change		
Variable	Study	Age range	Young–old	Old–old	Intercept	Linear slope	Quadratic
General cognitive ability	LSADT	70–97	0.51	0.38	0.76	0.06	
	SATSA	50–92	0.80	0.64	0.91	0.01	0.43
	OCTO	80–95		0.62[a]			
Verbal ability							
Analogies	SATSA	50–92	0.87	0.22	0.78	0.19	0.09
Information	OCTO	80–95		0.55[a]	0.68[b]	–[c]	
Information	SATSA	50–92	0.65	0.54	0.70	0.09	0.42
Synonyms	OCTO	80–95		0.55[a]	0.46[b]	–[c]	
Synonyms	SATSA	50–92	0.78	0.46	0.75	0.17	0.13
Vocabulary	NYT	58–90	0.73	0.71	0.88	0.33	
Spatial ability							
Block design	NYT	58–90	0.63	0.35	0.96	0.70	
Block design	OCTO	80–95		0.32[a]	0.62[b]	–[c]	
Block design	SATSA	50–92	0.89	0.31	0.80	0.35	0.56
Card rotations	SATSA	50–92	0.81	0.33	0.74	0.35	0.38
Figure logic	OCTO	80–95		0.32[a]	0.70[b]	–[c]	
Figure logic	SATSA	50–92	0.57	0.03	0.67	0.14	0.33
Memory							
Digit span forward	OCTO	80–95		0.27[a]	0.36[b]	–[c]	
Digit span backward	OCTO	80–95		0.49[a]	0.84[b]	–[c]	
Digit span	SATSA	50–92	0.36	0.63	0.52	0.35	
Picture memory	OCTO	80–95	0.47[a]	0.14[b]	–[c]		
Picture memory	SATSA	50–92	0.50	0.33	0.84	0.06	0.70
Prose recall	OCTO	80–95		0.04[a]	0.12[b]	–[c]	
Processing speed							
Digit symbol	NHLBI	59–80				–[d]	
Digit symbol	OCTO	80–95		0.62[a]	0.72[b]	–[c]	
Symbol digit	SATSA	50–92	0.67	0.64	0.85	0.03	0.75
Figure identification	SATSA	50–92	0.58	0.40	0.78	0.15	0.39

[a] The full OCTO-Twin sample is in the old–old age range; therefore, no young–old estimate of heritability is reported.
[b] Calculated from twin correlations provided in Johansson et al. (2004).
[c] Twin correlations for slope estimates were unstable, but indicated largely environmental influences (Johannson et al., 2004).
[d] MZ concordance for decline = 45% and DZ concordance for decline = 8%.
Note: NYT, New York Twin Study (McArdle et al., 1998); SATSA, Swedish Adoption/Twin Study of Aging (Reynolds et al., 2005); NHLBI, National Heart Lung Blood Institute Twin Study (Swan, LaRue, Carmelli, Reed, & Fabsitz, 1992); LSADT, Longitudinal Study of Aging Danish Twins (McGue & Christensen, 2002); OCTO-Twin, Origins of Variance in the Oldest Old (Johansson et al., 1999, 2004; McClearn, Johansson, Berg, & Pedersen, 1997).

Table 7.2, including data on heritability of change in general cognitive ability. The evidence suggests that individual differences in the level of cognitive performance reflect primarily genetic influences. Although linear change results almost entirely from nonshared environmental influences, both genetic and nonshared environmental factors impact accelerating decline. Therefore, over half of the variance in general cognitive decline reflects person-specific environmental influences lending support to theories of stochastic or chance processes in aging (Finch & Kirkwood, 2000).

Specific Cognitive Abilities

Even though measures of general cognitive ability provide an overall view of changes in functioning that occur with age, intelligence is not a unitary construct and neither is cognitive aging. Decades of gerontological research indicate longitudinal decline for spatial, fluid, and memory abilities, with relatively smaller age changes noted for verbal ability (e.g., Carmelli, Swan, LaRue, & Eslinger, 1997; Korten et al., 1997; Schaie, 1994; Singer, Verhaeghen, Ghisletta, Lindenberger, & Baltes, 2003; Small, Stern, Tang, & Mayeux, 1999). Two-component theories of intelligence (e.g., Lindenberger, 2001) predict greater cultural impact on aging trajectories for aging-resilient (i.e., crystallized) abilities and a more biological foundation for age changes in age-sensitive (i.e., fluid) abilities. On the whole, results from twin studies of specific cognitive abilities in older adults support these predictions.

Cross-sectional twin data report higher heritability estimates for measures of verbal and spatial abilities and lower heritability estimates for memory and processing speed (see Table 7.1). The differences in heritability estimates reported in Table 7.1, both between- and within-cognitive variables,

can be attributed to differences in the age ranges covered by the studies and to the multi-faceted nature of the constructs, especially as they relate to the aging brain. These issues can be addressed by including multiple measures of the constructs and by investigating longitudinal changes in heritability across the age ranges in question. Results of longitudinal twin studies of specific cognitive abilities are presented in Table 7.2. Measures of verbal ability from three different studies indicate high genetic influences on the level of performance, but limited genetic variance for either linear or quadratic rates of decline. In contrast, as predicted by two-component theories of intelligence, results for spatial abilities show high heritability for the intercept and at least moderate heritability for both linear and quadratic declines. The third pattern is evident for processing speed: high heritability for level of performance, low heritability for linear decline, and high heritability for accelerating decline. We will consider the genetic influences on processing speed further when we discuss the possible mediational role of processing speed in cognitive aging. Results for measures of memory performance are mixed. With the exception of digit span backward, OCTO-Twin reports minimal heritability for the intercept and consistently low heritability for linear decline; however, twin data can become particularly unstable in the latest part of the lifespan, limiting our ability to make strong inferences (Johansson et al., 2004). In addition, SATSA reports only linear trajectories for digit span and quadratic trajectories for picture memory; although in combination the results support at least moderate genetic influences on decline.

Relationships Among Specific Cognitive Abilities

Specific cognitive abilities are not independent of each other and, in fact, it is possible that age changes in one cognitive ability may mediate or drive age changes in other components of cognition. Mediational theories of age-related cognitive have identified processing speed as a factor that may underlie demonstrated declines in a variety of cognitive tasks (e.g., Birren, 1964; Salthouse, 1996). Using data from twin studies of older adults, we can investigate not only the extent of the relationship between age changes in speed and age changes in cognition but also the underlying nature of that relationship. Genetic and environmental influences on the relationship between processing speed and cognitive aging have been investigated on three levels. First, cross-sectional studies demonstrate that correlations between processing speed and various measures of cognitive ability in middle to late adulthood are almost entirely genetically mediated (Finkel & Pedersen, 2000; Neubauer, Spinath, Riemann, Angleitner, & Borkenau, 2000; Posthuma, de Geus, & Boomsma, 2001; Posthuma, Mulder, Boomsma, & de Geus, 2002). Thus, a significant proportion of the genetic influences on cognitive ability in the second half of the lifespan arises from genetic factors affecting processing speed. Second, analysis of longitudinal twin data indicates that with age, an increasing proportion of genetic variance for cognitive ability can be attributed to genetic influences on processing speed (Finkel & Pedersen, 2004). Finally, by analyzing longitudinal twin data with sufficient time points to estimate quadratic patterns of decline, we find that it is not the linear age changes but the accelerating age changes in cognitive performance that share genetic variance with processing speed, at least for fluid abilities (Finkel, Reynolds, McArdle, & Pedersen, 2005).

Applying standard behavioral genetic and growth curve methods, we can investigate the genetic and environmental contributions to the covariance among specific cognitive abilities. To extend our understanding of these longitudinal relationships, however, it would be informative to be able to determine whether one cognitive variable is the leading indicator of subsequent changes in cognitive performance, as well as the extent of genetic and environmental influences driving the system. By using latent difference scores, instead of latent growth curves, McArdle and Hamagami (2003) have proposed a model that taps the dynamic interaction between age changes in specific cognitive abilities. In other words, the bivariate dual change score model allows for the identification of leading indicators of cognitive change: the extent to which changes in one variable drive changes in a related variable. They applied the model to vocabulary and block design measures from the New York Twin Study. They found small but significant coupling from block design to vocabulary scores, indicating that age changes in block design lead to age changes in vocabulary. Estimates of genetic variance for vocabulary changed only slightly over the age range when the dynamic coupling with block design was included in the model: heritability for vocabulary was stable instead of declining when the impact of block design was removed. The analyses need to be repeated with variables are more strongly correlated (McArdle & Hamagami, 2003).

Covariates of Primary Cognitive Aging

In addition to cognitive measures that mediate cognitive aging, we can also consider environmental and biological variables that may account for some of the genetic and environmental contributions to age changes in cognitive performance. A review of the evidence for environmental measures as sources of environmental variance in cognitive abilities in adulthood reported mixed success (Finkel & Pedersen, 2001). Moreover, it is important to distinguish

between environmental phenotypes and environmental etiology. Behavioral genetic methods can be used to investigate whether the relationships between cognitive aging and its covariates are explained via genetic or environmental pathways. For example, researchers have questioned the extent to which apparently environmental variables truly reflect environmental influences, as opposed to genetic influences (e.g., Plomin, 1994; Rowe, 1994). Occupation, education, and attitudes toward education explained most of the shared environmental variance in cognitive performance. However, only a very limited proportion of the nonshared environmental variance could be explained by measured environmental variables, primarily social class, occupation, and smoking history. More success has been achieved in identifying environmental variables that account for a portion of the genetic variation in cognitive abilities. For example, including education as a covariate in latent growth curve models of cognitive ability indicated that education shared genetic variance with the model intercept, but environmental variance with rate of change (Reynolds et al., 2002).

Biological variables have also been proposed as candidates for sources of genetic variance in cognitive abilities. Analyses of data from the Minnesota Twin Study of Adult Development and Aging reported only small and nonsignificant genetic correlations between physical activity or health factors and measures of cognitive performance (Finkel & McGue, 1993, 1998). In contrast, investigations using data from the Swedish Adoption/Twin Study of Aging reported that pulmonary function shared significant genetic variance with four measures of cognitive performance: information, digit symbol, block design, and digit span backward (Emery, Pedersen, Svartengren, & McClearn, 1998). Similarly, using growth curve models, researchers found that the covariance between pulmonary function and level of performance was primarily genetically mediated, although the covariance with decline in cognitive performance was mediated by nonshared environmental factors (Reynolds et al., 2002).

Identifying Genes Related to Primary Aging

Moving beyond anonymous components of genetic and environmental variance to measurable genes and environment has become one of the goals of behavioral genetic research. The apolipoprotein E *(APOE)* gene, coding for the brain cholesterol transporter apolipoprotein E, has been most often studied with respect to normal cognitive aging. The *APOE* e4 allele has been identified as a potential risk variant for normative cognitive change based on studies reporting consistent association with Alzheimer's disease risk (Strittmatter et al., 1993). In addition to well-known links of *APOE* e4 and AD-associated neuropathology [e.g., senile plaques containing Aβ deposits, neurofibrillary tangles (Ohm et al., 1995; Takahashi, Nam, Edgar, & Gouras, 2002)], studies indicate that the apoE protein may be involved in neuronal development and plasticity (Nathan et al., 2002; Ohm et al., 2003; Teter et al., 2002). While several population-based or community-based studies of individuals have indicated a positive association with *APOE* e4 and cognitive change (Deary et al., 2002; Hofer et al., 2002; Mayeux, Small, Tang, Tycko, & Stern, 2001; Mortensen & Hogh, 2001), findings are not entirely consistent (Anstey & Christensen, 2000; Pendleton et al., 2002; Small et al., 2000). The memory domain evidences the most consistent findings (Anstey & Christensen, 2000; Bretsky, Guralnik, Launer, Albert, & Seeman, 2003; Nilsson, Nyberg, & Backman, 2002; Reynolds, Jansson, Gatz, & Pedersen, 2006a; Wilson et al., 2002), even in studies removing participants with slight indications of dementia (Mayeux et al., 2001). A recent twin-based association study added to the consensus by finding significant association of APOE with change in working memory (i.e., digit span) in nondemented Swedish twins (Reynolds, Prince, Feuk, Gatz, & Pedersen, 2006b).

Findings for other gene candidates have begun to appear relatively recently though with few if any replications published to date (e.g., de Frias et al., 2005; Harris et al., 2005; Reynolds, Jansson, et al., 2006a; Reynolds, Prince, et al., 2006b). The genes encoding serotonin 2A receptors (*HTR2A*) and catechol-*O*-methyltransferase (*COMT*) are of particular interest given their involvement in brain regions associated with learning and memory. In particular, working memory, episodic, and semantic performance have been associated with serotonin function and/or proteins involved in the catabolism or breakdown of dopamine, i.e., catechol-*O*-methyltransferase. Evidence of their potential biological importance has been marshaled across a variety of designs including neuroimaging studies (Egan et al., 2001; Sheline, Mintun, Moerlein, & Snyder, 2002), mRNA (Akil et al., 2003; Amargos-Bosch et al., 2004; but see Bray, Buckland, Hall, Owen, & O'Donovan, 2004), and, for serotonin 2A, in vivo receptor activity manipulations in primates (Williams, Rao, & Goldman-Rakic, 2002).

Serotonin 2A *(HTR2A)* may play a role in memory-related formation of synaptic connections (Kandel, 2001). Furthermore, age-related decreases in serotonin 2A receptors have been noted in the hippocampus and prefrontal cortex (Sheline et al., 2002) with evidence of downregulated gene expression in the frontal cortex beginning at midlife (Lu et al., 2004). Episodic memory performance in young adults (de Quervain et al., 2003) and recognition memory change in nondemented Swedish twins (Reynolds et al., 2006a) have been associated with the gene encoding serotonin 2A (*HTR2A*).

The Val108/158 Met *COMT* functional variant has been associated with prefrontal cortex ERP P300 latencies (Tsai et al., 2003), cognitive stability and flexibility in schizophrenics (Nolan, Bilder, Lachman, & Volavka, 2004),

working memory performance in schizophrenics and healthy adults (Bruder et al., 2005; Egan et al., 2001; Malhotra et al., 2002), and declarative memory performance (de Frias et al., 2004; Harris et al., 2005). Most recently the COMT variant was associated with cognitive change over 5 years in nondemented Swedish adults ranging from 35 to 85 years at baseline with respect to executive function (de Frias et al., 2005).

Secondary Aging

Secondary aging effects are a result of environmental factors, such as those due to lifestyle or many disease processes (Berger, 2005). Examples of disease that result in loss of cognitive abilities are the dementias, such as vascular dementia and Alzheimer's disease (AD). All-cause dementia prevalence is approximately 6% at age 60 years and older (Bowler, 2005; Ferri et al., 2005). Alzheimer's disease is by far the most common form of dementia representing approximately two-thirds of dementia cases (Ferri et al., 2005). Prevalence rates for AD increase with age reaching 45% by age 95 years (Nussbaum & Ellis, 2003). Whereas vascular dementia appears to be influenced by shared and nonshared environmental factors without evidence of genetic influence (Bergem, Engedal, & Kringlen, 1997), late-onset AD is due to multifactorial causes and is highly heritable (Gatz et al., 1997, 2006a).The largest population-based study to date estimates heritability as high as 79% for prevalent AD with remaining variation due to nonshared environmental effects, and with no significant evidence for sex differences (Gatz et al., 2006a). Thus, individual differences in risk for Alzheimer's disease is largely due to genetic differences. One might argue that Alzheimer's disease (AD) represents a primary aging process given the high heritability and the reflection that if one lived long enough one would eventually evidence characteristics of the disease (Ebly, Parhad, Hogan, & Fung, 1994). However, evidence suggests that AD is not inevitable given that elderly into their 90s do not necessarily show clinical evidence of AD even in the case where subsequent postmortem autopsies indicate AD-like neuropathology (Morris, 1999). Additionally, while the prevalence of AD increases with age, a recent retrospective family-history study indicates that familiality of AD likely decreases with age based on negative relationship between AD risk and age of onset of family members with AD (Silverman, Ciresi, Smith, Marin, & Schnaider-Beeri, 2005).

Candidate Genes and AD

Consistent association has been observed for *APOE* e4 and Alzheimer's disease risk both in family-based studies (Strittmatter et al., 1993) and numerous case–control studies (Rubinsztein, & Easton, 1999). No other AD gene candidate has achieved such coherent findings. Indeed a compendia of 62 candidate gene makers was recently published indicating after correcting for multiple tests, only *APOE* remained significantly associated with AD risk as well as AD-relevant biomarkers (i.e., CSF Aβ; CSF tau) (Blomqvist et al., 2006). That said, it is apparent that APOE does not fully account for the genetic bases of AD with indications that there may be four to five major genes yet to locate (Warwick Daw et al., 2000). Additional studies indicate potential genomic regions where additional candidates may lie, including regions on chromosomes 1, 9, 10, and 19 that achieved genome-wide significance (Blacker et al., 2003; Kehoe et al., 1999).

Head Injury

Head injury with loss of consciousness is an oft-reported environmental event that increases the risk for Alzheimer's disease (AD) based primarily on case–control studies (Fleminger, Oliver, Lovestone, Rabe-Hesketh, & Giora, 2003) but the effect is also found in community-based samples (Schofield et al., 1997). A compelling population-based cohort study of World War II military veterans indicates that moderate head injury with loss of consciousness during military service significantly increased the risk of dementia as well as AD (Plassman et al., 2000). Head injury may also synergistically interact with *APOE* e4 status in the risk of AD as described below.

Antioxidants

Antioxidants have been touted as potentially decreasing the risk of cognitive decline and AD (Kontush & Schekatolina, 2004). Specifically, taking vitamin supplements or eating food rich in vitamins C and E may reduce free radical damage or oxidative stress and thus stave off or delay cognitive decline (Kontush & Schekatolina, 2004; Maxwell, Hicks, Hogan, Basran, & Ebly, 2005; M. C. Morris, Evans, Bienias, Tangney, & Wilson, 2002). Community-based and population-based prospective studies suggest that both dietary and supplemental vitamin E and/or vitamin C intake may be related to lessened cognitive change (M. C. Morris et al., 2002; Maxwell et al., 2005), though not all have found a reduced risk of incident dementia or AD (Maxwell et al., 2005). Antioxidant use in the context of behavior genetic designs has yet to be explored though such analyses may prove useful in determining the nature of the antioxidant use/cognitive decline relationship, particularly in discordant twins.

"Use It or Lose It"

Education may be protective against cognitive decline and risk of AD (Anstey & Christensen, 2000). The nature of the protective association is not clearly understood as educational attainment is influenced by both genetic and environmental factors (Baker, Treloar, Reynolds, Heath, & Martin, 1996; Heath & Berg, 1985; Lichtenstein & Pedersen, 1997; Tambs, Sundet, Magnus, & Berg, 1989). Higher education levels may lead to greater cognitive reserve resulting in greater hardiness that may delay a clinical presentation of AD, or education may serve as a proxy for health and nutritional habits such that as those with higher education may have better access to resources leading to a healthier lifestyle. For example, a recent study suggests that exercise frequency is associated with reduced risk of or delayed onset of dementia (Larson et al., 2006). Consistent with the reserve capacity hypothesis, education, cognitive ability, and mental status performance in the SATSA twin study were associated phenotypically due to a common genetic factor (Pedersen, Reynolds, & Gatz, 1996). Epidemiological studies are also supportive: educational attainment remains associated with cognitive change even when relevant health variables are controlled (Lee, Kawachi, Berkman, & Grodstein, 2003). That said, there may be evidence of an environmental explanation as well: cotwin control or discordant twin pair analyses of Swedish twins provide evidence for "use it or lose it" as a protective factor against dementia or AD including the cognitive complexity of one's lifetime occupations (Andel et al., 2005) and participation in leisure activities (Crowe, Andel, Pedersen, Johansson, & Gatz, 2003).

Early Life SES-Related Factors

Lower SES in early life may be associated with a cascade of influences relevant to later cognitive aging, including poorer health and nutrition and lower rates of educational and occupational achievements. Epidemiological studies have reported that having a higher number of siblings, lower paternal occupational status and residing in urban locales before 18 may increase the risk of AD (Moceri et al., 2001; Moceri, Kukull, Emanuel, van Belle, & Larson, 2000). However, the Religious Orders Study reported that early childhood SES and community-level SES were predictive of cognitive ability but not cognitive decline or an increased risk of AD (Wilson et al., 2005). In AD-discordant twin pairs, early adult tooth loss before the age of 35 years was a significant risk factor for AD in the HARMONY study that includes twins from the Swedish Twin Registry aged 65 years and older. Adult tooth loss before the age of 35 years may be a marker of poorer early life health and/or an indicator of inflammation processes detrimental to neuronal health (see Gatz et al., 2006b).

Tertiary Aging

Longitudinal studies have indicated that cognitive performance in those 3–6 years from death is lower than those who survive (Johansson & Berg, 1989; Small, Fratiglioni, von Strauss, & Backman, 2003; Wilson, Beckett, Bienias, Evans, & Bennett, 2003). There may be an attenuation of effect when controlling for cardiovascular disease and stroke (Hassing et al., 2002), while others have not found an association with cause of death (Small et al., 2003) suggesting a common process may be at play. Results from an investigation of genetic influences on low cognitive functioning in late adulthood indicated little or no heritability (Petrill et al., 2001). The authors suggested that nonsignificant heritability at the low end of cognitive ability may be attributable to the processes of terminal decline. Their interpretation highlights the question: To what extent is terminal decline in cognitive functioning influenced by genetic and environmental factors? Regardless of whether there is a genetic component to terminal decline of cognitive abilities, it is possible that the timing of entry into terminal decline results from environmental factors. Consequently, twin similarity for cognitive performance may decrease in late adulthood as the abilities of each member of a twin pair begin to decline at a slightly different time, even though the decline itself may be genetically influenced. In fact, analyses of cognitive data from the same sample of twins aged 80 and older as presented by Petrill et al. (2001) support this idea. As one or both members of a twin pair approached death, twin similarity for cognitive performance decreased, indicating both heterogeneity in timing of decline and a decreasing role for genetic influences on cognitive performance with approaching mortality (Johansson et al., 2004). An investigation including imputation of age at death reached a similar conclusion: genetic variance for the cognitive task was significantly lower when age at death was included in the model (Pedersen et al., 2003). It will require closely spaced assessments of cognitive performance in twins both before and during the period of terminal decline to provide sufficient data to differentiate genetic and environmental influences on timing of terminal decline versus rates of decline.

Future Directions

Dynamic Models

To best capture the nature of cognitive aging it would be ideal to capture the cognitive aging process in real time considering the push and pull relationships of the multiple processes

leading up to the points of change. As that is not possible, dynamic change models may provide a fruitful approach to better understand the nature of cognitive change (see McArdle & Nesselroade, 2003; and Chapter 2, this volume). Simply correlating rate of change for two traits does not capture dynamic change but rather indicates how rates of static change are associated (McArdle & Nesselroade, 2003), e.g., if one is changing more rapidly on perceptual speed do they tend to change more rapidly on working memory? One cannot tell if change in a particular trait precedes change in the other because there is no information about the timing of change in each trait. Only one application of dynamic models to longitudinal twin data of cognitive abilities has been published to date (McArdle & Hamagami, 2003). Using dynamic approaches and identifying lead–lag relationships between two or more traits across age may move the field closer to identifying the mechanistic nature of the associations, in addition to understanding whether the relationship is due to common genetic and/or environmental influences (McArdle & Hamagami, 2003; McArdle & Nesselroade, 2003).

Distinguishing Primary, Secondary, and Tertiary Cognitive Aging

Whether one can clearly distinguish primary, secondary, and tertiary cognitive aging is important to understanding the nature(s) of cognitive aging. The search for relevant candidate genes and environments indeed bear upon this. On the one hand, if primary cognitive aging is universal then one would expect heritability to be zero as there would be no individual differences. Rather perhaps we should search for what affects the entry or timing into decline as it is clear that chronological age is only a proxy: some age cognitively at a quicker pace than others despite the same chronological age. As to secondary aging, it would be expected that environmental factors would be largely important though it is clear that even age-associated diseases such as Alzheimer's are highly heritable. Indeed, some consider AD to represent the extreme end of the continuum of cognitive change, even suggesting that the search for genes for IQ is likely to turn up genes relevant to AD and vice versa (Plomin & Spinath, 2004). The candidate gene *APOE* fits neatly within the continuum view, given its relationship both with cognitive decline and AD. Finally, distinguishing tertiary cognitive aging from normative aging and that due to disease/environmental factors is not likely to be any easier. There is no clear agreement as to when tertiary aging begins. More studies that follow participants to the end and applying growth models where the time metric is years to death may provide invaluable evidence for distinguishing tertiary cognitive aging from the others.

Identifying Genes Associated with Cognitive Aging

Given the increase in heritability indicated during the majority of adulthood (as indicated in Fig. 7.1), it is surprising that researchers have not experienced more success in identifying genes that are associated with cognitive aging. To date, research has demonstrated the impact of only handful of genes on aspects of primary, secondary, and tertiary aging. It may be that genes involved in cognitive aging account for such a small proportion of individual differences in aging trajectories that current studies lack sufficient power to detect them. In contrast, the presence of gene-by-environment interactions (see our discussion below) or complex gene–environment pathways is limiting the ability of researchers to detect cognitive aging genes. As the search progresses, it will be vital to investigate the differential role, if any, the identified genes have with regard to primary, secondary, and tertiary aging processes.

Gene–Environment Interactions

More and more studies are reporting the presence of gene–environment interactions for human behavioral traits (e.g., Caspi et al., 2002, 2003). Little is known with respect to cognitive aging, save for the findings of a possible synergistic effect of head injury coupled with positive *APOE* e4 status on the risk of AD (Jellinger, 2004; Tang et al., 1996). An indicator of possible gene–environment interaction in the normative cognitive aging literature is the pattern of increasing nonshared environmental variance with age (e.g., Reynolds et al., 2005); any unspecified variance due to gene–environment interaction will be included as nonshared environmental variance (Falconer, 1989). Future studies should examine the possibility of G $\times$ E interaction given the tools and knowledge available, including examination of within-pair differences for cognitive change in MZ twins stratified by measured genotype (Martin, 2000).

References

Akil, M., Kolachana, B. S., Rothmond, D. A., Hyde, T. M., Weinberger, D. R., & Kleinman, J. E. (2003). Catechol-O-Methyltransferase genotype and dopamine regulation in the human brain. *Journal of Neuroscience, 23*, 2008–2013.

Amargos-Bosch, M., Bortolozzi, A., Puig, M. V., Serrats, J., Adell, A., Celada, P., et al. (2004). Co-expression and in vivo interaction of serotonin1A and serotonin2A receptors in pyramidal neurons of prefrontal cortex. *Cereb Cortex, 14*, 281–299.

Andel, R., Crowe, M., Pedersen, N. L., Mortimer, J., Crimmins, E., Johansson, B., et al. (2005). Complexity of work and risk of

Alzheimer's disease: A population-based study of Swedish twins. *Journals of Gerontology, Series B: Psychological and Social Sciences, 60*, P251–P258.

Anstey, K., & Christensen, H. (2000). Education, activity, health, blood pressure and apolipoprotein E as predictors of cognitive change in old age: A review. *Gerontology, 46*, 163–177.

Baker, L. A., Treloar, S. A., Reynolds, C. A., Heath, A. C., & Martin, N. G. (1996). Genetics of educational attainment in Australian twins: Sex differences and secular changes. *Behavior Genetics, 26*, 89–102.

Bergem, A. L., Engedal, K., & Kringlen, E. (1997). The role of heredity in late-onset Alzheimer disease and vascular dementia: A twin study. *Archives of General Psychiatry, 54*, 264–270.

Bergeman, C. S. (2007). Behavioral genetics. In Birren, J. E. (Ed.), *Encyclopedia of gerontology* (2nd ed.). New York: Academic Press.

Berger, K. S. (2005). *The developing person through the lifespan* (6th ed.). New York: Worth Publishers.

Birren, J. E. (1964). *The psychology of aging*. Englewood Cliffs, NJ: Prentice-Hall.

Blacker, D., Bertram, L., Saunders, A. J., Moscarillo, T. J., Albert, M. S., Wiener, H., et al. (2003). Results of a high-resolution genome screen of 437 Alzheimer's disease families. *Human Molecular Genetics, 12*, 23–32.

Blomqvist, M. E., Reynolds, C., Katzov, H., Feuk, L., Andreasen, N., Bogdanovic, N., et al. (2006). Towards compendia of negative genetic association studies: An example for Alzheimer disease. *Human Genetics*, *119*, 29–37.

Bouchard, T. J., Jr., Lykken, D. T., McGue, M., Segal, N. L., & Tellegen, A. (1990). Sources of human psychological differences: The Minnesota Twin Study of Twins Reared Apart. *Science, 250*, 223–228.

Bowler, J. V. (2005). Vascular cognitive impairment. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*(Suppl 5), v35–v44.

Bray, N. J., Buckland, P. R., Hall, H., Owen, M. J., & O'Donovan, M. C. (2004). The serotonin-2A receptor gene locus does not contain common polymorphism affecting mRNA levels in adult brain. *Molecular Psychiatry, 9*, 109–114.

Bretsky, P., Guralnik, J. M., Launer, L., Albert, M., & Seeman, T. E. (2003). The role of APOE-epsilon4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. *Neurology, 60*, 1077–1081.

Bruder, G. E., Keilp, J. G., Xu, H., Shikhman, M., Schori, E., Gorman, J. M., et al. (2005). Catechol-O-methyltransferase (COMT) genotypes and working memory: Associations with differing cognitive operations. *Biological Psychiatry, 58*, 901–907.

Busse, E. W. (2002). Scope and development in the twentieth century. In M. S. John Pathy, A. J. Sinclair, & J. E. Morley (Eds.), *Principles and practice of geriatric psychiatry* (2nd ed., pp. 7–8). New York: John Wiley & Sons Ltd.

Carmelli, D., Swan, G. E., LaRue, A., & Eslinger, P. J. (1997). Correlates of change in cognitive function in survivors from the Western Collaborative Group Study. *Neuroepidemiology, 16*, 285–295.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., et al. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297*, 851–854.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*, 386–389.

Crowe, M., Andel, R., Pedersen, N. L., Johansson, B., & Gatz, M. (2003). Does participation in leisure activities lead to reduced risk of Alzheimer's disease? A prospective study of Swedish twins. *Journals of Gerontology, Series B: Psychological and Social Sciences, 58*, P249–P255.

de Frias, C. M., Annerbrink, K., Westberg, L., Eriksson, E., Adolfsson, R., & Nilsson, L. G. (2004). COMT gene polymorphism is associated with declarative memory in adulthood and old age. *Behavior Genetics, 34*, 533–539.

de Frias, C. M., Annerbrink, K., Westberg, L., Eriksson, E., Adolfsson, R., & Nilsson, L. G. (2005). Catechol *O*-methyltransferase Val158Met polymorphism is associated with cognitive performance in nondemented adults. *Journal of Cognitive Neuroscience, 17*, 1018–1025.

de Quervain, D. J. F., Henke, K., Aerni, A., Coluccia, D., Wollmer, M. A., Hock, C., et al. (2003). A functional genetic variation of the 5-HT2a receptor affects human memory. *Nature Neuroscience, 6*, 1141–1142.

Deary, I. J., Whiteman, M. C., Pattie, A., Starr, J. M., Hayward, C., Wright, A. F., et al. (2002). Cognitive change and the APOE epsilon 4 allele. *Nature, 418*, 932.

Ebly, E. M., Parhad, I. M., Hogan, D. B., & Fung, T. S. (1994). Prevalence and types of dementia in the very old: Results from the Canadian Study of Health and Aging. *Neurology, 44*, 1593–1600.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., et al. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *PNAS, 98*, 6917–6922.

Emery, C. F., Pedersen, N. L., Svartengren, M. S., & McClearn, G. E. (1998). Longitudinal and genetic effects in the relationship between pulmonary function and cognitive performance. *Journal of Gerontology: Psychological Sciences, 53B*, P311–P317.

Falconer, D. S. (1989). *Introduction to quantitative genetics* (3rd ed.). New York: John Wiley & Sons.

Ferri, C. P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., et al. (2005). Global prevalence of dementia: A Delphi consensus study. *The Lancet, 366*, 2112–2117.

Finch, C. E., & Kirkwood, T. B. L. (2000). *Chance, development, and aging*. New York: Oxford University Press.

Finkel, D., & McGue, M. (1993). The origins of individual differences in memory among the elderly: A behavior genetic analysis. *Psychology and Aging, 8*, 527–537.

Finkel, D., & McGue, M. (1998). Age differences in the nature and origin of individual differences in memory. *International Journal of Aging and Human Development, 47*, 217–239.

Finkel, D., & Pedersen, N. L. (2000). Contribution of age, genes, and environment to the relationship between perceptual speed and cognitive ability. *Psychology and Aging, 15*, 56–64.

Finkel, D., & Pedersen, N. L. (2001). Sources of environmental influence on cognitive abilities in adulthood. In E. L. Grigorenko & R. J. Sternberg (Eds.), *Family environment and intellectual functioning: A life-span perspective* (pp. 173–194). Mahwah, NJ: Lawrence Erlbaum Associates.

Finkel, D., & Pedersen, N. L. (2004). Processing speed and longitudinal trajectories of change for cognitive abilities: The Swedish Adoption/Twin Study of Aging. *Aging, Neuropsychology, and Cognition, 11*, 325–345.

Finkel, D., Pedersen, N. L., & McGue, M. (1995a). Genetic influences on memory performance in adulthood: Comparison of Minnesota and Swedish twin studies. *Psychology and Aging, 10*, 437–446.

Finkel, D., Pedersen, N. L., McGue, M., & McClearn, G. E. (1995b). Heritability of cognitive abilities in adult twins: Comparison of Minnesota and Swedish data. *Behavior Genetics, 25*, 421–431.

Finkel, D., Reynolds, C. A., McArdle, J. J., & Pedersen, N. L. (2005). The longitudinal relationship between processing speed and cognitive ability: Genetic and environmental influences. *Behavior Genetics, 35*, 535–549.

Fleminger, S., Oliver, D. L., Lovestone, S., Rabe-Hesketh, S., & Giora, A. (2003). Head injury as a risk factor for Alzheimer's disease: The evidence 10 years on; a partial replication. *Journal of Neurology, Neurosurgery, and Psychiatry, 74*, 857–862.

Gatz, M., Pedersen, N. L., Berg, S., Johansson, B., Johansson, K., Mortimer, J. A., et al. (1997). Heritability for Alzheimer's disease:

The study of dementia in Swedish twins. *Journal of Gerontology: Medical Sciences, 52*, M117–M125.

Gatz, M., Reynolds, C. A., Fratiglioni, L., Johansson, B., Mortimer, J. A., Berg, S., et al. (2006a). Role of genes and environments for explaining Alzheimer's disease. *Archives of General Psychiatry, 63*, 168–174.

Gatz, M., Mortimer, J. A., Fratiglioni, L., Johansson, B., Berg, S., Reynolds, C. A., & Pedersn, N. L. (2006b). Potentially modifiable risk factors for dementia in identical twins. *Alzheimer's & Dementia, 2*, 110–117.

Harris, S. E., Wright, A. F., Hayward, C., Starr, J. M., Whalley, L. J., & Deary, I. J. (2005). The functional COMT polymorphism, Val 158 Met, is associated with logical memory and the personality trait intellect/imagination in a cohort of healthy 79 year olds. *Neuroscience Letters, 385*, 1–6.

Hassing, L. B., Johansson, B., Berg, S., Nilsson, S. E., Pedersen, N. L., Hofer, S. M., et al. (2002). Terminal decline and markers of cerebro- and cardiovascular disease: Findings from a longitudinal study of the oldest old. *Journals of Gerontology*, *Series B: Psychological and Social Sciences, 57*, P268–P276.

Hayakawa, K., Shimizu, T., Ohba, Y., & Tomioka, S. (1992). Risk factors for cognitive aging in adult twins. *Acta Geneticae Medicae Gemellologiae, 41*, 187–195.

Heath, A. C., & Berg, K. (1985). Effects of social policy on the heritability of educational achievement. *Progress in Clinical and Biological Research, 177*, 489–507.

Hofer, S. M., Christensen, H., Mackinnon, A. J., Korten, A. E., Jorm, A. F., Henderson, A. S., et al. (2002). Change in cognitive functioning associated with apoE genotype in a community sample of older adults. *Psychology and Aging, 17*, 194–208.

Horn, J. (1988). Thinking about human abilities. In J. R. Nesselrode & R. B. Cattell (Eds.), *Handbook of multivariate experimental psychology.* New York: Plenum Press.

Jellinger, K. A. (2004). Head injury and dementia. *Current Opinion in Neurology, 17*, 719–723.

Johansson, B., & Berg, S. (1989). The robustness of the terminal decline phenomenon: Longitudinal data from the Digit-Span Memory Test. *Journal of Gerontology, 44*, P184–P186.

Johansson, B., Hofer, S. M., Allaire, J. C., Maldonado-Molina, M. M., Piccinin, A. M., Berg, S., et al. (2004). Change in cognitive capabilities in the oldest old: The effects of proximity to death in genetically related individuals over a 6-year period. *Psychology and Aging, 19*, 145–156.

Johansson, B., Whitfield, K., Pedersen, N. L., Hofer, S. M., Ahern, F., & McClearn, G. E. (1999). Origins of individual differences in episodic memory in the oldest-old: A population-based study of identical and same-sex fraternal twins aged 80 and older. *Journal of Gerontology: Psychological Sciences, 54B*, P173–P179.

Kandel, E. R. (2001). The molecular biology of memory storage: A dialogue between genes and synapses. *Science, 294*, 1030–1038.

Kehoe, P., Wavrant-De Vrieze, F., Crook, R., Wu, W. S., Holmans, P., Fenton, I., et al. (1999). A full genome scan for late onset Alzheimer's disease. *Human Molecular Genetics, 8*, 237–245.

Kontush, A., & Schekatolina, S. (2004). Vitamin E in neurodegenerative disorders: Alzheimer's disease. *Annals of the New York Academy of Sciences, 1031*, 249–262.

Korten, A. E., Henderson, A. S., Christensen, H., Jorm, A. F., Rodgers, B., Jacomb, P., et al. (1997). A prospective study of cognitive function in the elderly. *Psychological Medicine, 27*, 919–930.

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P., et al. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine, 144*, 73–81.

Lichtenstein, P., & Pedersen, N. L. (1997). Does genetic variance for cognitive abilities account for genetic variance in educational achievement and occupational status? A study of twins reared apart and twins reared together. *Social Biology, 44*, 77–90.

Lee, S., Kawachi, I., Berkman, L. F., & Grodstein, F. (2003). Education, other socioeconomic indicators, and cognitive function. *American Journal of Epidemiology, 157*, 712–720.

Lichtenstein, P., & Pedersen, N. L. (1997). Does genetic variance for cognitive abilities account for genetic variance in educational achievement and occupational status? A study of twins reared apart and twins reared together. *Social Biology, 44*, 77–90.

Lindenberger, U. (2001). Lifespan theories of cognitive development. In N. J. Smelser & P. B. Baltes (Eds.), *International encyclopedia of the social and behavior sciences* (pp. 8848–8854). Oxford, England: Elsevier.

Lu, T., Pan, Y., Kao, S. Y., Li, C., Kohane, I., Chan, J., et al. (2004). Gene regulation and DNA damage in the ageing human brain. *Nature, 429*, 883–891.

Malhotra, A. K., Kestler, L. J., Mazzanti, C., Bates, J. A., Goldberg, T., & Goldman, D. (2002). A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *American Journal of Psychiatry, 159*, 652–654.

Martin, N. G. (2000). Gene–environment interaction and twin studies. In T. D. Spector, H. Snieder, & A. J. MacGregor (Eds.), *Advances in twin and sib-pair analysis* (pp. 144–150). London: Greenwich Medical Media.

Maxwell, C. J., Hicks, M. S., Hogan, D. B., Basran, J., & Ebly, E. M. (2005). Supplemental use of antioxidant vitamins and subsequent risk of cognitive decline and dementia. *Dementia and Geriatric Cognitive Disorders, 20*, 45–51.

Mayeux, R., Small, S. A., Tang, M., Tycko, B., & Stern, Y. (2001). Memory performance in healthy elderly without Alzheimer's disease: Effects of time and apolipoprotein-E. *Neurobiology and Aging, 22*, 683–689.

McArdle, J. J., & Hamagami, F. (2003). Structural equation models for evaluating dynamic concepts within longitudinal twin analyses. *Behavior Genetics, 33*, 137–159.

McArdle, J. J., & Nesselroade, J. R. (2003). Growth curve analysis in contemporary psychological research. In J. A. Schinka & W. F. Velicer (Eds.), *Handbook of psychology: Research methods in psychology* (Vol. 2, pp. xxiii, 711pp.). New York, NY: John Wiley & Sons, Inc.

McArdle, J. J., Prescott, C. A., Hamagami, F., & Horn, J. L. (1998). A contemporary method for developmental-genetic analyses of age changes in intellectual abilities. *Developmental Neuropsychology, 14*, 69–114.

McClearn, G. E., Johansson, B., Berg, S., & Pedersen, N. L. (1997). Substantial genetic influences on cognitive abilities in twins 80 or more years old. *Science, 276*, 1560–1563.

McGue, M., & Christensen, K. (2002). The heritability of level and rate-of-change in cognitive functioning in Danish twins aged 70 years and older. *Experimental Aging Research, 28*(4), 435–451.

Moceri, V. M., Kukull, W. A., Emanuel, I., van Belle, G., & Larson, E. B. (2000). Early-life risk factors and the development of Alzheimer's disease. *Neurology, 54*, 415–420.

Moceri, V. M., Kukull, W. A., Emanual, I., van Belle, G., Starr, J. R., Schellenberg, G. D., et al. (2001). Using census data and birth certificates to reconstruct the early-life socioeconomic environment and the relation to the development of Alzheimer's disease. *Epidemiology, 12*, 383–389.

Morris, J. C. (1999). Is Alzheimer's disease inevitable with age?: Lessons from clinicopathologic studies of healthy aging and very mild Alzheimer's disease. *Journal of Clinical Investigation, 104*, 1171–1173.

Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., & Wilson, R. S. (2002). Vitamin E and cognitive decline in older persons. *Archives of Neurology, 59*, 1125–1132.

Mortensen, E. L., & Hogh, P. (2001). A gender difference in the association between APOE genotype and age-related cognitive decline. *Neurology, 57*, 89–95.

Nathan, B. P., Jiang, Y., Wong, G. K., Shen, F., Brewer, G. J., & Struble, R. G. (2002). Apolipoprotein E4 inhibits, and apolipoprotein E3 promotes neurite outgrowth in cultured adult mouse cortical neurons through the low-density lipoprotein receptor-related protein. *Brain Research, 928*, 96–105.

Neubauer, A. C., Spinath, F. M., Riemann, R., Angleitner, A., & Borkenau, P. (2000). Genetic and environmental influences on two measures of speed of information processing and their relation to psychometric intelligence: Evidence form the German Observational Study of Adult Twins. *Intelligence, 28*, 267–289.

Nilsson, L. G., Nyberg, L., & Backman, L. (2002). Genetic variation in memory functioning. *Neuroscience and Biobehavioral Reviews, 26*, 841–848.

Nolan, K. A., Bilder, R. M., Lachman, H. M., & Volavka, J. (2004). Catechol O-methyltransferase Val158Met polymorphism in schizophrenia: Differential effects of Val and Met alleles on cognitive stability and flexibility. *American Journal of Psychiatry, 161*, 359–361.

Nussbaum, R. L., & Ellis, C. E. (2003). Alzheimer's disease and Parkinson's disease. *New England Journal of Medicine, 348*, 1356–1364.

Ohm, T. G., Glockner, F., Distl, R., Treiber-Held, S., Meske, V., & Schonheit, B. (2003). Plasticity and the spread of Alzheimer's disease-like changes. *Neurochemical Research, 28*, 1715–1723.

Ohm, T. G., Kirca, M., Bohl, J., Scharnagl, H., Gross, W., & Marz, W. (1995). Apolipoprotein E polymorphism influences not only cerebral senile plaque load but also Alzheimer-type neurofibrillary tangle formation. *Neuroscience, 66*, 583–587.

Pedersen, N. L., Reynolds, C. A., & Gatz, M. (1996). Sources of covariation among Mini-Mental State Examination scores, education, and cognitive abilities. *Journals of Gerontology: Series B: Psychological Sciences and Social Sciences, 51B*, P55–P63.

Pedersen, N. L., Ripatti, S., Berg, S., Reynolds, C. A., Hofer, S. M., Finkel, D., et al. (2003). The influence of mortality on twin models of change. *Behavior Genetics, 33*, 161–169.

Pendleton, N., Payton, A., van den Boogerd, E. H., Holland, F., Diggle, P., Rabbitt, P. M., et al. (2002). Apolipoprotein E genotype does not predict decline in intelligence in healthy older adults. *Neuroscience Letters, 324*, 74–76.

Petrill, S. A., Johansson, B., Pedersen, N. L., Berg, S., Plomin, R., Ahern, F., et al. (2001). Low cognitive functioning in nondemented 80+-year-old twins is not heritable. *Intelligence, 29*, 75–83.

Plassman, B. L., Havlik, R. J., Steffens, D. C., Helms, M. J., Newman, T. N., Drosdick, D., et al. (2000). Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology, 55*, 1158–1166.

Plomin, R. (1994). *Genetics and experience*. Newbury Park, CA: Sage Publications.

Plomin, R., & Spinath, F. M. (2004). Intelligence: Genetics, genes, and genomics. *Journal of Personality & Social Psychology, 86*, 112–129.

Posthuma, D., de Geus, E. J. C., & Boomsma, D. I. (2001). Perceptual speed and IQ are associated through common genetic factors. *Behavior Genetics, 31*, 593–602.

Posthuma, D., Mulder, E. J. C. M., Boomsma, D. I., & de Geus, E. J. C. (2002). Genetic analysis of IQ, processing speed and stimulus-response incongruency effects. *Biological Psychology, 61*, 157–182.

Reynolds, C. A., Finkel, D., Gatz, M., & Pedersen, N. L. (2002). Sources of influence on rate of cognitive change over time in Swedish twins: An application of latent growth models. *Experimental Aging Research, 28*, 407–433.

Reynolds, C. A., Finkel, D., McArdle, J. J., Gatz, M., Berg, S., & Pedersen, N. L. (2005). Quantitative genetic analysis of latent growth curve models of cognitive abilities in adulthood. *Developmental Psychology, 41*, 3–16.

Reynolds, C. A., Jansson, M., Gatz, M., & Pedersen, N. L. (2006a). Longitudinal change in memory performance associated with HTR2A polymorphism. *Neurobiology of Aging, 27*, 150–154.

Reynolds, C. A., Prince, J. A., Feuk, L., Gatz, M., & Pedersen, N. L. (2006b). Longitudinal memory performance during normal aging: Twin association models of APOE and other Alzheimer candidate genes. *Behavior Genetics, 36*, 185–194.

Rowe, D. C. (1994). *The limits of family influence: Genes, experience, and behavior*. New York: Guilford.

Rubinsztein, D. C., & Easton, D. F. (1999). Apolipoprotein E genetic variation and Alzheimer's disease: A meta-analysis. *Dementia and Geriatric Cognitive Disorders, 10*, 199–209.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review, 103*, 403–428.

Schaie, K. W. (1994). The course of intellectual development. *American Psychologist, 49*, 304–313.

Schaie, K. W. (1996). Intellectual development in adulthood. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging* (pp. 266–286). San Diego, CA, US: Academic Press, Inc.

Schofield, P. W., Tang, M., Marder, K., Bell, K., Dooneief, G., Chun, M., et al. (1997). Alzheimer's disease after remote head injury: an incidence study. *Journal of Neurology, Neurosurgery and Psychiatry, 62*, 119–124.

Sheline, Y. I., Mintun, M. A., Moerlein, S. M., & Snyder, A. Z. (2002). Greater loss of 5-HT(2A) receptors in midlife than in late life. *American Journal of Psychiatry, 159*, 430–435.

Silverman, J. M., Ciresi, G., Smith, C. J., Marin, D. B., & Schnaider-Beeri, M. (2005). Variability of familial risk of Alzheimer disease across the late life span. *Archives of General Psychiatry, 62*, 565–573.

Singer, T., Verhaeghen, P., Ghisletta, P., Lindenberger, U., & Baltes, P. B. (2003). The fate of cognition in very old age: Six-year longitudinal findings in the Berlin Aging Study (BASE). *Psychology and Aging, 18*, 318–331.

Small, B. J., Fratiglioni, L., von Strauss, E., & Backman, L. (2003). Terminal decline and cognitive performance in very old age: does cause of death matter? *Psychology and Aging, 18*, 193–202.

Small, B. J., Graves, A. B., McEvoy, C. L., Crawford, F. C., Mullan, M., & Mortimer, J. A. (2000). Is APOE–epsilon4 a risk factor for cognitive impairment in normal aging? *Neurology, 54*, 2082–2088.

Small, S. A., Stern, Y., Tang, M., & Mayeux, R. (1999). Selective decline in memory function among healthy elderly. *Neurology, 52*, 1392–1396.

Strittmatter, W. J., Saunders, A. M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G. S., et al. (1993). Apolipoprotein E: High-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proceedings of the National Academy of Sciences of the United States of America, 90*, 1977–1981.

Sundet, J. M., Tambs, K., Harris, J. R., Magnus, P., & Torjussen, T. M. (2005). Resolving the genetic and environmental sources of the correlation between height and intelligence: A study of nearly 2600 Norwegian male twin pairs. *Twin Research and Human Genetics, 8*(4), 307–311.

Swan, G. E., Carmelli, D., Reed, T., Harshfield, G. A., Fabsitz, R. R., & Eslinger, P. J. (1990). Heritability of cognitive performance in aging twins. The National Heart, Lung, and Blood Institute Twin Study. *Archives of Neurology, 47*, 259–262.

Swan, G. E., LaRue, A., Carmelli, D., Reed, T. E., & Fabsitz, R. R. (1992). Decline in cognitive performance in aging twins: Her-

itability and biobehavioral predictors from the National Heart, Lung, and Blood Institute Twin Study. *Archives of Neurology, 49*, 476–481.

Swan, G. E., Reed, T., Jack, L. M., Miller, B. L., Markee, T., Wolf, P. A., et al. (1999). Differential genetic influence for components of memory in aging adult twins. *Archives of Neurology, 56*, 1127–1132.

Takahashi, R. H., Nam, E. E., Edgar, M., & Gouras, G. K. (2002). Alzheimer beta-amyloid peptides: Normal and abnormal localization. *Histology and Histopathology, 17*, 239–246.

Tambs, K., Sundet, J. M., & Magnus, P. (1986). Genetic and environmental contributions to the covariation between the Wechsler Adult Intelligence Scale (WAIS) subtests: A study of twins. *Behavior Genetics, 16*, 475–491.

Tambs, K., Sundet, J.M., Magnus, P., & Berg, K. (1989). Genetic and environmental contributions to the covariance between occupational status, educational attainment, and IQ: A twin study. *Behavior Genetics, 19*, 209–222.

Tang, M. X., Maestre, G., Tsai, W. Y., Liu, X. H., Feng, L., Chung, W. Y., et al. (1996). Effect of age, ethnicity, and head injury on the association between APOE genotypes and Alzheimer's disease. *Annals of the New York Academy of Sciences, 802*, 6–15.

Teter, B., Xu P.-T., Gilbert, J. R., Roses, A. D., Galasko, D., & Cole, G. M. (2002). Defective neuronal sprouting by human apolipoprotein E4 is a gain-of-negative function. *Journal of Neuroscience Research, 68*, 331–336.

Tsai, S.-J., Yu, Y. W.-Y., Chen, T.-J., Chen, J.-Y., Liou, Y.-J., Chen, M.-C., et al. (2003). Association study of a functional catechol-*O*-methyltransferase-gene polymorphism and cognitive function in healthy females. *Neuroscience Letters, 338*, 123–126.

Warwick Daw, E., Payami, H., Nemens, E. J., Nochlin, D., Bird, T. D., Schellenberg, G. D., et al. (2000). The number of trait loci in late-onset Alzheimer disease. *American Journal of Human Genetics, 66*, 196–204.

Williams, G. V., Rao, S. G., & Goldman-Rakic, P. S. (2002). The physiological role of 5-HT2A receptors in working memory. *Journal of Neuroscience, 22*, 2843–2854.

Wilson, R. S., Beckett, L. A., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2003). Terminal decline in cognitive function. *Neurology, 60*, 1782–1787.

Wilson, R. S., Scherr, P. A., Hoganson, G., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2005). Early life socioeconomic status and late life risk of Alzheimer's disease. *Neuroepidemiology, 25*, 8–14.

Wilson, R. S., Schneider, J. A., Barnes, L. L., Beckett, L. A., Aggarwal, N. T., Cochran, E. J., et al. (2002). The apolipoprotein E epsilon 4 allele and decline in different cognitive systems during a 6-year period. *Archieves of Neurology, 59*, 1154–1160.