Chapter 4
Cognition in Middle Adulthood

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For purposes of this chapter, we define middle adulthood as the period between the ages of 40 and 60 years. We use the terms middle adulthood, midlife, and middle age interchangeably to represent this period. We first address some important general issues with respect to behavior genetic research on cognition in middle adulthood. Next, we review some of the extant empirical findings, focusing first on general cognitive ability and then on specific abilities. We present a seemingly disproportionate subset of the results from our Vietnam Era Twin Study of Aging (VETSA). The reason is simply that the large majority of behavior genetic studies have focused on younger or older individuals, whereas the VETSA is one of the very few studies with extensive midlife data.

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4.1 Key Issues

4.1.1 Midlife: An Understudied, but Important Transitional Period for Cognitive Aging

Finch (1991) noted that midlife was an understudied period in gerontological research. About a decade later, Bouchard and McGue (2003) pointed to the "extreme paucity" of genetic studies of general cognitive ability in adult twins. There are now some important behavior genetic studies of cognitive aging in adults, but the emphasis in those studies has been primarily on later life (see Chap. 5 for a review). Indeed, it can be said that behavior genetic research focusing on middle adulthood remains in its infancy. Although we do address some issues of change from early adulthood, we wished to focus primarily on cognitive function between the ages of 40 and 60 years in this chapter. However, only modest numbers of people in this age range have been included in the major twin studies of cognitive aging. For example, middle-aged groups in the Swedish Adoption Twin Study of Aging (SATSA) and Minnesota Twin Study of Adult Development and Aging (MTSADA) combined, comprised about 145 twin pairs with a mean age of about 60 (range 50–64; Finkel et al. 1995a).

When studying older adults, we need a baseline from which to gauge change. One could argue that young adulthood can provide that baseline, but that leaves at least two decades as a "black hole." Midlife provides a more proximal baseline for understanding later life cognitive changes. There is also growing evidence suggesting that treatments for dementia are ineffective because neuronal degeneration has already progressed too far by the time of intervention (Sperling et al. 2011). The National Institute on Aging-Alzheimer's Association workgroups have made mild cognitive impairment (MCI) and earlier preclinical stages of Alzheimer's disease priorities in order to better understand the transition to dementia (Albert et al. 2011; Sperling et al. 2011). Genetic factors are, of course, important determinants of Alzheimer's disease (Gatz et al. 2006; for a review see Chap. 7). Together, these factors argue for more intensive behavior genetic studies of cognitive function during middle adulthood.

4.1.2 Understanding Trajectories of Midlife Cognitive Aging

Middle adulthood is particularly relevant to the central question of when cognitive decline begins. The fact that mean level change for some cognitive functions tends to be small or absent until or just past late midlife (McArdle et al. 1998; Rönnlund et al. 2005; Schaie 2005) may give the impression that cognition in middle adulthood is of little interest in its own right. Longitudinal studies indicate linear declines in episodic memory from age 60, but there is also evidence of declines in processing speed (Finkel et al. 2005; Hertzog et al. 2003; Rönnlund et al. 2005; Schaie 1996) and spatial processing occurring earlier (Finkel et al. 2005). Working memory

and executive functions represent cognitive abilities that are very important for effective daily functioning, and they are also among the more age-sensitive cognitive domains (West 1996). As we will highlight throughout this chapter, despite their importance, these two domains have received little attention in behavior genetic studies of cognitive aging in middle-aged or older adults.

Some cross-sectional studies suggest that relatively linear declines in several cognitive abilities take place prior to age 60, beginning in young adulthood (Salthouse 2009). A key methodological issue with regard to these different views has been the idea that cross-sectional studies may overestimate age-related differences due to cohort effects, whereas longitudinal studies may underestimate age-related change due to retest effects. Although it was not a behavior genetic study, the Whitehall II study, which had the largest cohorts of middle-aged and older adults, did find significant cognitive declines over a 10-year period in both longitudinal and cross-sectional analyses of 5-year age cohorts ranging in age from 45 to 70 at baseline (Singh-Manoux et al. 2011). For example, there were longitudinal declines in reasoning, verbal fluency, and episodic memory ranging from 2.9–3.6% in men and 2.6–4.2% in women. There were also increases of 0.7–0.8% in vocabulary. All the changes were statistically significant. Cross-sectional comparisons in Whitehall II suggested declines for men that were similar to their longitudinal findings, but cross-sectional results suggested larger declines than longitudinal data for women. The demonstration of cognitive declines in the youngest age bracket (45–49) of the Whitehall II study argues strongly for cognitive change taking place as early as middle adulthood. The fact that practice effects have been observed even after 5 years (Rönnlund et al. 2005) makes the latter finding all the more striking because there was no adjustment for practice effects.

Adjusting for education had little impact on the longitudinal Whitehall II results, but it did substantially reduce the cross-sectional differences. Adjusting for education is a common approach to account for cohort differences, which presumably reflect, at least in part, educational differences. For example, the average educational attainment of individuals born before 1920 is lower than that for individuals born after 1950. On the other hand, it is worth noting that using educational attainment in this way has some serious limitations as can be seen in our study, the VETSA (Kremen et al. 2006). There were 1,237 middle-aged male twins almost all of whom were between the ages of 51 and 59 (four turned 60 just prior to coming to the laboratory) in wave 1 of the VETSA. We were in the relatively unique situation of having available actual general cognitive ability scores from early adulthood (at an average age of 20 years) for all VETSA participants. The Lothian and Aberdeen Birth Cohort studies (see Chap. 5) similarly had general cognitive data from age 11. Not surprisingly, the majority of VETSA participants had 12 years of formal education at the initial VETSA assessment when they averaged 55 years of age. As an illustration of the limitation of using education in this way, although this subset of VETSA participants all had the same amount of education, there was still substantial variability in their general cognitive ability scores at age 20 with scores ranging from the 10th to the 99th percentile.

The aforementioned studies suggest that without characterizing cognitive function in middle adulthood (i.e., before age 60), key points of transition may be missed. Moreover, non-twin studies show that even with little group mean change, some subgroups still do manifest significant changes. For example, Schaie et al. (2004) found that 15% of people in their early 40s to early 60s showed significant declines, primarily in executive, attention, and episodic memory functions. These subgroups are perhaps the most likely to be highly informative about risk and protective factors for cognitive aging. Divergent patterns of change after 55 have also been noted for working memory and inductive reasoning (Hertzog et al. 2003).

Another important construct with regard to cognitive trajectories is that of MCI. MCI is now generally considered to be the predementia stage of Alzheimer's disease (Albert et al. 2011) and may, therefore, be considered an important transition phase. Studies of MCI have focused on people who are 65 and older, but we have assessed multiple criteria sets for neuropsychologically defined MCI in the younger VETSA participants. To ensure that MCI classifications truly represented decline from prior levels of function, all definitions were based on scores adjusted for general cognitive ability measured at age 20, on average. To our knowledge, this is the youngest and the only middle-aged sample (adults in their 50s) to be systematically assessed for MCI. Our preliminary findings show that, as in studies of older adults, the prevalence of MCI varies dramatically depending on the definition. The heritability of MCI varied greatly as well. However, we did find that MCI can be identified in people this young. There was also partial validation for the diagnoses in that an index of hippocampal atrophy was greatest in participants with amnestic MCI (Jak et al. 2013). Ongoing follow-up assessments will be the key to determining the optimal definition of MCI. These preliminary findings further highlight the importance of further behavior genetic study of cognition in middle adulthood, and increased emphasis on individual or subgroup differences in level of performance and differences in cognitive trajectories. It could be possible that we were able to detect MCI in the middle-aged VETSA sample because, as suggested by some researchers (Roberts et al. 2012), men are more likely than women to develop MCI. However, in almost all studies cited by Roberts et al. and a review by Panza et al. (2005), there were no sex differences in incidence or prevalence of MCI.

4.1.3 Approaches to Cognitive Aging: Lumping Versus Splitting

As suggested by cross-sectional data (Salthouse 2009), aging-related changes in cognitive trajectories can affect both general ability (*g*) and specific cognitive abilities. Specific cognitive domains that appear to be most affected by aging are processing speed, executive function, and memory. The fact that *g* accounts for 40–50% of the variance in different cognitive measures (Deary et al. 2004) means a full understanding of cognitive aging will require a greater focus on specific cognitive abilities beyond *g*. In an early approach to this issue, Pedersen et al. (1994) showed that there were significant genetic influences on 12 of 13 cognitive measures that were independent of *g* in the SATSA.

With respect to specific cognitive abilities, behavior genetic studies of cognitive aging—particularly for middle adulthood—have been largely at the level of broad domains such as processing speed, memory, and spatial processing. Components of executive functions and working memory—which is closely related to executive function (Friedman et al. 2006)—are prime candidates because they are mediated by neural systems linked to the prefrontal cortex, the parenchymal region with the largest age-related shrinkage (Raz 2000). However, these functions have received very little attention in behavior genetic studies of middle-aged and older adults. In a nongenetic, longitudinal analysis covering ages 18–95, specific abilities accounted for 61 % of the variance in cognitive change for all ages; 33 % was accounted for by domain-specific change in the four domains that were examined (abstract reasoning, spatial processing, verbal episodic memory, and processing speed), and 28 % was accounted for by test-specific change in the 12 tests on which the domains were based (Tucker-Drob 2011). Because most of the variance is accounted for by specific, rather than global, abilities, we favor an approach that leans even more strongly toward further splitting. That includes extending studies even beyond test-specific variance to examine component processes *within* cognitive tests in order to learn which specific underlying processes may be accounting for age-related changes.

Tests within the same domain involve different cognitive processes, and even a single test always consists of multiple component cognitive processes. Experimental psychology and neuroscience-oriented approaches focus on relatively fine-grained component processes in order to understand how particular cognitive functions are carried out. It is our view that these approaches will be most useful for elucidating the determinants of good or poor performance because one goal of these approaches is to isolate the component processes. For example, spatial processing is a broad cognitive construct that can include several component processes linked to different brain pathways. The dorsal visual stream includes posterior parietal cortex and is responsible for object location and visual control of actions, whereas the ventral stream includes inferior temporal cortex and is responsible for visual perception and object recognition (Goodale and Milner 1992).

Factor analysis has been the major approach to identifying cognitive dimensions in behavior genetic studies of aging, but there are some important limitations to this approach. Components derived from factor analysis are typically still at a relatively broad level. In addition, factor analysis alone—without solid theory and evidence from studies of brain–behavior relationships—is insufficient for determining the subcomponents of cognitive functions or abilities. Suppose, for example, that one factor analyzes digit span, story recall, and a number of visual–spatial tasks. It is likely that digit span and story recall will load on a "memory" factor, but a wealth of neuroscientific evidence indicates that those tests are linked to different neural circuitry underlying different memory systems; digit span, a short-term/working memory test is more strongly associated with prefrontal circuitry, whereas story recall is more strongly associated with the hippocampus (Fuster 1995). Functional neuroimaging also demonstrates that elucidating specific components—even within a single test—is crucial for understanding brain and cognition. Without this level

of analysis, it is difficult to know what exactly accounts for good performance or for age-related declines.

In our view, an integrative approach that maps the twin method onto the cognitive neuroscience approach, which aims to isolate component cognitive processes, has powerful advantages. Genetic factors are clearly of importance for explaining individual differences in cognitive abilities (Bouchard and McGue 2003), but the breakdown of component processes at the phenotypic level will not necessarily be the same as it is at the genetic level. However, factor analysis of cognitive measures in behavior genetic studies of middle-aged and older adults are usually performed at the phenotypic level. The resulting phenotypic factors are then typically subjected to biometrical modeling. A somewhat different picture may emerge if a genetic factor analysis is conducted. In this chapter, we show some examples of this approach.

The emphasis in cognitive research has shifted quite a bit since the major twin studies of aging (SATSA and MTSADA) were begun. To their credit, the investigators on these studies have made very important contributions with limited sets of cognitive measures. Moreover, the need for both large samples and extensive measures is a substantial impediment to integrated twin-cognitive neuroscience studies. Greater effort is needed toward developing collaborative twin studies of aging that would include substantial numbers of middle-aged adults with at least a core set of the same cognitive and neuroimaging measures. Besides the issue of sample size, such efforts would require work to determine the best measures to be included.

4.1.4 Importance of Phenotype Definition/Refinement

Simply finding significant genetic influences for particular cognitive functions may seem uninteresting given the general rule of thumb that all human behavioral characteristics are heritable (Turkheimer 2000). However, another rule of thumb, the construct–measurement fallacy states that because a cognitive domain is heritable, it cannot be assumed that any measure within that domain will be heritable (Kremen and Lyons 2011). Almost all studies have found no, or virtually no, heritability for the Wisconsin Card Sorting Test (Kremen et al. 2007a). In the VETSA sample, the first trial of the California Verbal Learning Test (CVLT) was not heritable (see Table 4.1B). Surely, the executive function and memory domains tapped by these measures are influenced by genes as indicated by the heritability of other tests of these abilities, but these particular measures did not consistently manifest individual differences based on genetic factors. Thus, although all cognitive abilities may be heritable, not all measures of those abilities will necessarily show that heritability. We might refer to these as "fallible indicators" (Meehl 1977). So-called missing heritability is acknowledged as a serious problem for genetic association studies (Maher 2008), and inclusion of a cognitive phenotype that is not consistently found to be heritable in twin studies is only likely to compound the problem.

Behavior genetic studies—particularly multivariate twin analyses—are useful tools for refining phenotypes in cognitive aging studies. By separating out component processes with specific genetic influences from the overall score on a cognitive

Table 4.1 Heritability estimates (h^2) for individual cognitive tests assessed during midlife in VET Registry twins

Cognitive test	h^2	95% CI	Cognitive test	h^2	95% CI
A. *Earlier VET Registry Study: average age = 47.9 (Range: 41–58)*					
Verbal ability			*Short term memory*		
Word recognition (WRAT) (Kremen et al. 2007b)[a]	0.49	(0.28; 0.74)	Digit span forward (Kremen et al. 2008)[a]	0.22	(0.15; 0.65)
Executive functions			*Working memory*		
Tower of London execution speed (Kremen et al. 2009)[a]	0.32	(0.10; 0.58)	Reading span (Kremen et al. 2007b)[a]	0.49	(0.38; 0.58)
Tower of London attempts to complete (Kremen et al. 2009)[a]	0.29	(0.07; 0.56)	Digit transformation (Kremen et al. 2008)[a]	0.50	(0.41; 0.58)
Wisconsin Card Sorting Perseverations (Kremen et al. 2007a)			Non-spatial delayed alternation task (Kremen et al. 2011a)	0.25	(0.03; 0.45)
Wisconsin Card Sorting Categories (Kremen et al. 2007a)			Spatial delayed alternation task (Kremen et al. 2011a)	0.00	(0.00; 0.25)
B. *VETSA: average age = 55.4 (Range: 51–60)*					
General cognitive ability			*Working memory*		
Age 55 AFQT (Lyons et al. 2009)[a]	0.57	(0.42; 0.74)	Digit span backward	0.41	(0.14; 0.53)
Verbal ability			Spatial span backward	0.35	(0.09; 0.53)
WASI vocabulary	0.42	(0.22; 0.65)	Letter number sequencing	0.38	(0.13; 0.59)
Verbal memory			Letter number sequencing adjusted for digit span forward	0.28	(0.00; 0.42)
Logical memory immediate recall	0.52	(0.30; 0.59)			
Logical memory delayed recall	0.53	(0.34; 0.60)	AX-CPT AX errors (Kremen et al. 2011b)[a]	0.20	(0.01; 0.37)
CVLT-2 trial 1 recall	0.00	(0.00; 0.21)	AX-CPT BX errors (Kremen et al. 2011b)[a]	0.28	(0.03; 0.40)
CVLT-2 trial 2 recall	0.17	(0.00; 0.39)	*Inhibitory control*		
CVLT-2 trial 3 recall	0.15	(0.00; 0.39)	Stroop color/word condition	0.49	(0.25; 0.63)
CVLT-2 trial 4 recall	0.37	(0.17; 0.45)	Stroop color/word interference	0.23	(0.00; 0.39)

Table 4.1 (continued)

Cognitive test	h^2	95% CI	Cognitive test	h^2	95% CI
B. *VETSA: average age = 55.4 (Range: 51–60)* (continued)					
CVLT-2 trial 5 recall	0.29	(0.00; 0.43)	AX-CPT AY errors (Kremen et al. 2011b)[a]	0.24	(0.19; 0.39)
CVLT-2 total trials 1–5 (Panizzon et al. 2011)[a]	0.36	(0.10; 0.55)	*Set-shifting*		
CVLT-2 short delay free recall (Panizzon et al. 2011)[a]	0.24	(0.05; 0.48)	D-KEFS Trail Making (condition 4) (Vasilopoulos et al. 2012)[a]	0.62	(0.53; 0.72)
CVLT-2 long delay free recall (Panizzon et al. 2011)[a]	0.35	(0.10; 0.56)	D-KEFS Trail Making (condition 4 adjusted for condition 2)	0.13	(0.00; 0.42)
Visual spatial memory					
Visual reproductions immediate recall	0.38	(0.12; 0.54)	Category switching total correct	0.31	(0.10; 0.40)
Visual reproductions delayed recall	0.42	(0.24; 0.50)	Category switching adjusted for category fluency	0.20	(0.00; 0.29)
Processing speed					
D-KEFS Trail Making (condition 2) (Vasilopoulos et al. 2012)[a]	0.34	(0.26; 0.43)	Category switching accuracy	0.19	(0.00; 0.28)
D-KEFS Trail Making (condition 3) (Vasilopoulos et al. 2012)[a]	0.43	(0.34; 0.53)	*Abstract reasoning*		
Stroop word condition	0.65	(0.54; 0.70)	WASI matrix reasoning	0.43	(0.20; 0.62)
Stroop color condition	0.60	(0.46; 0.66)	*Verbal fluency*		
Short term memory			Letter fluency total correct	0.62	(0.49; 0.68)
Digit span forward	0.51	(0.27; 0.63)	Category fluency total correct	0.54	(0.43; 0.61)
Spatial span forward	0.44	(0.27; 0.52)	*Visual spatial ability*		
			Card/mental rotation	0.46	(0.23; 0.62)
			Hidden figures	0.72	(0.57; 0.77)

VET Vietnam Era Twin, *CI* confidence interval, *VETSA* Vietnam Era Twin Study of Aging, *WASI* Wechsler Abbreviated Scale of Intelligence, *AFQT* (Armed Forces Qualification Test)

[a] Results based on multivariate analyses

test, these analyses essentially reduce the "genetic signal-to-noise ratio." Doing so may increase the likelihood of positive findings in genetic association studies. In addition, the genetic underpinnings of the particular cognitive processes that are most important for cognitive aging may be different from what is observed at the phenotypic level. This integrative behavior genetic and neuroscience-oriented approach has been utilized in twin studies of children or very young adults (e.g., Ando et al. 2001; Luciano et al. 2001), but rarely has it been applied to middle-aged or older adults.

4.2 Empirical Findings on Midlife Cognition

4.2.1 Studies of General Cognitive Ability

In this section, we review findings in the domain of general cognitive ability. Several nongenetic studies have demonstrated considerable stability for general cognitive ability during the period from youth through middle to later adulthood. In their review, Deary et al. (2000) concluded that "the genetic and environmental sources of this remarkable stability of individual differences in human intelligence must be sought." (p. 54). As noted, however, most of the relevant studies of cognitive ability have been based on child and adolescent samples.

4.2.1.1 Heritability of General Cognitive Ability (g)

In the SATSA, Pedersen et al. (2002, 1992) reported that the heritability for a psychometrically derived *g* variable was 0.81. Using hierarchical multiple regression, they found that heritability did not change as a function of age between the ages of 50 and 84 years. In another study of the SATSA sample using a cohort sequential design, Finkel and McGue (1998) observed a significant decrease in the genetic variance for general cognitive ability measured on three occasions separated by 3-year intervals. The younger cohorts in their study ranged from 41 to 68 years and their older cohorts ranged from 62 to 84 years. The heritability of their *g* measure decreased from about 0.80 for the three younger cohorts to about 0.60 for the three older cohorts. The longest longitudinal interval between assessments was 6 years.

Finkel et al. (1995b) compared subsamples from the SATSA and the MTSADA. Using a cross-sectional approach, they divided the samples into three age groups, two of which are relevant to our focus on development from young adulthood to late middle age (younger adults were 27–50 years; middle-aged adults were 50–65 years). Utilizing principal-components factor analysis to derive a *g* factor, they found a heritability of 0.81 for both age groups of the MTSADA and SATSA groups. The data from MTSADA and SATSA suggested no change in the heritability of cognitive ability during the period from young adulthood to late middle age.

Posthuma et al. (2001a) used cross-sectional data from an extended twin design study from the Netherlands Twin Registry (Boomsma 1998). They reported

that heritabilities did not differ between cohorts with mean ages of 26.2 and 50.4 years. For the combined sample, heritability was 0.85 for Verbal IQ and 0.69 for Performance IQ. Several other papers utilized samples that overlapped with those in the Posthuma et al. (2001a) paper. Both Brans et al. (2010) and Hulshoff Pol et al. (2006) studied samples of twins and their siblings drawn from a cohort at the University Medical Centre Utrecht (Baaré et al. 2001) and the Netherlands Twin Registry (Boomsma 1998). The mean age in the Hulshoff Pol paper was about 37 years (range not provided). The heritability of verbal IQ was 0.84 and the heritability of Performance IQ was 0.67. Brans et al. (2010) studied twins and siblings (mean age = 29.6 years ± 7.5 years). The heritability of Full Scale IQ was 0.86 (95% confidence interval [CI]: 0.75; 0.92).

Some studies have investigated samples that might be considered to be on the border between late middle age and old age. For example, Plomin et al. (1994) studied a sample of older twins on two occasions separated by 3 years (mean ages 64 and 67). They observed a heritability of about 0.80 for general cognitive ability at both times. In the VETSA, which is the only longitudinal twin study focused exclusively on midlife, the heritability of general cognitive ability was 0.49 at about age 20 years and 0.57 at about age 55 years (Lyons et al. 2009). This increase in heritability was not statistically significant.

There is something of a consensus that there is an increase in the influence of genetic factors with age, and that the influence of shared environmental factors decreases with age, at least until middle age (McCartney et al. 1990; McGue et al. 1993; Plomin and Spinath 2004). Haworth et al. (2010) analyzed cross-sectional data from a combined sample of 11,000 twin pairs drawn from four countries. Heritability of general cognitive ability (based on different measures in different studies) increased linearly from childhood to late adolescence ($h^2 = 0.41$ at age 9 years; $h^2 = 0.55$ at age 12 years; and $h^2 = 0.66$ at age 17 years). As suggested by Haworth et al., one mechanism that probably influences increasing heritability of cognitive ability is gene–environment (GE) correlation. GE correlation refers to differential exposure to environmental conditions depending on one's genotype. Passive GE correlation (e.g., shared home environments determined by parents' genetic propensities that may be conducive to intellectual development) may be more of a factor in childhood. Active GE correlation (e.g., genetic propensities lead one to seek out individual-specific environments that may be more conducive to intellectual development) may be more of a factor in adulthood.

Vogler (2006) suggested that the heritability of cognitive functioning during adulthood seems to be relatively stable over time with some decline in heritability in older cohorts, and the results of a number of studies are consistent with Vogler's conclusion (Finkel et al. 1995b; Finkel et al. 1998; Lyons et al. 2009; McGue and Christensen 2002; Posthuma et al. 2001a). Reynolds et al. (2005) administered cognitive assessments at ages 50, 60, 70, and 80 years and observed an inverted U-shaped pattern for genetic variance; that is, genetic variance increased somewhat from age 50 to 60 followed by a decrease. Among studies of adults, the limited number of studies that utilized a true longitudinal design, the short time intervals utilized, and the preponderance of subjects older than 65 years preclude drawing

strong conclusions about the issue of whether the magnitudes of genetic and environmental influences change over the course of middle adulthood. The VETSA results from age 20 to 55 did indicate just a slight, but nonsignificant increase in genetic variance, but we are unaware of any other longitudinal studies in this age range.

4.2.1.2 Genetic or Environmental Influences on Change in General Cognitive Ability

Several studies have investigated the extent to which genetic factors contribute to stability and change of cognitive ability during adulthood. McGue and Christensen (2002) observed a heritability of 0.76 for the mean score on their cognitive measures. However, they found a heritability of only 0.06 for the linear change in cognitive scores from four testing occasions over a 6-year period. Plomin et al. (1994) found a phenotypic stability of 0.92 over a test/retest interval of 3 years, with genetic factors accounting for almost 90% of the stability. Reynolds et al.'s (2005) *g* measure demonstrated a nonsignificant heritability of linear change of 0.01, whereas nonshared environmental influences explained 99% of the variance. The acceleration of cognitive change over time or "change in the change" (the quadratic trend) had a heritability of 0.43 with a contribution from the nonshared environment of 0.57. In the VETSA, stability in general cognitive ability primarily reflected genetic and shared environmental influences; 22.4% of the correlation between age 20 and 55 performance was due to shared environmental factors, 71.3% was due to genetic factors, and 6.3% due to nonshared environments. Largely (98.3%), changes were due to aspects of the environment, primarily aspects that were not shared by the twins (Lyons et al. 2009).

Longitudinal twin data are required to determine the extent to which the same or different genetic influences are operating during different developmental periods. Several studies have addressed this issue during childhood and adolescence (summarized in Lyons et al. 2009). However, VETSA is unique in addressing this question during the period from young adulthood to late middle age. In VETSA, the genetic correlation for general cognitive ability from early adulthood to late middle age was 1.0, which indicates that the same genes were operating at both times (Lyons et al. 2009).

4.2.1.3 Molecular Genetic Studies

Molecular genetic approaches are increasingly being applied to the investigation of behavioral and psychological traits. Although our focus is primarily on twin studies, we do touch briefly on some molecular genetic studies. Deary and colleagues (2010b) and Sabb et al. (2009) reviewed the published reports of individual genes that influence intelligence or general cognitive ability. Although a number of studies have reported individual genes that contribute to cognitive ability (e.g., Pan et al. 2011; Zhang et al. 2010), Deary et al. concluded that molecular genetic studies have

failed so far to produce replicable findings that identify individual genes that influence intelligence. The conclusion of the Sabb et al. review was that the variance in intelligence explained by specific genes that have thus far been identified is only about 5.5%, leaving most of individual sources of genetic influence unidentified.

A recent report by Davies and colleagues (2011) illustrates an approach that applies molecular genetic methods to assess the total contribution of individual genetic markers to general cognitive ability without specifying particular functional genetic variants presumed to be responsible for the observed associations. This approach, based on the premise that for traits that are likely to be highly polygenic, the influence of many genes, each of small effect, will be missed if stringent significance levels are required for each single nucleotide polymorphism (SNP). This approach had been successfully applied to height data (Yang et al. 2010). Davies et al. (2011) carried out a genome-wide SNP analysis on a sample of 3,511 unrelated adults. They had extensive phenotypic information for cognitive functioning in their participants. They created measures representing crystallized and fluid intelligence. They found that linkage disequilibrium between the examined SNPs and genetic variants that accounted for variation in the cognitive measures explained 40% of the variation among individuals for crystallized intelligence and 51% for fluid intelligence. They concluded that their estimates represent a lower bound for the actual heritability of these traits. They also concluded, reflecting an emerging consensus, that the very substantial genetic influence on general cognitive ability in all likelihood reflects the actions of a very large number of genes, each with small effect.

Deary et al. (2012) were the first to apply the same approach to a bivariate analysis in which they examined genetic influences on general cognitive ability measures during childhood and late life. Their conclusion was that some genetic variants influencing *g* in old age are different from those operating during childhood. However, the evidence for their conclusion is ambiguous because the genetic correlation they reported based on the same measure in childhood and old age was not significantly different from 1.0. Therefore, it may well be that the same genes were operating on both occasions as was the case from early adulthood to late middle age in the VETSA data. Resolution of this important issue will require further study.

4.2.2 Studies of Specific Cognitive Abilities

In this section, we review some of the findings about specific cognitive abilities or cognitive domains. Not all cognitive abilities appear to be equally sensitive to aging, and they may not necessarily follow the same pattern as measures of general cognitive ability. We think that it is necessary to elucidate more specific abilities in order to understand genetic and environmental influences on cognitive aging. As noted, there is little behavior genetics research on specific cognitive abilities, especially component processes of specific abilities, in middle adulthood and beyond. As the VETSA is one of the few behavior genetic studies with a detailed cognitive assessment in middle adulthood, we have included a Table (Table 4.1B) of heritability estimates for many of the cognitive measures from that study.

4.2.2.1 Verbal Ability

Cross-sectional twin studies in adulthood have shown moderate-to-high heritability of verbal ability, ranging from 0.52 to 0.85, in middle-aged and older adults (e.g., Finkel et al. 1995b; Pedersen et al. 1992; Posthuma et al. 2001a; Reynolds et al. 2005). Verbal abilities show relatively little change in middle adulthood and old age, and what change there is appears to be largely due to environmental factors (Reynolds et al. 2005). Verbal (letter and category) fluency is a more age-sensitive verbal ability, particularly with regard to risk for Alzheimer's disease. However, measures of verbal fluency are essentially absent from behavior genetic studies of cognition. Letter and category fluency have been found to have moderate-to-high heritability in the VETSA (0.62 and 0.54, respectively; see Table 4.1B).

4.2.2.2 Visual–Spatial Ability

High heritability estimates have typically been found for spatial abilities, ranging from 0.60 to 0.90 in SATSA and MTSADA (Finkel et al. 1995b; Pedersen et al. 1992; Reynolds et al. 2005). In the VETSA, Hidden figures was the most highly heritable individual cognitive test ($h^2 = 0.72$; see Table 4.1B); however, this test may include a strong executive component. Visual–spatial abilities warrant greater study. They are often more susceptible to aging than most verbal abilities, and there is also evidence for significant genetic influences on change in visual–spatial abilities over time, including a substantial quadratic component (Reynolds et al. 2005).

4.2.2.3 Episodic Memory

The construct of episodic (declarative) memory—involving recollection of facts and events—comprises multiple processes such as attention, encoding, learning, storage, and recall both immediately and after delay. These processes may occur in different modalities as well (e.g., verbal or visual). Genetic and environmental influences on memory in studies of aging have largely examined episodic memory at the broad domain level, so that these component processes and their interrelationships have seldom been examined, particularly in middle-aged adults.

Episodic memory (based on immediate recall) is moderately heritable during adulthood. SATSA participants were divided into young adult, middle-aged (mean age = 59 [range 50–64]), and older. There were similar age groups in the MTSADA: young adult, middle-aged (mean age = 61 [range 50–64]); and older (Finkel et al. 1995a). Heritabilities for memory in the SATSA middle-age group were 0.50 (Thurstone picture memory [visual]) and 0.40 (Names and faces [visual–verbal]). Heritabilities in the MTSADA were 0.63 for visual–spatial memory (Wechsler visual reproductions) and 0.56 for verbal memory (Wechsler logical memory).

As seen in Table 4.1B, heritabilities of several episodic memory measures were examined in the VETSA and in an earlier study of twins from the Vietnam Era Twin Registry. VETSA participants had a mean age of 55 (range: 51–60), whereas the

latter study included 693 participants with a mean age of 48 years (range: 41–58). About 25 % of the VETSA participants also participated in the earlier study. The list of measures in the table is not complete because analyses have not been completed for all measures. At age 55, both verbal and spatial episodic memory abilities appear to be moderately heritable. Most of the more commonly used measures were in the 0.30–0.50 range. However, note that several individual CVLT trials were not significantly heritable, particularly trial 1, which is considered to be more of an auditory attention measure and one on which examinees are often a bit overwhelmed (Delis et al. 2000; See also section 4.2.2.4.).

Only a few studies have included multivariate genetic analyses of different memory abilities. In both the MTSADA and SATSA, heritabilities of memory measures were similar in all age groups so they were combined in multivariate genetic analyses (Finkel et al. 1995a). In both studies, there was common memory factor—which included digit span (a short-term/working memory measure)—with a very high heritability of 0.83. All the MTSADA memory measures showed significant levels of residual genetic variance, i.e., genetic variance that was test-specific. Only one of the SATSA measures (digit span) had significant residual genetic variance. The findings indicated that for logical memories (story recall) and visual reproductions (figure recall) some genetic influences were specific to each of these different modalities. Such findings suggest that significant findings from genome-wide genetic association studies of memory could be obscured by combining verbal and visual–spatial memory tests, or by trying to replicate results across modalities.

Singer et al. (2006) evaluated associations among general visual–spatial memory, spatial working memory, inspection time, reaction time, and general verbal ability in adult female twins. Four visual memory tests were consolidated into a single visual memory factor. General visual memory and spatial working memory had a correlation of 0.42. Heritability estimates were 0.57 for general visual memory and 0.31 for spatial working memory. The genetic correlation between the two was 0.80. Age was significantly negatively associated with both general visual memory ($r = -0.42$) and spatial working memory ($r = -0.43$). The average age in this study was 55 years, but with an age range of 18–76, it is unclear what the results tell us about middle adulthood. Several studies with very wide age ranges have an average age in the midlife range, but caution should be exercised in making strong inferences about middle adulthood based on those samples. On the other hand, the heritability estimate for visual memory in this study of women was very similar to the estimate in the all-male VETSA sample.

Swan et al. (1999) examined genetic and environmental influences on memory components using the CVLT in older adults (mean age = 71.8 years; SD = 2.9). After factor analyzing CVLT measures at the phenotypic level and then examining genetic and environmental influences on the phenotypic factors, they found a general learning and memory factor. In the VETSA, the genetic architecture of CVLT-II verbal learning, short- and long-delay free recall was assessed in almost 1,200 male twins in their fifties (Panizzon et al. 2011). Learning was defined as the total words recalled across the five learning trials. Because variation in delayed recall impairment is a cardinal symptom of Alzheimer's disease, delayed recall might be influenced by

some genetic factors distinct from the other memory component processes. Thus, the individual measures were subjected to a multivariate genetic analysis. A higher-order latent genetic factor with a heritability of 0.36 influenced variation in all three measures; however, there were additional specific genetic influences that accounted for approximately 10% of the overall variance in learning. Both learning and free recall involve storage and retrieval, but acquisition is not involved in free recall because no information is presented. Only the learning trials involve acquisition of presented information. Consequently, these results suggest that the genetic influences specific to the learning trials are genetic influences that are specific to acquisition processes in memory. Thus, in genetic studies, a composite of immediate and delayed recall may be useful, but it is probably best to examine learning measures separately. Ongoing follow-up assessments will be needed to determine if these processes are differentially affected by aging. It is also possible that there could be some different genetic influences on short- and long-delayed recall in later life.

Longitudinal studies of episodic memory that include middle adulthood are rare. There were linear declines in visual–spatial episodic memory (Thurstone's picture memory) over time in SATSA twins such that declines from age 50–60 were similar to declines from age 80–90 (about 4 percentage points per decade; Finkel et al. 2003). Men had greater variability in change than women, but results were mixed with regard to sex differences in the average amount of decline. Latent growth curve analysis showed that the heritability of linear change over time in this memory measure was only 0.06, and the contribution of shared environment was 0.53 (Reynolds et al. 2005). However, the quadratic trend for accelerated decline was highly heritable ($h^2 = 0.70$). Thus, visual memory declines influenced primarily by environmental factors were observed during late midlife. There was also genetically influenced accelerated change that most likely occurred later in life.

Genetic influences on memory and acceleration of changes in the composite (verbal, visual, digit span) memory measure in the SATSA were evenly split between genetic influences that were shared with, and independent of processing speed (Finkel et al. 2005). Finkel et al. (2007) then found evidence to support the notion that processing speed was a leading indicator of age changes in memory. Much work is still needed with respect to uncovering the specific genetic and environmental mechanisms—including brain changes—that underlie the relationship between processing speed and different components of memory.

In summary, there needs to be more focus on subgroups of people who may experience episodic memory decline during middle adulthood. Behavior genetic studies also need to examine possible leading indicators of change in episodic memory other than processing speed. Finally, further investigation of the genetic and environmental influences on specific component processes is needed. For example, the finding of genetic influences specific to acquisition as opposed to retrieval and recall (Panizzon et al. 2011) calls for further study of which specific memory processes may account for age-related changes.

4.2.2.4 Apolipoprotein E (*APOE*) and Episodic Memory

The *APOE* gene is certainly not the only gene that is important for episodic memory, but it is singled out here because of the importance of the *APOE*-ε4 allele in risk for Alzheimer's disease (Farrer et al. 1997). In nonpathological aging, some of its effects appear to be independent of risk for Alzheimer's disease (Deary et al. 2002). Meta-analyses indicate that the ε4 allele does affect normal cognitive aging, but findings have been mixed as to whether it is associated with memory deficits in middle adulthood or whether the effects appear primarily in later life (Small et al. 2004; Wisdom et al. 2011). Some studies have shown episodic memory deficits in middle-aged ε4 carriers (e.g., under 60 years of age; Flory et al. 2000; Schultz et al. 2008), but others did not find an effect in individuals under 65 (Jorm et al. 2007). A negative finding was also reported in 70-year-old adults (Luciano et al. 2009). Based on the VETSA data (see Table 4.1B), CVLT trial 1 was not heritable. Because it was the measure used in the study of Jorm et al., one would indeed predict their negative finding. Thinning of prefrontal cortex has been associated with the *APOE*-ε4 allele in middle-aged men (Fennema-Notestine et al. 2011), but this effect appeared to precede cognitive differences. Not all ε4 carriers are expected to develop dementia, and it may be that subtle effects in middle age are missed because only a subgroup is affected. Also, although it is important in risk for Alzheimer's disease, *APOE* still accounts for only a small proportion of the variance in Alzheimer's disease.

Not taking other factors into account may also obscure the relatively subtle differences that may be present in nondemented middle-aged individuals. Interactions with other factors, including other genes, may obscure *APOE* effects in middle adulthood. We found verbal memory deficits in ε4 carriers in the first 626 VETSA participants (Schultz et al. 2008), but that finding did not hold up in the full sample of 1,237. However, based on an animal model (Raber et al. 2002), we predicted that protective effects of androgens would result in an *APOE* genotype × testosterone interaction. We did observe such an interaction; smaller hippocampal volumes were observed only in those with both *APOE*-ε4 and low testosterone (Panizzon et al. 2010). The same pattern was found for verbal memory based on Wechsler logical memories. Interestingly, there was no main effect of *APOE* genotype in analyses of *APOE* alone, but the main effect of *APOE* became significant after testosterone was included in the models.

APOE is a cholesterol transporter that can affect brain lipid homeostasis (Poirier 2003). Testosterone is synthesized from cholesterol through a series of steps, and it affects androgen receptor function. The hippocampus is rich in androgen receptors in both men and women and the ε4 allele is associated with reducing the binding of testosterone to androgen receptors (Panizzon et al. 2010; Raber et al. 2002). Thus, having an ε4 allele could lead to reduced efficiency of hippocampal androgen receptors and increased risk for memory impairments. Testosterone declines with age in both men and women beginning in one's thirties, and these processes may have a greater impact in those with greater testosterone declines (Panizzon et al. 2010). It is uncertain whether this pattern exists in women, but testosterone levels have been

positively correlated with verbal memory in older women (Wolf and Krischbaum 2001).

4.2.2.5 Short-Term and Working Memory

Working memory represents the ability to temporarily store and process information for future goals (Baddeley 1992). Thus, it comprises processes involving short-term memory (storage) and executive functions. The processes of maintenance and manipulation of information in short-term memory are sometimes referred to as working memory; however, we refer to maintenance alone (e.g., digits forward) as short-term memory and we use the term working memory to refer to processes involving manipulation or processing of information in short-term memory. In contrast to hippocampal-dependent episodic memory, there is a large literature showing that prefrontal cortical regions play a central role in neural systems underlying working memory (Fuster 1995). For these reasons, we think it is best to avoid lumping short-term and working memory measures with episodic memory measures. Even if they go together in a factor analysis, that should not outweigh what is known about brain and memory. Consider the well-known case of H.M. After bilateral medial temporal excision he could not form new (episodic) memories, but his digit span performance remained intact (Corkin 2002). On the other hand, genetic influences that are unique to either episodic or working memory might be found in a genetic factor analysis even if phenotypic factor analysis shows only a single factor.

Short-term/working memory tasks vary substantially across studies and heritability estimates range from 0.00 to 0.65. Digit span, either forward or backward, tends to be moderately heritable in middle adulthood, generally ranging from about 0.40 to 0.65 (Table 4.1A, B and Finkel et al. 1995a; Karlsgodt et al. 2010). For the most part, its heritability appears to be similar in young and middle adulthood (Finkel et al. 1995a). Similar heritabilities have been found for spatial span and letter–number sequencing (Table 4.1B and Karlsgodt et al. 2010), and Posthuma et al. (2003) found a heritability of 0.65 for a composite arithmetic and letter–number sequencing measure. In contrast, variants of classic spatial and nonspatial delayed response or delayed alternation tasks appear to have little or no heritability; estimates ranged from 0.00 to 0.25 (Table 4.1A and Karlsgodt et al. 2010; Kremen et al. 2011a).

As already noted, given close links between working memory and executive functions, there is a strong need to elucidate executive and other components of working memory beyond individual tests. Almost all behavior genetic studies of this kind have been conducted in children or very young adults (e.g., Ando et al. 2001; Friedman et al. 2008). Such studies are needed in middle and later adulthood because non-twin studies indicate that these functions are among the more susceptible to age effects, there is substantial age-related prefrontal shrinkage relative to other parenchymal regions, and these functions are important for successful daily functioning.

A study of young adults (average age 19.9 years) decomposed the genetic structure of spatial and verbal memory in relation to general verbal and visual ability using

rotation-arrow and verification-word tasks (Ando et al. 2001). These tasks could be subdivided into spatial or verbal storage, and spatial or verbal executive efficiency functions. Heritabilities were 0.43 for the verbal executive and 0.49 for the spatial executive components. The best fitting model indicated multiple sources of genetic influences on the four functions including a common factor, two modality-specific factors (verbal and spatial), and a storage-specific factor that explained a significant amount of the variance (11–43 %). Genetic influences specific to the verbal and visual working memory storage components were also identified.

As described earlier (section 4.2.2.3), the spatial working memory measure of Singer et al. (2006) had a heritability of 0.31. Its correlation with general visual memory was 0.42, and 0.16 with general verbal ability; it had little or no correlation with processing speed (e.g., *r* with inspection time = 0.00). The observed associations were largely due to shared genetic influences, but they also clearly indicate genetic influences that were specific to spatial working memory. Again, as noted earlier, given the age range of 18–76, it is difficult to know how to interpret these findings with respect to middle adulthood.

A series of investigations into working memory were conducted in Vietnam Era Twin Registry twins (average age 48 years; range 41–58). The approach taken was not to focus simply on measures that might be associated with working memory, but to include the simpler abilities that comprise more basic cognitive components of a more complex working memory test. Kremen et al. (2007b) examined overlap between short-term memory (digits forward), reading ability (word recognition), and verbal working memory (reading span). Overall heritabilities were 0.27 for digits forward, 0.51 for reading, and 0.52 for reading span. A common latent phenotype explained all the genetic influences on reading and digits forward, but there were specific genetic influences only on reading span. The interpretation was that the specific genetic influences must reflect the executive component of reading span, i.e., the dual processing required for simultaneously reading aloud and holding some element in memory.

Verbal working memory was assessed in the same sample using a digit transformation task in which participants heard four digits and after a pause were instructed to add 3 or 4 to each digit. Heritabilities of add-3 and add-4 were roughly double the heritability of storage only (digits forward). The additional executive function demands of the add-3 or add-4 tasks (i.e., both storage and manipulation) appeared to increase the variance of individual genetic differences from 25 % for digits forward to 48 % and 53 % for the digit transformation scores. A two-factor model suggested the possibility of a second set of genetic factors specifically influencing the executive (manipulation) component. These results suggested that new genetic influences might come into play if demand continues to increase beyond a certain threshold, a threshold that may change with task difficulty and with age. Together, these studies suggest that, in part, there are genetic influences that are specific to the executive components of working memory, and those are likely to be the most age-sensitive processes.

In summary, measures of working memory have only partial genetic overlap with episodic memory, processing speed, or general cognitive ability, suggesting

the presence of some distinct underlying influences. Separating executive components from other abilities that affect performance on working memory tasks also appears to be important. There were no genetic influences on change over time in digit span performance in the SATSA (Reynolds et al. 2005), but it is important to remember that different working memory measures tap different processes. To our knowledge, there are no other studies that examine the role of genetic and environmental influences on age-related change or age differences in working memory during adulthood despite the fact that performance on most working memory tasks decreases with age. A few functional MRI twin studies in young adults have shown heritable activation in prefrontal and other brain regions using Sternberg task and n-back working memory tasks (Blokland et al. 2008; Koten et al. 2009). In their extended pedigree study with a very wide age range, Karlsgodt et al. (2010) found a genetic correlation of 0.59 between spatial delayed response and integrity of the superior longitudinal fasciculus, which connects frontal and parietal cortices. These studies further support the value of more extensive examination of working memory and prefrontal cortex in behavior genetics studies of cognitive aging. The VETSA project has begun work along these lines in middle-age adults (see section 4.2.2.7).

4.2.2.6 Executive Function

Executive functions refer to cognitive control processes that help to integrate more simple functions by regulating thinking and behavior. They include planning, organization, shifting mental set (cognitive flexibility), and inhibitory control (resistance to interfering, task-irrelevant stimuli). Working memory is closely linked to many executive functions. For example, one well-known approach includes working memory among three major executive functions: (1) mental set shifting, (2) updating and monitoring working memory representations, and (3) inhibition of prepotent responses (Miyake et al. 2000). Thus, some tests discussed in this section include working memory components and the decision on whether to include them in this or the working memory section (4.2.2.5) is necessarily somewhat arbitrary. One such test is the Wisconsin Card Sorting Test, a measure of executive function that requires set shifting, but also has a strong working memory updating component. Review of a handful of studies estimating heritability of this test showed that it was almost always at or near zero (Chou et al. 2009; Kremen et al. 2007a). Although it is a classic executive function test, twin studies have thus shown that it is unlikely to be useful for genetic association studies of executive function.

Kremen et al. (2009) examined the genetic architecture of the Tower of London test, a measure of planning and problem-solving in VET Registry twins (mean age = 48 years; Table 4.1A). Interestingly, even though phenotypic analyses revealed only one general factor, the best fitting genetic model indicated two correlated genetic factors: speed and efficiency. Genetic influences accounted for 38% of the variance in the six Tower of London measures.

A major theory of the cause of age-related cognitive declines focuses on reduced efficiency of the executive function of inhibitory control or response inhibition

(Hasher and Zacks 1988). Barkley (1997) distinguished three interrelated processes believed to constitute response inhibition: (1) inhibiting a prepotent response, (2) stopping an ongoing response, and (3) interference control. The Stroop color-word task has a condition called "interfernce" but it primarily involves inhibition of a prepotent response. Johnson et al. (2003) found that genetic influences accounted for 54% of the variance in color-word scores, and 35% of variance in the Stroop interference condition. Color-word scores were correlated −0.33 with age in their sample, which ranged in age from under 30 to over 70. Correlations of interference with age were not reported, but color-word and interference were highly correlated. Interestingly, color-word performance tended to increase with age until about 60 and then decline, suggesting that late middle adulthood may be a key transition period. In the mostly younger sample (mean age=24 years) of Taylor (2007), heritability was 0.57 for color-word performance but only 0.17 for interference. In the VETSA, heritability of the color-word performance was 0.49, and heritability of the interference score was 0.23. The latter two heritability estimates for Stroop interference did not reach statistical significance, the cross-sectional results from all these studies suggest that heritability of Stroop color-word and interference control is consistent from young to late adulthood. However, the age-related performance differences reported by Johnson et al. suggest that ongoing follow-up of the VETSA sample may capture a key transition period. The extent to which expected declines after age 60 may be due to genetic or environmental influences remains to be seen.

Tests of executive function always measure the complex executive processes along with the more simple processes that underlie them. Performance on these processes is also likely to be genetically correlated. Thus, adjusting the more complex function for the more simple ones to isolate the executive component may run the risk of removing too much of the genetic variance. It appears that this is what happened in the case of Stroop interference and adjusted set-shifting measures in the VETSA (see Table 4.1B). One strategy for addressing this problem may be to utilize multivariate twin analysis. Vasilopoulos et al. (2012) used this approach to examine the Delis-Kaplan Executive Function System Trail Making test. Conditions included: visual search ($h^2=0.35$), number sequencing ($h^2=0.34$), letter sequencing ($h^2=0.43$), and letter–number switching ($h^2=0.62$). There was a common genetic factor, and the heritabilities of number and letter sequencing conditions (processing speed and sequencing) were each completely explained by the common genetic factor. However, a significant 21% of the genetic variance in set shifting (switching condition) was accounted for by measure-specific genetic influences that were independent of the common factor. As seen in Table 4.1B, adjusting the Trails set-shifting condition for the nonswitching conditions yielded a lower and nonsignificant heritability, but the multivariate analysis strongly suggested genetic influences specific to set-shifting ability. Like previous phenotypic factor analytic studies, a phenotypic factor analysis in this study resulted in only one factor.

Neuropsychologists have long considered set shifting to be a key executive function and the inability to show a separate factor has been somewhat puzzling. There was only one latent factor in the twin analysis but the twin method was still able to show specific genetic influences on set shifting, consistent with its being a different

cognitive function. For genetic studies of cognitive aging, it will be important to differentiate the speed and executive components of this test as these may manifest differential change with age.

4.2.2.7 Context Processing

Context processing, which addresses working memory and executive function, has received considerable attention in the phenotypic literature. It refers to internally represented, task-relevant information being used to influence planning and behavior (Braver et al. 2005). Although it is probably unfamiliar to most behavior genetics researchers, it is a mechanism that can account for several age-related cognitive changes. Reduced prefrontal dopamine availability with aging is associated with response slowing and signal-to-noise reductions resulting in internal representations (context maintenance) that are more susceptible to decay over time (working memory) and to the effects of task-irrelevant inputs (inhibitory control; Braver et al. 2005; Kremen et al. 2011b). Since the development of the context-processing model in the mid-1990s, a key point has been that there was a single mechanism underlying working memory and cognitive control components of context processing.

The AX-CPT (continuous performance test) has been frequently used to assess context processing. Participants are presented letters, one at a time, on a screen and they must press a target button for an X, but only when it is immediately preceded by an A. By making most of the cue-probe pairs AX trials like the one described, a prepotent response tendency is created toward incorrect X probes (referred to as BX trials, i.e., X preceded by a non-A cue) and toward false alarms when A cues are followed by a non-X probe (referred to as AY trials). If context processing is intact, BX trials will require little inhibitory control because representation of the non-A cue will be well maintained. Older adults, who have context processing deficits, have poorer BX performance than young adults do. However, if context maintenance and response preparation are strong, AY trials will require greater inhibitory control because the A cue provides a strong expectation of a target probe. Less efficient context maintenance in older adults reduces the strength of this expectation, and hence, reduces the need for inhibitory control. Consistent with this framework, older adults make fewer errors and have faster response times on AY trials compared with young adults (e.g., Braver et al. 2005). This pattern represents a very rare instance of faster responding in older adults, thus indicating that processing speed alone cannot account for age-related cognitive declines. In sum, AX and BX trials emphasize proactive cognitive control (using context cues to prepare responses), whereas AY trials emphasize reactive control (adjusting responses after seeing the probe).

The first twin study of context processing was conducted in the VETSA sample (ages 51–59; Kremen et al. 2011b). Heritability of signal detection (an overall index of the ability to differentiate target from nontarget) was 0.40, and about one-quarter of the variance in each component was accounted for by genetic influences. A single common genetic factor accounted for accuracy on AX, BX, and AY trials with specific genetic influences only for AY trials. There were significant genetic correlations between general cognitive ability and proactive control (AX and BX

performance), but not reactive control. The presence of independent genetic influences underlying reactive control processes indicates that, in contrast to phenotypic studies, there must be more than one underlying mechanism.

There is some cross-sectional, phenotypic evidence that older adults tend to rely on reactive control more than young adults (Braver et al. 2009), suggesting that there should be a shift with age in the balance of proactive and reactive control. Given these findings, elucidating the genetic factors underlying proactive and reactive control processes is likely to be an important component of understanding cognitive aging. Age-related changes could be due to the fact that proactive control requires more metabolic/neuronal resources (Braver et al. 2007). It has also been argued that reduced efficiency of inhibitory control underlies many aging-related cognitive deficits (Hasher and Zacks 1988), and reduced use of proactive control makes one more susceptible to proactive interference. Longitudinal studies will be needed to determine whether and when a shift from proactive to reactive control takes place.

Reaction time was unrelated to chronological age in the narrow age range of the VETSA sample. Interestingly, however, participants with slower reaction time on noncontext processing trials were performing more like older adults. That is, slower reaction time on noncontext processing (BY) trials (typical of older adults) was associated with fewer AY errors and more BX errors. Although this pattern did not generalize to other reaction time measures, it could be a marker for larger or earlier cognitive declines as the VETSA participants age.

4.2.2.8 Processing Speed

Processing speed is a key cognitive variable in studies of aging given evidence (mainly cross-sectional) that age-related processing speed declines account for many other cognitive declines (Salthouse 1985). The concept of processing speed may be viewed as relatively simple. Everyone knows what is meant by processing speed, but its measurement is not necessarily straightforward. It is conceptualized as a simple or basic process (a cognitive primitive) underlying more complex cognitive abilities, but it is very difficult to avoid confounding by other cognitive abilities in tests of processing speed. For example, digit symbol—a classic processing speed measure—also involves elements of visual scanning and working memory. Deary et al. (2010a) reported phenotypic correlations among five widely used processing speed measures in older adults. Not counting correlations between variants of the same test (e.g., simple and choice reaction time), the median correlation was only 0.28. Their results highlight an important feature, namely, that different processing speed measures may actually measure fairly different phenomena. Similar variability may be reflected in the heritability estimates.

Most processing speed measures—including components of the trail making test, inspection time, and reaction time measures—have heritabilities generally in the 0.30–0.40 range (Finkel and McGue 2007; Posthuma et al. 2001a; Singer et al. 2006; Vasilopoulos et al. 2012). Several of those estimates were based on samples with very wide age ranges. Heritability of digit symbol/symbol digit appears to be

somewhat higher, in the 0.60–0.70 range in the MTSADA and SATSA (Finkel et al. 1995b). All these may underestimate the genetic influences on "true" processing speed based on the findings of Posthuma et al. (2001b). Utilizing electroencephalography (EEG) recordings to assess speed of encoding and accessing of information, they found a heritability of 0.83 in a middle-aged cohort.

Some cross-sectional studies have shown a significant though modest relationship between processing speed and general cognitive ability in late middle-age and older adulthood, and this association is almost entirely mediated by genetic influences (e.g., Finkel and Pedersen 2000; Posthuma et al. 2001a). In longitudinal biometric dual-change score models, genetic variance for processing speed was a leading determinant of variation in changes for spatial and memory, but not verbal, abilities across time in the SATSA (Finkel et al. 2009). Luciano et al. (2005) examined causal genetic models between processing speed (inspection time) and IQ in a cross-sectional study. Rather than a causal relationship in either direction, their evidence suggested that the covariation between intelligence and processing speed was explained by pleiotropy (i.e., some of the same genes influencing both phenotypes). Based on their bivariate model for processing speed and Performance IQ, for example, we estimated a genetic correlation of approximately 0.55. Although this does indicate pleiotropy, it indicates substantial nonshared genetic influences as well. In sum, processing speed can be a leading indicator, but the results suggest that it may be neither a necessary nor a sufficient condition.

4.3 Summary and Future Directions

Middle adulthood remains an understudied period in phenotypic and behavior genetic studies of cognitive aging. Further study focused specifically on middle adulthood is needed for understanding cognitive changes during midlife itself and for understanding midlife cognition as a "gateway" to cognition in old age. The available data suggest that there are some cognitive changes during midlife itself. However, because these changes tend to be small on average, a greater focus on subgroups of individuals who are manifesting earlier declines will be important. One dilemma is that in order to have adequate power to draw conclusions about a subgroup, larger sample sizes will be needed. Most studies, to date, include a relatively wide age range, but not enough middle-adult participants to examine subgroup or individual differences, particularly within-individual differences in trajectories over time.

Behavior genetic studies of cognitive aging in both middle and older adulthood have also had somewhat limited cognitive test batteries. It will be important for test selection to be guided by the goal of elucidating more specific cognitive component processes that may drive cognitive aging, i.e., a greater emphasis on splitting rather than lumping. Behavior genetic studies can be particularly enlightening in this regard. As shown in some of our examples, behavior genetic analysis of a well-chosen set of cognitive measures may reveal underlying influences that are different from what can be observed at just the phenotypic level. This approach not only helps to elucidate cognitive processes, it also serves to refine phenotypes for other stud-

ies including genetic association studies. Although we have emphasized splitting, behavior genetic analyses may also indicate that combining measures into a more general phenotype is sometimes optimal. That would be the case, for example, for the short- and long-delay free recall phenotypes in our study of the CVLT (section 4.2.2.3). The same genes influenced both phenotypes, and pleiotropic effects like this do justify combining measures. However, without this sort of decomposition of cognitive components, it is not possible to know the most appropriate way to combine or differentiate measures.

Measures of general cognitive ability can be advantageous given their greater reliability over specific ability measures and greater ease of administration. General ability measures also tend to have higher heritabilities than specific ability measures, which may mean greater statistical power for behavioral genetic analyses. However, as suggested by Tucker-Drob's (2011) results, they are disadvantageous in that the variance in cognitive change is mostly accounted for by specific domains and tests. Moreover, as can be seen from cognitive neuroscience and neuroimaging studies, it seems fairly clear that if the ultimate goal is to understand the mechanisms underlying cognitive aging, it will be necessary to study specific cognitive abilities and even subprocesses underlying specific abilities.

As we have noted, the emphasis on elucidating component processes is consistent with cognitive science and cognitive neuroscience approaches. Simply examining an overall score on a test might miss a key underlying subprocess that may be driving cognitive changes with age. When we refer to mapping the twin method onto these approaches, we simply mean examining these subprocesses in behavior genetic studies rather than only at the phenotypic level. With respect to cognitive neuroscience, it would mean the behavior genetic examination of brain–behavior relationships (e.g., with neuroimaging; for a review, see Chap. 8). Feasibility is clearly an important issue when it comes to neuroimaging twin studies, but recent studies have been able to obtain relatively large twin samples in neuroimaging studies (VETSA, Older Adult Twin Study, NIMH, Australian Twin Sample). Collaborative efforts are extremely important so that sample sizes can be increased. Methods have been in place for some time now for combining magnetic resonance imaging (MRI) samples across sites and platforms. The Enhanced Neuroimaging through Meta-Analysis (ENIGMA) consortium, for example, includes about 10,000 subjects with MRI and genotyping (including some twins). It may actually be easier to combine samples with structural MRI data than to combine samples with neurocognitive data because neurocognitive studies often use different tests even though they may be assessing the same cognitive domains.

A clear limitation is that much of the behavior genetic data on cognition in middle adulthood comes from the VETSA, which has only male participants. One of the better (albeit non-behavior-genetic) studies for examining sex differences may be the Whitehall II study (Singh-Manoux et al. 2011) because it is a very large study with data on middle-aged adults ($n = 7{,}390$). They found no sex differences (overlapping confidence intervals) in percent change over 10 years in their five different cognitive measures. Nevertheless, factors such as different probabilities of various health events, different risks for depression, differences in life expectancy, or dif-

ferences in age-related hormonal changes may play a role in cognitive function in middle age and beyond.

Another important limitation of behavior genetic studies of middle and older adults is the lack of working memory and executive function tests. Although processing speed is most often studied as a leading indicator, working memory and executive functions (including context processing) are also strong candidates for genetically mediated leading indicators (also suggested by candidate gene studies). In a longitudinal phenotypic study, Hultsch et al. (1998) found that working memory was a stronger predictor of later episodic memory than processing speed in older adults. Given the importance of these functions for daily living and the evidence of age-related changes in prefrontal cortex (which plays a key role in mediating these functions), substantially increased emphasis on these functions along with a greater focus on underlying component cognitive processes is warranted in longitudinal behavior genetic studies of middle-aged and older adults.

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