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Age-moderation of genetic and environmental contributions to cognitive functioning in mid- and late-life for specific cognitive abilities

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ABSTRACT

Age moderation of genetic and environmental contributions to Digits Forward, Digits Backward, Block Design, Symbol Digit, Vocabulary, and Synonyms was investigated in a sample of 14,534 twins aged 26 to 98 years. The Interplay of Genes and Environment across Multiple Studies (IGEMS) consortium contributed the sample, which represents nine studies from three countries (USA, Denmark, and Sweden). Average test performance was lower in successively older age groups for all tests. Significant age moderation of additive genetic, shared environmental, and non-shared environmental variance components was observed, but the pattern varied by test. The genetic contribution to phenotypic variance across age was smaller for both Digit Span tests, greater for Synonyms, and stable for Block Design and Symbol Digit. The non-shared environmental contribution was greater with age for the Digit Span tests and Block Design, while the shared environmental component was small for all tests, often more so with age. Vocabulary showed similar age-moderation patterns as Synonyms, but these effects were nonsignificant. Findings are discussed in the context of theories of cognitive aging.

1. Introduction

Cross-sectional and longitudinal research has consistently found that average cognitive test performance declines in late life (Salthouse, 2009). Nonetheless, there are marked individual differences in the timing and rate of cognitive aging, and late-life cognitive function is relatively etiologically distinct from cognitive function at earlier ages (Wilson et al., 2002). Late-life general cognitive ability (GCA) is also moderately to strongly heritable, with minimal shared environmental contributions (Johnson, McGue, & Deary, 2014). An important but largely unaddressed question concerns whether the magnitudes of genetic and environmental contributions to late-life cognitive ability differ from those at earlier life stages.

A prominent finding from the behavioral genetic literature is that heritability of behavioral phenotypes increases with age. In a meta-analysis of relevant twin studies, Bergen, Gardner, and Kendler (2007) reported that heritability of diverse behavioral phenotypes including anxiety, externalizing psychopathology, social attitudes, and GCA all increased with age. Other research has documented age-related declines in the importance of shared environmental influences for GCA (Haworth et al., 2010). There are, however, several important limitations in this literature. First, most of the research has focused on transitions from childhood to early adulthood; much less is known about the magnitudes of genetic and environmental contributions beyond

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early adulthood (Tucker-Drob & Briley, 2014). Second, research on cognitive transitions from childhood to early adulthood has focused almost exclusively on GCA rather than specific cognitive abilities, despite evidence of domain specific variation in their developmental trajectories. Third, most of the research has focused on standardized, rather than raw, components of variance. Greater heritability, a standardized metric, may be a consequence of less raw environmental contribution to variance, greater genetic variance, or both.

The magnitudes of genetic and environmental contributions to late-life cognitive function might differ from those at earlier ages for several reasons. Reduction in evolutionary pressures in late life as compared to other life stages is posited to lead to amplification of stochastic (i.e., random, Finch & Kirkwood, 2000) and epigenetic processes (Fraga et al., 2005). For example, many individual-level factors (i.e., blood pressure, and physical exercise) are associated with late-life cognitive functioning but not with cognitive status at younger ages (Anstey & Christensen, 2000). The cumulative effect of these factors might be reflected by increased environmental contributions to phenotypic variance with age (c.f., Baltes, Reese, & Lipsitt, 1980). Alternatively, changes in the magnitudes of genetic contributions may reflect amplification of existing genetic factors or mechanisms of gene-environment interplay (Reynolds, Finkel, & Zavala, 2013). For instance, genetic factors that protect against environmental influences leading to cognitive decline (e.g., active developmental processes, Scarr & McCartney, 1983) can lead to greater genetic variance in late life. High educational attainment, occupational complexity, and intellectually-stimulating activities may reflect genetically influenced selections that promote cognitive reserve and prevent decline (Bosma et al., 2002).

Behavioral genetic research on cognitive abilities does not always provide consistent evidence for age differences in relative magnitudes of genetic influences. Finkel and Reynolds (2010) reviewed the behavioral genetic literature on cognitive aging and concluded that heritability of GCA appears to increase through approximately age 60 and declines thereafter. Yet, in a subsequent large cross-sectional study of 2332 Danish twins age 46 to 96 years, McGue and Christensen (2013) reported that the magnitude of genetic influence on a measure of GCA was stable across age. Unlike the differential patterns observed by independent studies, recent meta-analyses of twin studies have better convergence to the patterns observed. In a recent meta-analysis of twin studies, Reynolds and Finkel (2015) reported that the heritabilities of specific cognitive abilities including verbal, spatial and memory, were largely stable or slightly increasing with age. Similarly, a large-scale meta-analysis of all published twin studies by Polderman et al. (2015) also found consistent evidence for stable heritability across age groups across cognitive domains of clustered executive functioning and memory abilities. Although these meta-analyses seem to provide a clearer and more consistent pattern of the genetic and environmental contributions to late life, they may be also obscuring differential trajectories for specific cognitive abilities, and indeed losing important informative differences across time.

Limited sample sizes and study and country differences may contribute to the apparent inconsistency of results concerning age moderation of genetic influences. In many cases, heritability of late-life cognitive ability is estimated in samples with a few hundred twin pairs, making it difficult for a single study to distinguish heritability differences across a wide age range reliably. Moreover, studies do not always report parameter estimates for the same biometric model, making it difficult to compare estimates using meta-analytic methods. For example, the shared environmental contribution is not always reported and some reported heritability estimates are based on models dropping this component.

This study includes 14,534 participants from a twin study consortium to investigate age moderation of genetic and environmental influences on cognitive ability in mid- through late-life. The large sample, broad age range (26 to 98 years), and multiple cognitive abilities included (six tests representing four separate domains of cognitive functioning – short-term/working memory, processing speed, spatial processing, and verbal ability) make this the most comprehensive test to date of the hypothesis that the magnitudes of genetic and environmental influences on cognitive functioning differ in late-life compared to earlier life stages. In addition, the consortium this study is derived from provides a special opportunity to directly assess differential evidence found by independent studies, often from competing independent studies that are included in this consortium group, while simultaneously examining if there are informative differences across time that meta-analytic work may not have been able to observe.

2. Method

2.1. Participants

The sample was drawn from nine studies representing three separate countries (Sweden, Denmark, and the United States) from the Interplay of Genes and Environment across Multiple Studies (IGEMS) consortium (Pedersen et al., 2013). No studies had overlapping participants. To be included in our analysis, participants had to have completed at least one of six cognitive tests (described below), and have a Mini-Mental State Examination (MMSE) score of at least 24, following the typical cutoff for cognitive impairment (Tombaugh & McIntyre, 1992). A total of 1136 (7.8% of the total number of potential participants) were excluded based on this screen, leaving a sample of 14,534 (50.9% women) individual twins. The sample included 2341 pairs of monozygotic (MZ) twins, 2429 pairs of dizygotic-same sex twins (DZ-ss), and 929 pairs of dizygotic-opposite sex twins (DZ-os). The sample also included 3128 unpaired twins, who were informative with respect to age differences in means and variances and so were included in the analyses. For studies with longitudinal assessments, only data from the first test administration for each participant were used in the cross-sectional analyses reported here. Mean age at that measurement occasion was 61.3 years (Mdn = 59.82, *SD* = 13.0). The median was slightly lower than the mean, suggesting a positive skew, although the difference is about a one tenth of a SD. Demographic characteristics for each study, including sample size, gender ratio, age, zygosity and which cognitive tests were administered, are given in Table 1. Fig. 1 gives the age distribution of the total sample. Brief descriptions of each of the nine studies, separated by country of origin, are given below. Additional details concerning the methodology for each study can be found in the citations provided.

2.1.1. Sweden

IGEMS includes four Swedish studies whose samples were all ascertained from records from the Swedish Twin Registry: Swedish Adoption/Twin Study of Aging (SATSA; Pedersen et al., 1991), Aging in Women and Men (GENDER; Gold, Malmberg, McClearn, Pedersen, & Berg, 2002), Origins of Variance in the Oldest-Old (OCTO-Twin; McClearn et al., 1997), and Twin-Offspring Study in Sweden (TOSS; Neiderhiser, Reiss, Lichtenstein, Spotts, & Ganiban, 2007). Parallel cognitive assessments were used across SATSA, OCTO-Twin and GENDER, and all three studies were longitudinal. The Swedish studies are distinguished by the age range and zygosity represented. SATSA participants include same-sex twins, with a subsample of twins reared apart matched to a subsample of twins reared together by birthdate and county of birth and gender. SATSA in-person testing protocol (IPT) followed a cohort-sequential protocol. Those who had reached age 50 were invited to participate in IPT that began in 1986. At subsequent IPTs, typically conducted at 3-year intervals, SATSA-eligible twins who reached age 50 were invited to participate. Intake cognitive data were collected over four IPT sessions. The age range at initial cognitive testing was 50.0 to 88.0.

GENDER consists of opposite sex twin pairs born between 1906 and 1925. Intake cognitive assessments were completed during a four-year period starting in 1995, when the twins were between 70 and 81 years