CHAPTER

7

Cognitive and Physical Aging: Genetic Influences and Gene–Environment Interplay

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OUTLINE

INTRODUCTION

Maintaining or stimulating cognitive functioning while offsetting the extent and timing of cognitive decline (Salthouse, 2012; Schaie, 1989), particularly reducing dementia risk, has become of principal importance to the research community and to the related industries that have emerged with respect to brain training and other health-promoting activities. Past

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research has attempted to distinguish normative cognitive change from dementia-related loss, yet, the new criteria for Alzheimer's disease (AD) recognize a potentially long preclinical period (10 years or longer) under which physiological changes occur before clear clinical signs are manifest (Sperling et al., 2011). This stance implies: (i) that the etiologies underlying normative cognitive change and dementia risk may be partly shared, and (ii) that physiological changes occurring before clinical signs of dementia may indicate a shared etiology or even dynamic relationships between physical and cognitive functioning. Thus, in this chapter while we are focusing on relevant research in normative cognitive aging, we must also consider the associated etiologies of dementia and physical aging. Building on earlier *Handbook* chapters (Kremen & Lyons, 2011), we highlight newer directions in cross-domain work with physical aging traits (e.g., body mass index (BMI), pulmonary functioning, blood pressure (BP), heart rate variability, grip strength, functional ability), measured genetic and environmental influences, and biological markers of gene–environment interplay processes.

COGNITIVE FUNCTION

After decades of research, characterization of age changes in cognition has achieved a certain level of precision. Understanding and identifying the influences of neurobiological and psychosocial factors on cognitive aging, however, is an ongoing process. Behavior genetic approaches provide methods for examining the relative impact of genetic and environmental influences and their interplay, and the accumulating results have been summarized in several recent reviews of the literature (Finkel & Reynolds, 2009; Johnson, McGue, & Deary, 2014). Moreover, several twin studies of adult development and aging have recently combined forces both to increase power to detect subtle genetic and environmental effects and to resolve any conflicting results reported by individual studies (Pedersen et al., 2013).

General Cognitive Ability

We know that on average general cognitive ability tends to decline throughout adulthood; however, genetic and environmental influences on cognitive aging manifest an intriguing and perhaps unexpected pattern. Initial meta-analyses demonstrated that the heritability of IQ is about 50% in young adulthood (Bouchard & McGue, 1981). As twin studies of adulthood accumulated longitudinal waves of data, it became clear that heritability continues to increase throughout the first half of the adult lifespan, reaching estimates as high as 80% in middle adulthood (Pedersen, Plomin, Nesselroade, & McClearn, 1992). There is some debate about how genetic and environmental variances change in the second half of the lifespan, as cognitive aging accelerates and a lifetime of accumulating environmental influences begins to overwhelm the system. A recent review of longitudinal twin studies of aging reports declines in heritability in late adulthood with associated increases in environmental variance (Finkel & Reynolds, 2009). In contrast, others report stable heritability estimates for cognitive function in late adulthood (McGue & Christensen, 2013). Recent cross-sectional analyses using over 14,000 twins from nine twin studies representing three countries suggests relative stability in heritability estimates for some cognitive domains, but changes in heritability for other domains (Pahlen et al., 2014). However, even this analysis has a limited sample over age 80, the age at which some studies suggest heritability may decline (McClearn et al., 1997; Reynolds et al., 2005); therefore, the issue remains unresolved.

Specific Cognitive Abilities

As with investigations of mean cognitive aging trajectories, behavior genetic analyses have focused on specific cognitive abilities for increased precision in the understanding of influences on cognitive change. In general, heritability estimates within specific domains tend to be somewhat lower than estimates for general cognitive ability, with estimates ranging from 50% to 70% (Finkel & Reynolds, 2009). In addition to focusing on changes or stability in heritability, longitudinal twin data allows us to estimate the genetic and environmental influences on change in cognitive function, per se. In other words, latent growth models provide estimates of heritability of average functioning at various ages (intercept) and genetic influences on changes in functioning over time (slope). Behavior genetic decomposition of latent growth models suggests generally high heritability for intercepts across cognitive domains, little or no heritability for linear slope estimates across cognitive domains, and small to large effects for quadratic estimates that tap accelerating change with age (McArdle, Prescott, Hamagami, & Horn, 1998; McGue & Christensen, 2002; Reynolds et al., 2005). For example, heritability of intercept of the growth curve for a verbal ability factor was 79%, heritability of both linear and quadratic rates of change was 0%, indicating that change in verbal ability with age resulted entirely from unique environmental factors (Finkel, Reynolds, McArdle, & Pedersen, 2005). When the individual tests that comprise the verbal factor were examined, however, the results indicated that genetic influences on quadratic decline varied from 9% to 42% across tests. Results for the processing speed factor and component tests tended to be more consistent: heritability for both intercept and quadratic rates of change were 80%, suggesting a strong neurobiological basis for age changes in processing speed. However, recent multivariate behavior genetic analysis of growth models demonstrates that most of the genetic influences on change are shared across domains, with specific genetic variance on change for memory and spatial ability, only (Tucker-Drob, Reynolds, Finkel, & Pedersen, 2014). In other words, regardless of the different abilities tapped by each domain, the genetic influences on cognitive change appear to be more global than specific.

Recent advances in brain imaging allow researchers to identify other relevant components of cognitive functioning central to the aging process, beyond the traditional domains of verbal, spatial, memory, and speed. For example, some of the largest age-related changes in brain structures are associated with changes in executive function and working memory. Working memory can be tapped by measures of memory span that require participants to both store and process information. Backwards digit span, measures of letter-number span, and spatial span tend to be moderately heritable in middle and late adulthood (Karlsgodt et al., 2010; Kremen et al., 2007; Posthuma et al., 2003). Executive function is a complex phenotype comprised of inhibitory control and set-shifting in addition to working memory. Multivariate behavior genetic analyses tend to find both a common genetic factor and genetic influences specific to the individual executive function components (for a review see Kremen, Moore, Franz, Panizzon, & Lyons, 2014). However, most of this research has concentrated on young and middle-adulthood twins, and more investigation of working memory and other executive function components in the second half of the lifespan is needed.

Environmental Influences

In addition to investigating genetic influences on cognitive abilities, behavior genetic approaches also provide a mechanism for identifying environmental factors that influence

functioning, both shared rearing environment and nonshared environmental factors unique to each individual. Results of twin studies of aging indicate that environmental influences on cognitive aging generally take the form of unique nonshared factors that lead to differences among individuals from the same family; thus the rearing environment has little impact on cognitive function in the second half of the lifespan. Environmental factors that influence both mean cognitive performance and rates of decline include education and socioeconomic status, occupational complexity (Andel, Vigen, Mack, Clark, & Gatz, 2006; Finkel, Andel, Gatz, & Pedersen, 2009), lung function (Emery, Finkel, & Pedersen, 2012), and leisure activities, including social participation (Lövdén, Ghisletta, & Lindenberger, 2005). It is important to note that many of these ostensibly environmental variables are themselves influenced by genetic factors. Twin studies provide a methodology for disentangling shared genetic and environmental variance between cognitive function and "environmental" measures. For example, latent growth curve analyses of cognitive ability traits suggest that education shares genetic variance with performance levels, but environmental variance with rates of change (Reynolds, Gatz, & Pedersen, 2002). This outcome is generally consistent with related findings suggesting that environmental factors underlie associations between education and dementia risk (Gatz et al., 2007), even as levels of cognitive performance and functioning show patterns of partial genetic overlap with education (Pedersen, Reynolds, & Gatz, 1996). Lung function, which likely taps environmental factors such as smoking, exercise, and environmental exposures, shares both genetic and environmental variance with declines in fluid intelligence (Finkel, Reynolds, Emery, & Pedersen, 2013). Thus, phenotypic approaches can identify candidate environmental influences on cognitive decline, but behavior genetic methods are required to determine the exact nature of the relationship.

PHYSICAL FUNCTION

To fully understand the mechanisms of cognitive aging, it is important to consider the physical context in which that aging occurs. Although it is difficult to discuss various physical systems in isolation, we will consider more physiological aspects of physical function first, then more behavioral components. For the purposes of this summary, *physiological functioning* includes obesity, cardiovascular health, and lung function whereas *behavioral physical functioning* includes muscle strength and functional ability.

Physiological Functioning

Extensive research has documented that having a normal body mass index (BMI = 19–25 kg/m^2) in midlife is related to better health and survival; however, slightly elevated BMI (25–30) in late adulthood is associated with better health prognoses than normal BMI (Dahl, Lopponen, Isoaho, Berg, & Kivela, 2008; Romero-Corral et al., 2006). This "obesity paradox" is likely driven by disease processes that cause weight loss, emphasizing the role of BMI as a marker of general health. Mean BMI increases somewhat with age, but heritability estimates remain fairly constant at 70% throughout the second half of the lifespan (Nan et al., 2012; Silventoinen & Kaprio, 2009).

Of the several indices of cardiovascular health that have been included in twin studies of aging, BP is the most common. Behavioral genetics investigations suggest moderate genetic influences on BP: heritability near 45% for systolic BP and 34% for diastolic BP (Hong, de Faire, Heller, McClearn, & Pedersen, 1994; Vinck, Fagard, Loos, & Vlietinck, 2001). Some studies suggest decreasing genetic influences on BP with increasing age (Finkel et al., 2003; Hong et al., 1994; Tambs et al., 1993). In contrast, heritability estimates for elevated BP (hypertension) are higher, ranging from 46% to 63% (Kupper

et al., 2005; McCaffery, Papandonatos, Lyons, & Niaura, 2008). Recent investigations of cardiovascular health have focused on measures that require more sophisticated technology. Heart period variation, respiratory sinus arrhythmia, and other heart rate variability (HRV) indices from ECG are predictive of cardiac events and mortality. These ECG-based measures tend to be moderately to strongly heritable (30–55%), depending on the testing context: at rest versus experimentally induced stress conditions (De Geus, Boomsma, & Snieder, 2003; Kupper et al., 2004; Li et al., 2009; Snieder, van Doornen, Boomsma, & Thayer, 2007; Uusitalo et al., 2007). Environmental influences on cardiovascular health tend to be unique to the individual and include caffeine, smoking, BMI, and medications (Uusitalo et al., 2007). Investigations of serum lipids, primarily cholesterol and triglycerides, also provide insight into the nature of genetic and environmental influences on cardiovascular health. Heritability estimates are moderate to strong across serum lipid and lipoprotein traits, typically between 30% and 80% (Beekman et al., 2002; Goode, Cherny, Christian, Jarvik, & de Andrade, 2007; Nilsson, Read, Berg, & Johansson, 2009). After age 50, results for heritability of serum lipids are mixed, with reports indicating decreases, stability, or even small increases, depending on study design (cross-sectional or longitudinal) and lipid or lipoprotein constituent (Goode et al., 2007; Heller, de Faire, Pedersen, Dahlen, & McClearn, 1993). However, longitudinal studies suggest unique (new) genetic influences may emerge by midlife (Middelberg, Martin, & Whitfield, 2006) with possible amplification of heritable influences in late life (Goode et al., 2007).

Lung function is clearly related to cardiovascular health, but it is also associated with general functioning in several domains, including functional ability and cognition (Emery et al., 2012; Singh-Manoux et al., 2011). Lung function is moderately heritable in late adulthood, with estimates ranging from 30% to 50% (Hukkinen et al., 2011; Vasilopoulos et al., 2010; Whitfield, Wiggins, Belue, & Brandon, 2004). In particular, heritability varies based on the type of spirometric data (e.g., forced expiratory volume vs. full vital capacity). Behavior genetic analyses that differentiate genetic variance common to multiple measures and unique to each measure indicated primarily unique genetic variance for measures of lung function (Vasilopoulos et al., 2013). Thus even variables assumed to assess the same general domain of functioning can reveal complex etiologies.

Behavioral Physical Functioning

Heritability estimates for physical strength in adulthood range from 30% to 60% for both measures of upper body strength such as hand grip and measures of lower body strength such as knee extension (Finkel et al., 2003; Frederiksen et al., 2002; Tiainen et al., 2004, 2005). In addition, heritability of these measures of physical strength appears to be stable across adulthood (McGue & Christensen, 2013). Beyond simple strength, physical *function* measures tasks that generally have more ecological validity, such as Activities of Daily Living (ADL) or behaviors such as walking, balance, and chair stands. Unlike the results for physical strength, however, heritability estimates for physical functioning tend to be mixed, with evidence for significant age and gender effects (Christensen, Frederiksen, Vaupel, & McGue, 2003; Christensen, Gaist, Vaupel, & McGue, 2002; Finkel, Pedersen, & Harris, 2000; Finkel et al., 2003). As variability in functional measures increases with age, heritability estimates also increase, but heritability tends to be higher for women than for men (Christensen et al., 2003; Finkel, Ernsth-Bravell, & Pedersen, 2013). This gender difference likely reflects both different susceptibility to chronic disabling conditions and differential life experiences.

CROSS-DOMAIN INVESTIGATIONS

As we have seen, aging in both cognitive and physical domains results in part from genetic influences. The vital question, then, is to determine the extent to which the genetic factors that influence aging in one domain are also acting in other domains. In other words, it is possible that a single set of genes is having pleiotropic effects on the aging process, impacting aging in several domains. Research in this area has focused on the interrelationships between genetic and environmental influences on cognitive and physical function, as well as evidence for direct associations between brain structure and cognitive function in adulthood.

Interrelationships Between Cognitive and Physical Aging

As longitudinal twin studies of aging have continued to amass data, we have witnessed significant growth in behavior genetic investigations into the nature of the interrelationships between cognitive and physical aging. Some of the earliest work focused on the relationship between lung function and cognition, and accumulating evidence indicates a strong relationship between genetic influences on lung function and genetic influences on measures of fluid ability. For example, genetic variance in lung function at baseline was correlated with genetic variance in cognitive function 6 years later (Emery, Pedersen, Svartengren, & McClearn, 1998). Moreover, an analysis incorporating 19 years of longitudinal data for both lung and cognitive function indicated that genetic variance associated with lung function was in fact a primary contributor to subsequent change in fluid ability suggesting that the directional relationship from decreased pulmonary function to decreased cognitive function arises from genetic factors (Finkel, Reynolds et al., 2013).

More recent twin analyses have incorporated additional physiological measures of health. In a sample of Finnish twins, researchers found that the correlation between BMI at midlife and cognitive scores in late life was primarily genetically mediated. Additionally, indices of cardiovascular disease at midlife explained a portion of the difference in cognitive scores in discordant twin pairs (Laitala et al., 2011). In fact, evidence suggests that heritability estimates for measures of spatial ability and memory were significantly lower in a sample of untreated hypertensives, as compared with non-hypertensive and medicated hypertensive middle-aged men, absent any mean differences between the groups (Vasilopoulos et al., 2011). Thus, untreated hypertension may disrupt genetic influences underlying cognitive functioning, such as maintenance of brain structures and vasculature, even before cognitive deficits appear. Moreover, autonomic functioning, i.e., very low frequency HRV, may be implicated in verbal but not spatial memory performance in middle–age men without post-traumatic stress disorder (PTSD) based on between- and within-twin pair analyses (Shah et al., 2011); effects were apparent even when controlling for familial factors and hence implicating a role for (nonshared) environmental pathways (Shah et al., 2011).

In a cross-sectional twin analyses, the speed with which participants completed various functional ability tasks shared genetic variance with cognitive functioning in middle age but not later in adulthood, when processing speed explained most of the genetic variance in cognition (Finkel et al., 2000). Longitudinal twin analyses indicated significant shared genetic variance between functional ability and cognition. Three possible explanations for this relationship were supported by model-fitting: physical illness impacts subsequent cognitive function (e.g., hypertension), cognitive function as a contributor to the ability to maintain good health and lifestyle habits, and a biological process of

aging that affects both (Johnson, Deary, McGue, & Christensen, 2009). Future studies may help unpack these competing explanations.

Brain Structures

The recent integration of various methods of brain imaging into twin studies of aging has resulted in the proliferation of research into the genetic and environmental influences on the association between specific brain structures and specific cognitive functions. Although experience clearly shapes the brain, genetic influences account for 40–95% of individual differences in brain structures and function (Chavarría-Siles, Fernández, & Posthuma, 2014). Similar to results from longitudinal twin studies of cognitive abilities; genetic influences on change in brain volume over time appear to be minimal (Lessov-Schlaggar et al., 2012). Nevertheless, the associations between brain structures and cognitive functioning tend to be primarily genetically mediated. For example, Posthuma and colleagues reported that although the correlations between gray-matter volume and white-matter volume and intelligence tend to be modest ($r = 0.25$), the correlations reflect shared genetic variance only (Posthuma et al., 2002). Similarly, specific brain regions and structures (such as gray matter thickness and white matter hyperintensities) have been shown to share genetic variance with general intelligence and specific abilities such as working memory (Blokland et al., 2011; Hulshoff Pol et al., 2006; Joshi et al., 2011). Two concerns about this emerging field exist. First, most of the twin research is conducted on younger adults; few studies of middle-aged and older twins have incorporated brain imaging measures. The Vietnam Era Twin Study of Aging (VETSA) includes brain imaging (Kremen, Franz, & Lyons, 2013) and the National Heart, Lung, and Blood Institute (NHLBI) twin study reports that in a sample of older male twins, associations between white matter hyperintensities and cognitive function resulted for the most part from shared genetic variance (Carmelli, Reed, & DeCarli, 2002). Second, a variety of cognitive tasks may engage a particular brain region; hence, it is improbable that a designated region is "mapped" or central to a specific cognitive ability. Rather, knowledge of a region's functions should be evaluated against any newly observed relationships with task performance measures, as well as with related traits (Kanai & Rees, 2011).

Specific Genes Important to Cognitive and Physical Aging

The aforementioned studies indicate an important role for genetic influences on cognitive aging, physical functioning, and the relationships between the two domains. Indeed increases in genetic variance or heritability are typical at least through late adulthood even as nonshared environmental factors accumulate across the adult lifespan into old–old age. The search for genes that may potentiate or moderate normative cognitive aging, and the extent to which these overlap with physical functioning, are important issues to evaluate. Moreover, the extent to which measured environmental factors interact with genetic factors to moderate cognitive aging is receiving greater attention.

Association and linkage approaches are the two primary methods used in the identification of genes important to traits such as cognitive decline (Plomin, DeFries, Knopik, & Neiderhiser, 2013). Association studies evaluate correlational relationships between a variant of a particular gene, i.e., an allele, and cognitive change traits. While traditional association studies were conducted based on theoretical or biological evidence, millions of variants, primarily single nucleotide polymorphisms (SNPs), that appear frequently in populations (5% or higher) have been evaluated in genome-wide association studies (GWASs). Most recently, researchers have turned to whole-genome sequencing to evaluate rare

variants as many of the GWASs have explained a limited amount of variation in traits (Plomin et al., 2013). Linkage strategies trace the extent to which a genetic marker or mutation co-occurs with a disorder or trait, within families, and are useful to localize genes of interest (Plomin et al., 2013).

Cognitive Aging

For over 20 years, the gene encoding apolipoprotein E (*APOE*) has stood out as the primary genetic susceptibility factor for late-onset AD (Corder et al., 1993; Strittmatter et al., 1993), and more recently for non-pathological (normative) cognitive aging (Davies et al., 2014; Reynolds et al., 2006). GWASs of AD risk conducted over the last decade have revealed about 20 additional gene candidates and pathways (Lambert et al., 2013; Schellenberg & Montine, 2012), although a number of these have yet to be evaluated for normative cognitive aging. These gene pathways include: (i) cholesterol and lipid metabolism (e.g., *APOE*, *ABCA7*, *CLU, SORL1)*, (ii) cellular endocytosis or adhesion which play a role in protein absorption (*BIN1, CD2AP, FERMT2, PICALM*), (iii) immune/inflammatory response (e.g., *CR1*, *HLA-DRB5–DRB1* region, *INPP5D, MEF2C, MS4A4E/MS4A6A*), (iv) cell-signaling or synaptic functioning processes in hippocampal regions (e.g., *MEF2C*, *PTK2B, SLC24A4*), and (v) neural development (e.g., cell migration, *PTK2B*).

APOE and *SORL1* play a role in the lipid metabolism pathway and have been implicated in normative cognitive aging (Davies et al., 2014; Reynolds et al., 2006, 2013). *APOE*, although expressed in the periphery, is the primary transporter of cholesterol in the brain (Lambert et al., 2013; Schellenberg & Montine, 2012). The risk allele, *APOE* ε4, is associated with increased beta-amyloid (Aβ) protein deposition, a hallmark neuropathology observed in those with AD, but also observed at autopsy among aged individuals with no prior clinical signs of dementia (Caselli, Walker, Sue, Sabbagh, & Beach, 2010). The *SORL1* gene encoding sortilin receptor 1 (SorL1) plays a dual role: protein sorting and binding to the low-density lipoprotein (LDL) (http://www.ncbi.nlm.nih.gov/gene/6653). Moreover, SorL1 participates in the transport of the amyloid precursor (*APP)* protein, a precursor of Aβ (Gustafsen et al., 2013). Numerous common and rare *SORL1* SNPs and haplotypes have been associated with increased risk of AD (Jin et al., 2013; Reitz, Brayne, & Mayeux, 2011) and recently *SORL1* variants and risk scores (capturing multiple variants) were shown to predict differential accelerations in normative cognitive decline (Reynolds et al., 2013).

GWASs evaluating cognitive decline have not as yet extended findings beyond *APOE* for the above-noted AD-risk genes (Davies et al., 2014; De Jager et al., 2012). For example, cumulative impacts of susceptibility loci previously identified for cardiovascular disease, diabetes, or inflammatory/immune processes are not significantly associated with cognitive trajectories although the sample sizes may be a limiting factor (De Jager et al., 2012). In older adulthood, there appear to be numerous but small cumulative effects of common gene variants for fluid and crystalized intelligence performance (Davies et al., 2011), where, for example, as much as 51% of the variance in spatial performance was accounted for by thousands of SNPs; however, cognitive change was not evaluated. It may be that a focus on changes within specific cognitive domains will be more fruitful than global measures of cognitive change (Kremen et al., 2014). For example, recent findings for *SORL1* suggest a relatively greater number of associations with rate of cognitive change versus performance levels, particularly for spatial as well as episodic memory and verbal ability domains (Reynolds et al., 2013). Moreover, a focus on rarer variants via sequencing efforts may provide greater clarity on the impact of particular genes. Finally,

a focus on multiple gene variants, gene sets or gene pathways rather than specific gene variants (e.g., SNPs) may prove more illuminating as to mechanisms that underlie variability in maintenance of cognitive abilities into older age. Additionally, such efforts may point to the relative involvement of particular pathways and importantly the exclusion of other pathways (Lips et al., 2012; Ruano et al., 2010). Emerging work on older adult samples is now appearing that considers multiple genes. For example, a genome-scanning approach evaluated regional association of DNA variants and cognitive aging outcomes in three Scottish birth cohorts, providing suggestive evidence that a region on chromosome 5 containing the *PRRC1* gene may be important to fluid ability performance in late adulthood (ages 65–79 years) (Rowe et al., 2013). However, this region was not statistically associated with the residual-based cognitive change outcome (cognitive performance in late life residualized for age 11 cognitive ability). Promisingly, altered *PRRC1* expression was observed in the temporal cortical region (based on gene methylation assessments) and suggests follow-up work is warranted. Gene set analyses, considering multiple genes presumed to be related to the cognitive outcome trait, have been conducted using these three Scottish samples plus two English samples from the CAGES consortium (Hill et al., 2014). Here, researchers considered over 1400 genes that regulate postsynaptic density via the receptor complexes NMDA/MAGUK (*N*-methyl-D-aspartate/membrane-associated guanylate kinase), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and mGlu5 (metabotropic glutamate receptor 5). Results suggested genes regulating NMDA/MAGUK receptor complexes may be important to fluid ability performance. Replication was achieved in samples from Norway and Australia, with ages 18–79 and 15–30 years, respectively. Thus, specificity to late-life cognitive change is unclear. Extensive pathway-based searches have yet to be undertaken for cognitive change outcomes, especially cognitive trajectories. However, promising competitive pathway methods that compare a focal pathway against "control" pathways have been applied to IQ among adults with schizophrenia, where three synaptic gene pathways were identified, i.e., intracellular signal transduction, excitability, and cell adhesion and trans-synaptic signaling (Lips et al., 2012).

Physical Aging

Meta-analyses of *GWAS* focusing on BMI and related obesity traits have identified a number of genetic variants (Speliotes et al., 2010). In particular, the *Fat Mass and Obesity Associated* (*FTO*) gene candidate appears to show strengthening associations with BMI across childhood (Haworth et al., 2008) and into early adulthood but may lessen in impact into older adulthood (Graff et al., 2013). Additionally, the gene responsible for encoding brain-derived neurotrophic factor (*BDNF*) has been implicated in BMI (Speliotes et al., 2010). Analysis of an obesity genetic risk score incorporating information from a total of 32 single nucleotide polymorphisms identified in the meta-analysis (Speliotes et al., 2010) suggested prediction of adult BMI trajectories up to age 65 but not after (Dahl, Reynolds, Fall, Magnusson, & Pedersen, 2014).

A number of genes may regulate BP traits across a number of populations (e.g., *ATP2B1, CNNM2-NT5C2, FGF5, CASZ1, CSK-ULK3, MTHFR*) although others may be selective, e.g., in East Asian populations a *RPN6-PTPN11* gene variant has been implicated which is in proximity to the *ALDH2* gene involved in alcohol metabolism (Kato et al., 2011). Interestingly, a recent study revealed that the risk variant C677T in *MTHFR*, a gene which regulates plasma homocystine (folate) levels, may be associated with accelerating atrophy of white matter over time in those with mild cognitive

impairment (MCI), replicating findings in two samples (Rajagopalan et al., 2012). Other studies find equivocal evidence for genetic variants in *MTHFR* and association with cognitive aging or impairment (Ford et al., 2012; Moorthy et al., 2012), even while serum levels of homocysteine or vitamins B-12 and B-6 may be correlated with impaired cognitive performance (Ford et al., 2012; Moorthy et al., 2012).

APOE is associated with serum lipid profiles (Bennet et al., 2007), where carriers of *APOE* ε4 have poorer lipid profiles than those with the most common haplotype *APOE* ε3/ε3, while carriers of the rarer *APOE* ε2 have more positive lipid profiles on the whole, except for triglycerides (Bennet et al., 2007). Indeed, over 95 genes achieved significance at the genome-wide level in a GWAS of cholesterol, remarkably explaining between 25% and 30% of the genetic variance for serum lipids traits (Teslovich et al., 2010). As discussed above *APOE* figures prominently in cognitive aging and risk of AD.

GWASs for heart rate measures have identified a number of gene candidates (Deo et al., 2013). Two genes are associated with resting heart rate across populations: (i) *GJA1* encoding connexin 43 (the primary protein constituent in the myocardial gap junction), and (ii) *MYH6* that codes for a heavy-chain subunit of cardiac muscle myosin (Deo et al., 2013). Neither of these genes has been specifically implicated in GWAS efforts for AD or cognitive aging. The complexity of findings for HRV, i.e., population-specific gene variants coupled with environmental factors that may partly drive associations of HRV with verbal memory performance at midlife (Shah et al., 2011), suggest a multifaceted set of genetic and environmental influences that need further characterization.

A meta-analysis of GWAS studies on lung functioning of over 48,000 individuals of European ancestry, reported a total of 16 associated gene loci (Soler Artigas et al., 2011). Of the 16 loci, some genes are in lipid/cholesterol (e.g., *LRP1*) and immune pathways (e.g., *TGFB2*), pathways implicated for AD; however, the 16 specific candidates have not been identified in the largest GWAS meta-analysis of AD to date (Lambert et al., 2013).

Gene Pathways Underlying Cognition-Physical Functioning Dynamics

The lipid pathway, particularly typified by genes such as *APOE* and *SORL1*, may be an important pathway underlying associations between cognition and physical functioning traits. A predictive relationship between serum lipids and lipoprotein values on cognitive change exists and changes in serum lipids have been observed in those with MCI versus healthy elderly (Reynolds, Gatz, Prince, Berg, & Pedersen, 2010; Tukiainen et al., 2012). Moreover, further explorations of the protein sorting pathway that *SORL1* also participates in, i.e., vacuolar protein sorting 10 (VPS10) domain-containing receptor protein family, suggests that additional genes in this family are associated with AD (Reitz et al., 2013) and deserves further attention in evaluations of normative cognitive aging.

We also highlight synaptic plasticity pathways, and the *BDNF* gene as an exemplar. Brain-derived neurotropic factor (bdnf) is expressed in the prefrontal cortex and hippocampal regions, and is implicated in synaptic plasticity processes that occur during memory formation and the persistence of memories (Kambeitz et al., 2012). Curiously, variants in the *BDNF* gene have not been identified in GWAS of cognitive aging nor of AD risk, although *BDNF* has been identified in GWASs of BMI (Speliotes et al., 2010). Hence, there are reasons to re-consider *BDNF* with respect to cognitive aging, especially as it may partly underlie links between physical and cognitive functioning (Gomez-Pinilla & Hillman, 2013; Hotting & Roder, 2013). According to meta-analytic work, the val^{66}met BDNF polymorphism may be important to hippocampal-dependent

memory formation based on animal and human studies (Kambeitz et al., 2012). Specifically, the met allele is correlated with small decrements in declarative memory performance relative to val carriers (Kambeitz et al., 2012), perhaps due to decreased bdnf availability (Dincheva, Glatt, & Lee, 2012). Additionally, earlier meta-analysis work suggests significant heterogeneity in effect sizes for executive functioning traits (Mandelman & Grigorenko, 2012), which may deserve additional examinations. *BDNF* may predict late life cognitive change (Harris et al., 2006), perhaps in females specifically (Fukumoto et al., 2010; Komulainen et al., 2008; Laing et al., 2012). Most recently, additional *BDNF* variants have been associated with declines in cognitive functioning (i.e., 1-year change in ADAS-cog scores) as well as hippocampal and whole-brain atrophy across 2 years but not AD risk (Honea et al., 2013). Potential moderators of bdnf levels include exercise (higher: Erickson, Miller, Weinstein, Akl, & Banducci, 2012), gender (female lower: Lommatzsch et al., 2005), and age (older lower: Lommatzsch et al., 2005), among others.

GENETIC INFLUENCES ON ENVIRONMENTAL SENSITIVITY

Behavioral genetic methods allow us to investigate not just genes or environmental influences in isolation, but how they interact to impact cognitive and physical aging (Pedersen, et al., 2013; Reynolds, Finkel, & Zavala, 2014). Accumulating evidence suggests genetic (G), environmental (E), and G × E processes change over the life course in importance and make-up (Bell et al., 2012; Deary et al., 2012; McClearn, 2006; Reynolds, et al., 2005; Reynolds, Gatz, Berg, & Pedersen, 2007). Genetic effects may become increasingly stronger due to amplification of gene influences already in effect, while new gene influences may emerge to impact cognitive change at least until young-old age (Deary et al., 2012; Reynolds et al., 2005). In tandem, person-specific environmental factors may accelerate in importance—a potential signal of the presence of gene–environment interplay (Reynolds et al., 2005, 2007). Indeed, environmental contexts may have differential impacts on memory trajectories dependent on particular genotypes (Reynolds et al., 2007). For example, a within-pair analysis of monozygotic (MZ) pairs suggested that non-carriers of the *APOE* e4 risk allele and those homozygous for the major allele for estrogen receptor 1 alpha gene (*ESR1a*) variant rs1801132 showed greater disparities in semantic memory change versus those carrying respective risk alleles (i.e., *APOE* ε4, minor allele in rs1801132). Moreover, within-pair differences in memory trajectories correlated significantly with within-pair differences in depressive symptoms only among pairs who were *non-carriers* of these risk alleles. Hence, for those not already at high genetic risk for cognitive decline, environmental contexts stemming from experiencing lower or higher depressive symptoms may moderate memory trajectories. Indeed, dementia research suggests that perhaps due to already elevated risk, *APOE* ε4 carriers may be generally less responsive to environmental factors than non-ε4 individuals (Gatz, 2007). In contrast, other research suggests that those carrying *APOE*-ε4 may show greater responsiveness to particular dietary (e.g., altered triglycerides, C-reactive protein (CRP) levels) (Carvalho-Wells, Jackson, Lockyer, Lovegrove, & Minihane, 2012) or exercise/activity interventions (Erickson et al., 2012), as illustrated below, although additional work is needed.

Two models of genetic influences on environmental sensitivity have been increasingly contrasted in recent developmental psychopathology literature, i.e., the well-known diathesis-stress model versus the differential susceptibility model (Belsky, Pluess, & Widaman, 2013). The diathesis-stress model

suggests that environmental influences may be more impactful for some individuals than others (Zuckerman, 1999). For example, those who carry the *APOE* ε4 allele may be negatively impacted to a greater degree by exposures to low economic resources (Sachs-Ericsson, Corsentino, Collins, Sawyer, & Blazer, 2010) or alcohol consumption (Downer, Zanjani, & Fardo, 2014) than non-carriers. The differential susceptibility model suggests a cross-over effect; i.e., those with a risk genotype may, in deleterious environments, be more negatively affected but otherwise thrive in positive environments compared to those without the risk genotype who hold relatively steady regardless of the environment (Belsky, 1997, 2005; Belsky et al., 2009). Examples that approach an expected cross-over are: (i) in the context of a low physical activity environment, those with the *APOE* ε4 allele may show lower engagement of neural networks activated in semantic memory processing, but in a high activity context those with the ε4 allele show comparable activation to those not at risk (Smith et al., 2011); (ii) likewise, particularly detrimental effects of low exercise to those with ε4 may also be conferred with respect to higher β-amyloid deposition, while engagement in exercise may alleviate this enhanced risk (Head et al., 2012). While in these recent empirical examples higher physical activity did not lead *APOE* ε4 individuals to surpass non-ε4 individuals in positive outcomes, the mitigation of risk via physical activity was notable. In the literature at large, however, the direction of effects as to exercise/physical activity, *APOE* genotype, and cognitive performance benefits is not clear, suggesting additional work is necessary (Erickson et al., 2012).

The differential susceptibility model can be seen conceptually as a variant of the concept of antagonist pleiotropy wherein benefits of particular genotypes (to reproductive success) may be seen in earlier development but pose detrimental effects in late life (see Fabian & Flatt, 2011, for review). For example, young adult carriers of *APOE* ε4 may show enhanced memory performance comparative to non-ε4 individuals but any benefits may dissipate and ultimately reverse in late life (Jochemsen, Muller, van der Graaf, & Geerlings, 2012; Mondadori et al., 2007; Moreau et al., 2013; but see Bunce et al., 2013). In addition to these models, a number of additional models of gene–environment interplay have been proposed that may likewise explain possible synergies among genetic and environmental influences on cognitive and physical aging (Reynolds et al., 2014). Such models are essential to place into context a variety of complex empirical findings that are emerging as well as to evaluate competing models when designing new studies. Importantly, it will be necessary to take a life course approach to shifting dynamics of genes and environments in evaluating pathways to optimal or less optimal pathways to maintaining or improving cognitive functioning into late life (Reynolds et al., 2014).

Biomarkers of GE Interplay

Directly measureable evidence of gene–environment interplay is essentially feasible due to recent advances in the measurement of biomarkers such as methylation and telomere lengths. In the context of life course studies of cognitive aging, the addition of epigenetic biomarker measurement may lead to the uncovering of pathways that promote accelerating cognitive declines, and equally important, to those pathways that promote maintenance or improvements in cognitive functioning into old age. Epigenetic modifications that alter gene expression occur due to a variety of mechanisms including direct methylation of DNA (Day & Sweatt, 2012; Rakyan, Down, Balding, & Beck, 2011). Characteristically, the process of DNA methylation takes place with the addition of a methyl group to the DNA base cytosine within cytosine-guanine dinucleotides (CpGs), leading to long-term alterations in gene

expression. Of specific interest are CpG-rich regions that occur within or in the proximity of gene promoter regions such as CpG "islands" or "island shores" (Rakyan, Down, Balding, & Beck, 2011). Methylation has been measured in human brain, muscle, and leukocyte tissues (Fernandez et al., 2012). Moreover, methylation levels correlate with age, change in health traits, as well as dementia-associated neuropathology and neurological disorders (Bell et al., 2012; Boks et al., 2009; Fernandez et al., 2012). Recently, a methylation site in the vicinity of *PRRC1* (cg04431054) on chromosome 5 that altered expression in the temporal cortex predicted fluid ability scores (Wang et al., 2012).

DNA methylation occurs due to *nongenetic* (i.e., epigenetic) processes proposed to result from prenatal or early life exposures and at later points in the lifespan (Gottesman & Hanson, 2005). For example, it may be that low education and other life events lead to particular environmental exposures (Gatz et al., 2006) that elicit epigenetic modifications (Tehranifar et al., 2013). Although such links have yet to be empirically shown for cognitive aging, one may speculate that effects of epigenetic changes may accelerate or accumulate over time and lead to less optimal aging outcomes such as cognitive decline.

While DNA sequence variation and epigenetic processes are distinct by definition, evidence of significant twin concordance for methylation levels is apparent, suggesting genomic regulation of methylation (Coolen et al., 2011). In addition, heritability of DNA methylation may vary across particular genes (Bell et al., 2012; Boks et al., 2009). Moreover, whether epigenetic alterations facilitate or are outcomes of disease or aging, such as cognitive aging or dementia, is not understood (Chouliaras et al., 2010). To disentangle causal versus consequential sequences of events, longitudinal assessments of both cognitive performance and DNA methylation will be necessary. In addition, the extent to which methylation in non-brain matter (e.g., leukocytes) is relevant to cognitive aging is also a concern. Given that in vivo measurements in human brain matter are not yet possible, methods to identify the relevance of peripheral tissue methylation as markers of functionally relevant alterations in the CNS are important (Wang et al., 2012).

Telomere Length

Telomeres, i.e., DNA segments that cap the ends of chromosomes, have become of interest as a biomarker that may index aging and indeed environmentally mediated processes. Moreover, as discussed further below, recent work on telomeric influence on gene expression (telomere position effect, TPE) (Stadler et al., 2013) suggests the possible interplay between aging/environmental exposures and gene expression via telomere lengths. Telomeres shorten with each cell division and predict cell functioning and eventual senescence (Shawi & Autexier, 2008); for example, telomeric loss may be associated with increased risk of somatic mutation and damage during cellular division (Aubert & Lansdorp, 2008). Shorter telomere lengths are predicted by increasing age (Steenstrup et al., 2013), low education (Adler et al., 2013; Steptoe et al., 2011), psychosocial stress and adversity (Price, Kao, Burgers, Carpenter, & Tyrka, 2013), and illness (Fyhrquist & Saijonmaa, 2012; Kong, Lee, & Wang, 2013).

Telomere lengths are heritable based on studies of twins (Bakaysa et al., 2007; Broer et al., 2013), yet twin pair differences in telomere lengths predict pair differences in cognitive performance suggesting possible environmental mechanisms. Longer telomere lengths correlate with higher working and episodic memory performance (Valdes et al., 2008) while within-pair comparisons suggest that twins with shorter telomere lengths performed more poorly relative to their cotwins (Valdes et al., 2008). However, the full picture across studies suggests that the association between telomere lengths and cognitive decline and dementia risk

remains unclear (Devore, Prescott, De Vivo, & Grodstein, 2011; Hochstrasser, Marksteiner, & Humpel, 2012; Ma et al., 2013; Moverare-Skrtic et al., 2012; Zekry et al., 2010). Longitudinal studies are lacking yet they are needed to clarify temporal causality (Mather, Jorm, Parslow, & Christensen, 2010). Moreover, variations across tissue types sampled must be considered (e.g., buccal cells, leukocytes, brain tissues) (Thomas, O'Callaghan, & Fenech, 2008) as well as moderation by genotypes such as *APOE* (Wikgren et al., 2010).

Telomeres may influence gene expression even for those genes that sit relatively far from the telomeric region (100 kilobases), and hence pose implications for models of gene–environment interplay and aging. According to a study of the age-dependent disorder human facioscapulohumeral muscular dystrophy (FSHD) (Stadler et al., 2013), telomere shortening may lead to increased *DUX4* gene expression and hence to increased FSHD risk (Stadler et al., 2013). Although much work remains to be conducted, it may be speculated from this work that telomere shortening occurring as a consequence of age or due to environmental exposures may alter gene expression that could impact cognitive trajectories into late life.

SUMMARY AND FUTURE DIRECTIONS

Quantitative behavioral genetic studies suggest substantial genetic influences on cognitive performance across domains, albeit higher for processing speed and lower for memory traits. Meanwhile substantial genetic variation contributes to change in spatial and perceptual speed processes, but is less important or variable for change in traits in the verbal and memory domains. Across domains, person-specific environments tend to increase with age in their importance to cognitive aging. Together these patterns signal changing and perhaps dynamic gene–environment influences. Similar conclusions can be drawn for aging of physical traits. The extent of genetic and environmental influences on aging varies by physical trait, with evidence for increasing unique environmental influences but also for the possible onset of new gene expression in late adulthood. Sex differences in genetic and environmental variance for physical aging reflect gender differences in life experiences and exposures. These complicated physical aging trajectories provide a rich tapestry of potential influences on cognitive aging. Molecular studies, particularly those using GWAS methods, highlight the complexity of the search for specific genes for cognitive aging, although key variants identified for cognitive aging, particularly *APOE* or *SORL1* as well as *BDNF* (among other BMI-related genes) suggest interrelationships among etiologies contributing to cognitive and physical aging, or pleiotropic effects.

Additional lifespan research is necessary to evaluate the changing dynamics of genetic and environmental influences on cognitive aging, including shared and unique dynamics with physical aging traits. As described above, lipid and synaptic plasticity pathways are promising to consider, among others. Multiple studies indicate that both *APOE* and *SORL1* are associated with pathological and non-pathological cognitive aging and decline. Additional behavioral work is necessary to evaluate a role for *APOE* and *SORL1*, indeed the lipid pathway at large, on aspects of cognitive growth and decline patterns.

Indeed, complex sex- plus age-dependent effects may be evident over the entire life course. For example, recent work in the lipid pathway suggests that men's and women's cognitive trajectories may be differentially influenced by serum cholesterol and lipoprotein traits in periods of late adulthood (Reynolds et al., 2010) and likewise *SORL1* may have sex-dependent effects on cognitive trajectory features (Reynolds et al., 2013). Moreover, men

may be more likely to be diagnosed with MCI (Petersen et al., 2010; Roberts et al., 2012) and women with AD, including a greater risk conferred by carrying the *APOE* e4 allele (Genin et al., 2011). However, little evidence has emerged from quantitative behavioral genetic studies of qualitatively different heritable or environmental impacts on cognitive change (Finkel, Reynolds, Berg, & Pedersen, 2006). Work on motor functioning, however, suggests that important gender differences in life experiences for the cohorts in question can result in significant sex differences in genetic and environmental contributions to the aging process (Finkel, Ernsth-Bravell et al., 2014). Finally, further consideration of historical and emerging contexts is needed. For example, the extent to which cohort advances in education and other pervasive (positive and negative) environmental contexts might impact fundamental etiological processes underlying cognitive change is unclear. Hence, a greater understanding of complex life course or competing pathways to cognitive health in late life is warranted.

In sum, both quantitative genetic and molecular genetic approaches will remain necessary to achieve a fuller understanding of cognitive aging. Echoing an earlier *Handbook* chapter (Kremen & Lyons, 2011), we expect that future longitudinal behavioral genetic work, including examinations of biomarkers of gene–environment interplay across the life course, may provide a clearer picture of the contributions and dynamics of specific environmental and genetic factors that contribute to the diversity of cognitive aging outcomes. Fundamentally, cognitive aging *is* physical aging; therefore, future research will need to continue to incorporate the physical context of cognitive changes.

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