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Cognition in Context: Pathways and Compound Risk in a Sample of US Non-Hispanic Whites

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Abstract

The population of individuals with cognitive impairment and dementia is growing rapidly, necessitating etiological investigation. It is clear that individual differences in cognition later in life have both genetic and multi-level environmental correlates. Despite significant recent progress in cellular and molecular research, the exact mechanisms linking genes, brains, and cognition remain elusive. In relation to cognition, it is unlikely that genetic and environmental risk factors function in a vacuum, but rather interact and cluster together. The purpose of the present study was to examine whether aspects of individual socioeconomic status (SES) explain the cognitive genotype-phenotype association, and whether neighborhood SES modifies the effects of genes and individual SES on cognitive ability. Using data from non-Hispanic White participants in the 2016 wave of the Health and Retirement Study, a national sample of United States adults, we examined links between a polygenic score for general cognition and performance-based cognitive functioning. In a series of weighted linear regressions and formal tests of mediation, we observed a significant genotype-phenotype association that was partially attenuated after including individual education to the baseline model, although little reductions were observed for household wealth or census tract-level percent poverty. These findings suggest that genetic risk for poor cognition is partially explained by education, and this pathway is not modified by poverty-level of the neighborhood.

Keywords: cognition, polygenic score, education, wealth, neighborhoods, poverty

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Decades of research in behavioral genetics, with more recent evidence from molecular genetics, have demonstrated a genetic basis for many cognitive functions (Bouchard & McGue, 1981; Papassotiropoulos & de Quervain, 2011). Level of general intelligence is shared among members of the same family (Bouchard & McGue, 1981; Briley & Tucker-Drob, 2017), and specific genetic regions have been identified that are associated with specific abilities such as episodic memory, for example (Papassotiropoulos & de Quervain, 2011). Meanwhile, the mechanisms explaining how genes influence these various cognitive functions remain elusive. Given the phenotypic correlations among specific cognitive abilities, such as memory and mental status investigated in the current study, and multiple other psychosocial, socioeconomic, and health factors (Briley & Tucker-Drob, 2017), the mechanisms explaining the cognitive genotype-phenotype association may also be represented by multi-level factors spanning biology to broad social environments (Boardman, Daw, & Freese, 2013).

In this paper, we focus on social ecological factors that may either explain or modify associations between a genetic score for general cognition and tests of mental status and memory. Neighborhood environments, for example, such as those with greater levels of poverty, are associated with poorer performance on tests of memory and mental status (Aneshensel, Ko, Chodosh, & Wight, 2011; Wu, Prina, & Brayne, 2015) regardless of individual or family-level socioeconomic status (SES). Moreover, cognitive heritability is also attenuated among children who are raised in impoverished home environments (Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). That is, both average cognition *and* genetic contributions to variation in cognition are reduced among those residing in relatively impoverished environments. To date, little research has focused specifically on neighborhood context and genetic contributions to cognition, and among those that have (Englehardt, Church, Harden, & Tucker-Drob, 2018) few have used measured genotypes and none have specifically looked at older adults. The purpose of the present study is to determine whether this socioeconomic status x genetic interaction extends to broad neighborhood environments among this unique, older cohort. To this aim, we analyzed a measure of general cognitive ability that is constructed from four telephone interview-

based tests of memory and mental status (immediate and delayed recall, Serial 7s, and Backward Counting) that have been demonstrated to predict classification of older adults into normal, cognitively impaired without dementia, and demented groups at 74 percent accuracy in a large population study when compared to a sample of adults who have undergone psychiatric evaluation (Crimmins, Kim, Langa, & Weir, 2011).

Genetics of Cognition

Longitudinal analysis of twin and family data not only suggest a genetic inheritance for cognitive ability, but also that heritability of cognition increases with age (Tucker-Drob et al., 2013). While the baseline heritability estimates among very young children suggest an important role of genetics in cognition, the increasing role of genetics across the life course points to two important phenomena. First, there is a genotype-environment transaction whereby individuals with a greater number of genotypes related to higher performance on standard cognitive assessments sort into environments that stimulate further cognitive enhancements. Because of the increase in genetic influence on many cognitive functions across the life course (Tucker-Drob et al., 2013), it is possible that some of the sorting may be *evocative* in which teachers, counselors, and school administrators sort children into different educational tracks because of observable traits that are associated with unobservable genotypes. Second, there remains a possibility that specific genetic regions that may not have influenced cognitive abilities early in life become more relevant for cognition at later points in the lifespan.

In terms of the specific genetic regions that play a role in cognitive ability, early studies yielded evidence implicating several candidate genes, including COMPT, GRM3, PRNP, CHRFAM7a, and APOE (Papassotiropoulos & de Quervain, 2011). More recently, in the context of genome-wide association studies, researchers have posited the polygenicity of cognition, or that individual differences in cognition are likely the result of many genetic regions and their correlations with one another (e.g., Ware, Schmitz, Gard, & Faul, 2018). Taken together, findings from both behavioral and molecular genetics suggest that general intelligence and its many correlates, including specific abilities such as memory and mental status, are at least partially heritable (Tucker-Drob, Briley, & Harden, 2013).

Genetics of Socioeconomic Status

SES is often operationalized by an individual's education, income, occupation, or some combination. These aspects of SES, both in childhood and in midlife, are correlated with cognitive ability in later life (e.g., Greenfield & Moorman, 2019). The degree to which each of these aspects of SES has a genetic basis will be considered separately in the sections that follow. Before considering behavioral or molecular genetic evidence indicating the heritability of SES, social scientific investigation into the intergenerational transmission of SES will be considered.

Longitudinal analysis of child-parent SES correlations suggests that offspring's SES often resembles that of their parents' (Bjorklund, Jantti, & Solon, 2007; Braun & Stuhler, 2018). This pattern emerges regardless of whether children are reared by their biological or adoptive parents, although correlations are generally higher for those raised by biological parents. These studies have provided evidence for both genetic and environmental transmission of education attainment, with some, although smaller and less stable evidence for the intergenerational transmission of earned income. Suggested mechanisms explaining the intergenerational transmission of SES include parental investment in the child's human capital and role-modeling the performance of reliable work – both of which comprise an environmental influence – as well as genotypes associated with cognitive and education phenotypes that are passed from parent to child (Bjorklund et al., 2007). Others have observed that childhood human capital, including health and nutrition, cognitive abilities, and early educational experiences, explain up to 50 percent of the transmission of SES from parent to child (Carvalho, 2012).

Education**.** In an attempt to summarize existing knowledge regarding the heritability of education attainment, or the number of years of education an individual completes, a meta-analysis was conducted using samples of twins from the United States, Australia, and Western Europe (Branigan, McCallum, & Freese, 2013). Results of this meta-analysis suggested significant twin similarity on education attainment, and that this similarity was explained by both additive genetic influences ($h^2 \sim .40$) and shared environmental influences, or influences from environmental factors that were shared between members of the same family. Interestingly, the heritability of educational attainment varied significantly by sex, birth

cohort, and nationality, suggesting that environmental factors likely modify the genetic influence on educational attainment. This modification again highlights the importance of the gene-environment interaction perspective in this literature.

Years of educational attainment is among the social phenotypes for which molecular geneticists have contributed significant understanding, both in terms of identifying causal variants and in the ability to predict phenotypic variability (Plomin & von Stuum, 2018). Success in genetic prediction of this phenotype has been made possible given that education is commonly included as a covariate in genome-wide association studies, enabling the pooling of genetic effects over a large collection of studies. Current understanding suggests that over 10 percent of the variance in education attainment is explained by small genetic influences distributed over hundreds of single nucleotide polymorphisms (Lee et al., 2018). This finding further corroborates evidence from behavioral genetic methods, indicating twin similarity on educational outcomes (Branigan et al., 2013).

Income**.** Given the mounting evidence suggesting familial similarity of education attainment (Branigan et al., 2013), and that educational degrees often afford a wider range of occupational opportunities, it is unsurprising that familial similarity in lifetime earnings is also heritable (e.g., Hyytinen, Ilmakunnas, Johansson, & Toivanen, 2019). A recent investigation of twenty years' worth of earnings data yielded heritability estimates that reached 54 percent for men and 39 percent for women, with very little change in these estimates depending on the source of income considered (Hyytinen et al. 2019). The gender difference in heritability was attributed to factors such as intermittent leaves from work that may occur more frequently among women than men, and potential gender differences in genetically-influenced occupational choices (Hyytinen et al., 2019).

Findings from twin and family studies have are further supported by genome-wide association investigations, as a recent study observed 120 independent genetic loci, implicating 24 genes that were associated with income levels (Hill et al., 2019a). Further investigation demonstrated both genotypic and phenotypic associations between education and intelligence, an underlying latent factor thought to inform performance on various cognitive tasks (Hill et al., 2019b). Intelligence may not only set people's

trajectory toward greater education attainment (Hill et al., 2019b), which in turn enables people to obtain higher-paying, more prestigious occupations (Heckman, Stixrud, & Urzua, 2006). The literature indicating that individuals select into environments varying in levels of cognitive stimulation has already been discussed in the context of the genetics of cognitive development (Tucker-Drob et al., 2013). One of the environments most salient in the lives of adults is place of work. Evidence for genetic selection into specific occupations helps to clarify how genetic regions relevant for cognitive ability may systematically sort individuals into cognitively stimulating occupations, which in turn, afford people higher wages (van Ophem, Hartog, & Vijverberg, 1993).

Cognition, Education, and Income**.** The review above describes work in three primary areas in which genetic and environmental contributions are estimated independently for cognition and two components of socioeconomic status: education and income. Rowe, Vesterdal, and Rodgers (1998) use data from the National Longitudinal Study of Youth (NLSY) to estimate the extent to which genetic contributions to these three traits are unique or shared. They estimated univariate heritability values of .64, .68, and .42 for IQ, education, and income, respectively. Importantly, each of these traits appears to be influenced by a common genetic factor such that 68% of the correlation between IQ and education, and 59% of the correlation between IQ and income appears to be due to common genetic mediation. Their work focused on a younger cohort of adults (ages 28-35 in 1992) and they did not specifically examine the mechanisms in place. That is, while genetic correlation is an important component, others have shown (Wedow, Zacher, Huibregtse, Harris, Domingue, & Boardman, 2018) that environmental moderation of genetic correlation is also a critical perspective when describing the pathways that may undergird correlated genotypes.

Neighborhood selection**.** That environmental features may moderate genetic correlation is particularly important when it comes to work in the area of neighborhood effects. Neighborhood-health effects are often questioned, given that individual characteristics (including genetic background) may explain both the process through which people live in certain neighborhoods and the process through which people develop various health conditions (Pickett & Pearl, 2001). Indeed, researchers have

observed that adults who had been raised in the same family live in somewhat similar neighborhoods, at least as far as how safe neighborhoods are perceived to be (e.g., Robinette & Beam, 2018). Moreover, research with large samples of unrelated adults has demonstrated that people with similar genetic backgrounds cluster, at least at the state level (Domingue, Rehkopf, Conley, & Boardman, 2018). These studies suggest at least the potential that genetic backgrounds may sort people into their neighborhoods. With the growing availability of genetic data in large national surveys, it is becoming possible to examine genetic influences on selection into more granular, neighborhood levels. For example, using a variety of descriptive and empirical approaches, a recent study demonstrated that people with similar values on a polygenic score for education attainment cluster in neighborhoods that are similar in levels of population density, average education level, and median home values (Laidley, Vinneau, & Boardman, 2019). A plethora of research indicates phenotypic associations between various aspects of SES, whereby Individuals who earn higher educational degrees typically obtain higher-earning occupations, and more often than not, inhabit neighborhoods with average costs that are within their means. The above research suggests that common genetic influences may further elucidate correlations among these socioeconomic phenotypes and partially explain selection into specific neighborhoods.

Moreover, residing in neighborhoods with more socioeconomic disadvantage during midlife is a risk factor for poor cognitive abilities later in life, particularly for individuals who are themselves poor (Aneshensel et al., 2011; Wu et al., 2015). Several mechanisms have been identified for this association, including less cognitive stimulation in environments with lower average education levels, built environmental features that stymy the ability to engage in adequate physical activity, and social stressors that thwart social interaction and the development of coping reserves (Besser, McDonald, Song, Kukull, & Rodriguez, 2017; Wight et al., 2006). This body of research suggests the possibility that genetic predisposition for cognition may predict the specific neighborhoods in which people live, and that exposure to features of one's neighborhood (e.g., socioeconomic disadvantage) may then partially explain individual differences in cognitive abilities.

From Genes to Cognition: Social ecological mechanisms

Complex traits are thought to be the result of genetic influences, environmental influences, and correlations between the two, whereby genetic influences sort people nonrandomly into various environments (Boardman, Daw, & Freese, 2013; Plomin, DeFries, & Loehlin, 1977). Cognitive ability is not likely an exception to these posited gene-environment correlations (Briley & Tucker-Drob, 2017), and is likely informed by a unique form of gene-environment correlation (Tucker-Drob et al., 2013). Individual differences in genetic influences that predispose enhanced cognitive functioning likely also influence the degree to which individuals seek out cognitively stimulating experiences and environments. This unique form of active gene-environment correlation is said to be transactional, as cognitively stimulating environments provide the necessary resources to enable genetic predisposition for cognitive ability to manifest. In a recent paper, Englehardt et al. (2018) examined cognition and academic achievement using data on twins aged 7-20 from the Texas Twin Project (n = 1,728 pairs). Their analysis suggested that racial/ethnic status as well as a combination of multiple family (socioeconomic status, parental conflict), school (teaching characteristics, school performance), and neighborhood (socioeconomic status, residential instability) factors explained 100 percent of the variance in cognitive ability as measured by tests of intelligence. They highlighted that neighborhood SES explains roughly 20% of the variation in cognition and academic achievement when measured as a single indicator of context and they highlight the centrality of neighborhoods in our understanding of how, when, and for whom specific genetic variants may matter. Specifically, they conclude with a call for "'polyenvironmental risk scores' in an effort to better predict developmental outcomes and to quantify children's and adolescents' interrelated networks of experiences."

The transactional nature of genotypic and environmental influences on cognition described above, whereby genotypes for higher general cognitive performance sort people into cognitively stimulating environments, helps clarify both the development of cognitive abilities in youth (Tucker-Drob et al., 2013) as well as observed cognitive gene-by-environment interactions (G x E; e.g., Scarr-Salapatek, 1971; Turkheimer et al., 2003). Specifically, cognitive heritability may not be observed unless adequate

environmental resources are available to support genetic potential. For example, individuals from high SES backgrounds enjoy exposure to cognitively-stimulating resources that are largely unavailable to their lower SES counterparts. Furthermore, a study of nearly 2000 adult twins demonstrated that this gene x socioeconomic status interaction extends to intelligence in adulthood (Bates, Lewis, & Weiss, 2013).

Investigations of G x E often define the 'environment' as health behaviors or school and family characteristics (i.e., anything outside the genome), and these investigations rarely extend to neighborhoods (Boardman et al., 2013), although one influential example assessed neighborhood gene x socioeconomic status interaction in a sample of nearly 1000 twin pairs attending Philadelphia schools (Scarr-Salapatek, 1971). Results of the study yielded several conclusions. First, the degree of genetic relatedness was positively correlated with twin similarity on tests of intelligence (i.e., genetic influences). Second, intelligence was significantly higher among whites and those living in higher socioeconomic status census tracts compared to blacks and those living in lower socioeconomic status census tracts (i.e., environmental influences). Third, there was stronger evidence for heritability of intelligence among whites and those living in more advantaged, relative to blacks and those living in disadvantaged census tracts (i.e., differential heritability). Similar results were presented by Boardman et al. (2012) who show that the effect of the e4 allele in APOE had little to nothing to do with cognitive decline among residents of the most socially disorganized and disorderly neighborhoods in Chicago. The authors argue that the social environment is 'pushing' the phenotype in these communities and small genetic associations are nearly impossible to detect in light of the large amount of social 'noise.'

The scant existing research that does define the environment in G x E investigations at the neighborhood-level (Laidley et al., 2019; Scarr-Salapatek, 1971) has focused on cognitive and educational outcomes in youth, a portion of the lifespan characterized by growth and development. Even less attention has been afforded to cognitive outcomes in older adulthood when the focus is on maintenance, and perhaps decline in cognitive ability. The degree to which individuals are sorted into neighborhoods based on genotypes related to cognitive ability remains uncertain. This sorting is plausible, given that cognitive ability may predict years of education attainment, which then predicts

higher wage-earning occupations. Indeed, findings yielded from neighborhood-health research are often questioned, as it remains unclear how much of the published findings are better explained by characteristics of the residents (e.g., genes), rather than characteristic of a true contextual effect (Diez Roux & Mair, 2010).

As previously stated, the exact mechanisms linking cognitive genotypes to cognitive performance are far from fully described. Extrapolating from previously described investigation of educational genotypes (Laidley et al., 2019), there exists a potential that shared genetic regions predict not just general cognitive ability, education attainment, and then selection into broader, neighborhood environments. In the absence of more empirical investigations, it remains possible that exposure to various neighborhood environments may either partially explain (via a transactional model) or even modify (differential heritability across neighborhoods varying in socioeconomic status) the cognitive genotype-phenotype association.

The present study

In the present study, we situate our aims under the transactional gene-environment correlation framework (Tucker-Drob et al., 2013), whereby genetic influences on cognitive abilities predict socioeconomic characteristics such as education attainment that enable people to move into higher socioeconomic environments that in and of themselves, further modulate cognitive ability. We consider the degree to which genetic influences on cognition may systematically distribute individuals along the socioeconomic spectrum (via individual education and household wealth) and into socioeconomically-varying neighborhoods. We compare alternative scenarios in which neighborhood socioeconomic status either explains or modifies the cognitive genotype-phenotype association. The present study aims to further understanding by evaluating the following questions that are summarized in Figure 1:

1. Mediation: to what extent do aspects of socioeconomics status explain the association between the cognition polygenic risk score and cognition performance in later life?
2. Moderation: does the strength of the cognitive genotype-phenotype association differ for individuals residing in neighborhoods with low, average, or high rates of poverty?

3. Moderated mediation: are the hypothesized socioeconomic pathways between cognitive polygenic risk score and later life cognition comparable across neighborhoods with low, average, or high rates of poverty?

In doing so, we attempt to contextualize the meaning of polygenetic associations with their respective phenotypes. We feel that this is critical to work in this area that goes beyond the traditional gene-environment interaction perspective and it is very much aligned with recent calls to make this approach the norm. A recent publication summarizes this by stating that "[t]he expression of 'intelligence genes' may cluster inside the head, but this expression profile cannot be meaningfully evaluated without first considering the prior contributions of cumulative culture, which are invisible to standard methods within behavioral genetics" (Uchiyama, Spicer, & Muthukrishna, 2020). While this point highlights sociocultural mechanisms specifically, we feel that contextualizing genetic associations is consistent with current scientific thinking and much more in-line with individuals' day-to-day experiences.

Method

Participants and Procedures

Data for the present study came from the 2016 wave of the Health and Retirement Study (HRS), a national survey of men and women aged 51 years or more residing in the United States. Through telephone interviews, self-administered questionnaires, and biological sample collection, Health and Retirement Study researchers have observed mental and physical health, cognitive and physical functioning, and behavioral, demographic, and economic well-being every two years since 1992. Starting in 2006, saliva samples have been collected from which DNA has been extracted. Genotyping was conducted by the Center for Inherited Disease Research (CIDR) in 2011, 2012, and 2015 (RC2 AG0336495 and RC4 AG039029). Genotype data on over 19,000 Health and Retirement Study participants was obtained using the Illumina HumanOmni2.5 BeadChips (HumanOmni2.5-4v1, HumanOmni2.5-8v1, HumanOmni2.5-8v1.1), which measures ~2.4 million single nucleotide polymorphisms. Individuals with missing call rates >2%, SNPs with call rates <98%, Hardy-Weinberg Equilibrium p-value < 0.0001, chromosomal anomalies, and first-degree relatives in the Health and

Retirement Study were removed. Health and Retirement Study researchers have constructed polygenic scores for a myriad of complex traits, including general cognition, from this genetic data (for detailed information about polygenic risk score construction in the Health and Retirement Study data see Ware et al., [2018]). The RAND Institute has constructed various economic measures to track household-level wealth. Additionally, Health and Retirement Study respondent records, including all genetic, health, and sociodemographic information, can be linked with administrative data available in the Health and Retirement Study Contextual Data Resource (CDR). The Contextual Data Resource includes information about census tract-level poverty. The analytic sample used in the present analyses was restricted to home-dwelling individuals who identify as non-Hispanic White (n = 7,493) to adjust for potential genetic population stratification (Novembre & Stephens, 2008).

Measures

General cognition phenotype. Four cognitive tests conducted via the 2016 telephone interview were used in the present analyses (Ofstedal, Fisher, & Herzog, 2005). Memory was assessed with two tasks, immediate and delayed recall. These tasks, each yielding scores ranging from 0-10, ask participants to remember a list of 20 nouns right after hearing them for the first time, and again five minutes later. Working memory was assessed with the Serial 7's task, which requires participants to subtract increments of 7 from 100 with a final score ranging from 0-5. As a measure of mental status, Health and Retirement Study participants completed the Backwards Counting task. This task is completed by counting backwards one continuous number at a time starting at the number 20, and yields a score ranging from 0-2. A composite measure representing general cognitive ability, ranging from 0-27 with higher scores representing better cognition, was constructed by summing scores on these four individual scales (Crimmins et al., 2011). Descriptive statistics for all variables used in the analyses are presented in Table 1.

[Table 1 about here]

General cognition polygenic score. Health and Retirement Study researchers have constructed a polygenic risk score for general cognition, provided to the public in standardized form with a mean of 0 and a standard deviation of 1 (Ware et al., 2018). Positive values represent greater genetic predisposition for higher cognitive performance. Using data from a large meta-analysis (Davies et al., 2015), the score was constructed by calculating a weighted sum of single nucleotide polymorphisms reaching genome-wide significance with general cognitive ability.

Mediators. First, years of schooling was obtained from the Health and Retirement Study tracker file, coded continuously in years. Second, the RAND Institute has constructed a measure of household-level wealth that sums all sources of income from both participant and spouse (e.g., earnings, social security payments, Medicare Part B, pension and retirement, interest, rents, educational assistance, alimony), and subtracts from this all sources of debt (e.g., mortgages from primary and secondary homes, other home loans, and sources of debt not asked) (Bugliari et al., 2016).

Moderator. Census tract-level poverty was obtained from the Health and Retirement Study Contextual Data Resources. The Contextual Data Resource contains the American Community Survey five-year (2012-2016) estimate of the proportion of households within the census tract with income levels at or below the federal poverty threshold. For the purposes of conducting stratified models, a tertile variable was constructed that classified each participant into groups of equal size representing those living in low, moderate, and high poverty areas.

Covariates. Age was coded in years and gender was coded 0 = male, 1 = female. To further adjust for potential population stratification, genetic principle components were included as covariates (Ware et al., 2018). Principle component analysis is conducted by Health and Retirement Study researchers (Ware et al., 2018), and the resulting sample eigenvectors are provided to outside researchers for inclusion in statistical models to adjust for potential population stratification.

Statistical Analysis

All linear regression analyses were conducted in SAS version 9.4. For Question 1, coefficients representing the association between the cognitive polygenic risk score and telephone-based general cognitive performance were examined in a baseline model (Model 1) and models that introduced, one at a time, education (Model 2), household wealth (Model 3), and census tract poverty rate (Model 4). Model 5 included each of these potential mediators simultaneously. The Hayes Process macro was utilized to enable formal tests of mediation (Question 1), and moderated mediation (Question 3; Hayes, 2013). In models stratified by low, average, and high census tract poverty rate, coefficients representing the direct (Question 2) and indirect (Question 3) effects between the cognitive polygenic risk score and cognitive performance were examined. All models adjusted for age, gender, and genetic principle components (PCs; Novembre & Stephens, 2008).

Results

[Table 2 about here]

The results presented in Table 2 address one of the primary questions of our analyses. Specifically, of the three domains of socioeconomic status that we consider (e.g., education, wealth, and neighborhood poverty), to what extent is each factor implicated in the pathways between cognitive polygenic risk score and later life cognition (e.g., Mediation). Model 1 presents the baseline estimate of the Cognition polygenic risk score on later life cognition (b= .419, p<.0001) and it includes controls for age, sex, and the top 10 principle components. The second model adjusts for years of education which is strongly associated with later life cognition (b = .562, p<.001) and reduces the effect of the Cognition polygenic risk score by nearly 28% to b = .302 (p<.001). Thus, years of educational attainment mediates a significant portion of the Cognitive polygenic risk score – Cognition association in our study. Models 3 and 4 introduce controls for household wealth and neighborhood poverty, respectively. While each SES indicator is strongly related to later life cognition in the anticipated direction, neither reduced the baseline effect of the cognitive polygenic risk score in any meaningful way. That is, the association between the

genetic variants linked to cognition and later life cognitive function does not appear to operate through the accumulation of wealth or the selection into different types of neighborhoods. Model 5 includes the three measures of SES together; the effects of wealth and neighborhood poverty are both significantly reduced in magnitude suggesting that a large portion of the associations in Models 3 and 4 are operating through completed years of education. Likewise, the effect of the Cognitive polygenic risk score is virtually identical to the effect from Model 2 providing further evidence that any SES mediation is operating through educational attainment.

[Table 3 about here]

The results presented in Table 3 address our second and third questions. The second question focused on the extent to which the Cognitive polygenic risk score and later life cognition association is comparable across neighborhoods varying in poverty (e.g., moderation). While the direction of the effect sizes is in line with previous research in which genetic associations for cognition are more pronounced among residents of less impoverished communities (Boardman et al. 2012), the post-hoc tests for the differences in these associations indicate that they are not statistically different from zero. This is the case for the total and direct effect of the Cognitive polygenic risk score. In ancillary analyses, we also evaluated this same association with a cross-level interaction term between neighborhood poverty and cognitive polygenic risk score and, as with our results, this interaction term was negative (again indicating a weaker effect of the polygenic risk score in poor neighborhoods), but it was not statistically significant at the traditional .05 level.

Our final question has to do with neighborhood-level differences in the socioeconomic pathways of education and wealth (e.g., moderated mediation). That is, our results in Table 2 suggested that the bulk of the mediation was taking place though years of completed education, but it is possible that the relative influence of education or wealth may depend on the type of community in which one lives. With respect to education, we find no evidence that the extent to which education mediates the relationship

between Cognitive polygenic risk score and cognition depends on the poverty rate of one's neighborhood. The indirect effects of .119, .094, and .113 are all significantly different from zero but they are not significantly different from one another. However, we find some tentative evidence that wealth may be implicated in the linkage between Cognitive polygenic risk score and later life cognition, but only among those in neighborhoods with average poverty rates. This is shown in two ways. First, the indirect effect estimate (b=.015, p<.0498) is statistically significant and second, this estimate is significantly different from the estimate in High Poverty neighborhoods (p<.0406). These results are in line with the social push GxE perspective described in greater detail below.

Discussion

In the past, researchers have rarely had access to data rich enough to test the possibility of neighborhood gene-environment interplay in relation to cognition in a nationally representative sample of older adults. With such data at hand, the present study set out 1) to further characterize potential social ecological mechanisms underlying the cognitive genotype-phenotype association, 2) to examine the degree to which genetic influences on general cognitive ability sort people into their socioeconomic environments, and 3) to examine whether G x SES on cognition observed in the literature (Turkheimer et al., 2003) extends to neighborhood SES.

Results from the present study confirmed and replicated the cognitive genotype-phenotype association (Papassotiropoulos & de Quervain, 2011; Tucker-Drob et al., 2013), with individuals with higher polygenic risk score for general cognition performing better on telephone-administered tests of memory and mental status. Moreover, and regarding the first goal listed above, this cognitive genotype-phenotype association was partially explained by individual education attainment, with no evidence that household wealth further explains this association. These results suggest a social ecological mechanism linking genes to cognition, whereby higher polygenic scores for general cognition set individuals on trajectories towards obtaining more years of education, which may in turn stimulate greater maintenance of memory and mental status in older adulthood.

G x Neighborhood Socioeconomic Status

A large literature attests to associations between neighborhood SES and health, spanning psychosocial, physical, and cognitive outcomes (Diez Roux & Mair, 2010). This literature is often criticized for insufficient attention to potential selection bias (Picket & Pearl, 2001). Specifically, observed neighborhood SES-health associations may be spurious, and better explained by individual difference characteristics. Examples of studies in which individual-level SES and other sociodemographic characteristics that may bias observed neighborhood effects are adjusted abound, but to our knowledge, genetic risk for the outcome of interest has yet to be included as a potential covariate. Individuals in the present study living in higher poverty areas performed significantly worse on tests of memory and mental status, and this association persisted after including years of education and household poverty in the model (Model 5 in Table 2). A unique contribution of the present findings, however, and in support of our second goal listed above, is that the neighborhood-cognition association also persisted with the polygenic risk score for general cognitive functioning in the model. At least when it comes to cognitive outcomes associated with memory, the present results suggest there is little reason to assume that neighborhood-cognitive associations are an artifact of individual differences in genetic risk.

With regard to cognitive health and well-being, neighborhoods are broad environments that can offer opportunities for social interaction and engagement. In disadvantaged neighborhoods, however, such social interaction is impeded by social and physical deterioration which elicits mistrust and fear, often resulting in social withdrawal (Massey & Denton, 1993). With regard to the present results, it is possible that such social withdrawal may isolate residents from the benefits of informational and socioemotional exchanges which may boost cognitive functioning. In the present study, maintaining a residence in a neighborhood with a higher poverty rate was directly related to poorer cognitive ability. Finally, and in relation to our third goal listed above, neither the direct effect of cognitive genotypes on cognitive performance, nor the indirect effect of cognitive genotypes on cognitive performance through individual education, however, were modified by poverty rate of the census tract. It is likely that the neighborhood effects observed in the present study are better explained by other contextual features.

Limitations and Future Directions

Both the genetics (Harris & Deary, 2011; Levine, Harrati, & Crimmins, 2018) and the environmental influences on cognition may differ depending on whether one considers cognitive level versus cognitive change. With an ambitious set of hypotheses stated at the outset, the present study was focused on a single cross-section of memory and mental status among a nationally representative sample of older men and women. Future investigations should explore whether current results may differ when compared to models predicting cognitive change over longer periods of time. In a similar vein, the present analyses examined a polygenic score for general cognition, both its main and interactive effects, on performance on tests of memory and mental status. This polygenic score takes into account participants' genotypes only, and not also potential differential patterns of DNA methylation, or epigenetic effects, across individuals residing in neighborhoods varying in poverty level. Inclusion of such epigenetic effects will be an important direction for future research. Additionally, our theoretical model was driven by the hypothesis that social ecological factors (e.g., education attainment, household wealth, and neighborhood poverty) may mediate or moderate the general cognition genotype-phenotype association. Meanwhile, we are aware that associations also exist among these social ecological factors (i.e., individuals with more education likely accrue more wealth through higher wage-earning occupations). These more nuanced pathways were not specifically examined in the current analyses which focused on 1) individual socioeconomic mediators of the general cognition genotype-phenotype association, 2) gene-environment correlation, and 3) gene x environment interactions. Lastly, given the potential for population stratification to bias estimates, we followed standard procedures (Novembre & Stephens, 2008) and limited our analytic sample to non-Hispanic Whites. As such, results cannot be generalized to members of other, particularly marginalized racial/ethnic groups. Future research should investigate cross-racial comparisons.

Statistical geneticists often advise restricting an analytic sample to non-Hispanic Whites when using polygenic scores that are constructed among non-Hispanic whites to address ancestrally-distinct genetic architecture (Martin et al., 2017). Indeed, the Health and Retirement Study polygenic

score data provides separate polygenic risk score information for European and African ancestry respondents. Meanwhile, exposure to environmental hazards, which is more descriptive of the racial/ethnic minority experience when compared to non-Hispanic Whites (Roca, Ellen, & Oregan, 2013), may masque genetic effects on traits such as general cognitive ability among racial/ethnic minorities. Coupled with the fact that DNA samples are not collected from Health and Retirement Study respondents whose cognitive data are provided by proxy informants, precluding inclusion of the most cognitively-impaired individuals from analysis, the resulting sample is likely a select group of cognitively-intact, somewhat wealthier, racially/ethnically homogeneous individuals. More work is needed to address the potential of environmental moderation of genotype-phenotype associations across racially/ethnically diverse samples.

One additional limitation was our inability to differentiate between different models of gene-environment correlation which are critical with regards to issues of selection. That is, the three forms of gene-environment correlation include *active*, in which individuals with a particular genotype actively select into specific environments, *evocative* in which individuals are sorted into different environments because of observable traits that are linked to genotype, and *passive* in which individuals inherent both their genes and their environments from their parents. In this manuscript, we use a general language of selection which may give undo weight to the notion that selection is active on the behalf of the individual when, as others have shown (Boardman et al. 2012) evocative gene-environment correlation points to broad sorting processes that are outside of the individual's control. Readers should consider this distinction when considering the implications of our findings and we encourage researchers to explore these questions in their future work.

Declarations of interest: none

The work reported has not been submitted or published elsewhere.

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Figure 1. Conceptual Model for the Relationship between Polygenic Scores for Cognition, SES, and Cognition.

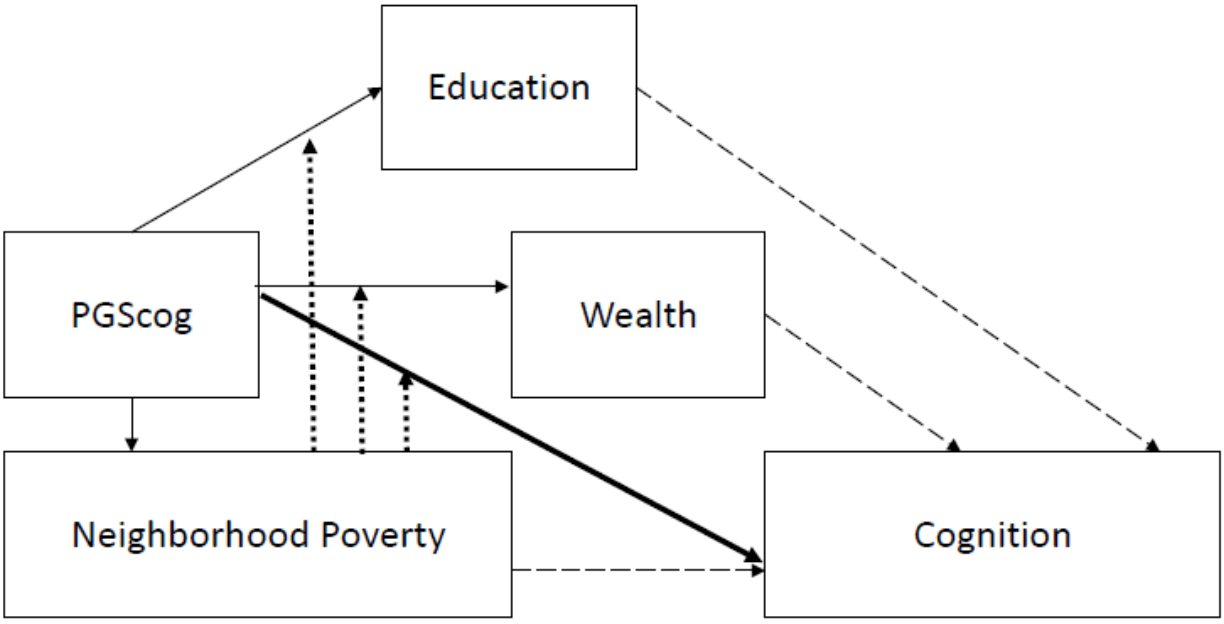

Table 1. Description of non-Hispanic White analytic sample (n=7,493)

	Mean **(*sd*)**	**Range**
Cognitive Performance	15.71 (4.25)	0-27
Cognitive polygenic risk score	0.00 (1.00)	-3.96-4.03
Individual Education (in years)	13.57 (2.40)	0-17
Household Wealth	$539,201 ($1,331,845)	$-999,870-31,016,883
Census Tract Poverty	0.15 (0.05)	0.04-0.39
Age	71.17 (10.26)	36-101
Sex at Birth (%)		
Men	41% 3072	
Women	59% 4421	

Note: All data from the Health and Retirement Study.

Table 2. Socioeconomic pathways for the genetic association to later life cognition (coefficient, *p*).

	Model 1		Model 2		Model 3		Model 4		Model 5	
Intercept	26.868	<.0001	17.907	<.0001	26.769	<.0001	27.633	<.0001	18.599	<.0001
Polygenic risk score	0.419	<.0001	0.302	<.0001	0.410	<.0001	0.421	<.0001	0.305	<.0001
Years of Education			0.562	<.0001					0.543	<.0001
Wealth (Millions$)					0.315	<.0001			0.128	<.0001
Neighborhood Poverty							-4.944	<.0001	-2.710	<.0006
Age (2016)	-0.161	<.0001	-0.144	<.0001	-0.162	<.0001	-0.161	<.0001	-0.145	<.0001
Sex [Female = 1]	0.550	<.0001	0.763	<.0001	0.588	<.0001	0.526	<.0001	0.754	<.0001
R squared	0.167		0.263		0.176		0.171		0.266	

Note: All data from the Health and Retirement Study (n = 7,493). All coefficients were yielded from simple linear regressions.

Table 3. Neighborhood moderation of polygenic influences on cognition and mediated pathways

			Neighborhood Poverty Rate						T-test difference in effects		
	Full Sample		Low Poverty		Avg. Poverty		High Poverty		Low-Avg.	Low-Hi	Hi-Avg.
Total Effect	0.419	<.0001	0.475	<.0001	0.349	<.0001	0.413	<.0001	0.283	0.602	0.604
Direct Effect	0.305	<.0001	0.353	<.0001	0.240	<.0025	0.301	<.0003	0.307	0.644	0.597
Indirect Effect	0.114	<.0001	0.122	<.0001	0.109	<.0004	0.112	<.0005	0.746	0.803	0.951
Education	0.111	<.0001	0.118	<.0001	0.094	<.0009	0.113	<.0003	0.526	0.907	0.643
Wealth	0.003	<.0731	0.004	<.1486	0.015	<.0498	-0.002	<.5535	0.195	0.237	0.041
Neighborhood Poverty	0.000	<.8745									
% Mediated	0.272		0.257		0.312		0.271				
R squared	0.266		0.252		0.273		0.269				
N	7493		2534		2501		2458				

Note: All data from the Health and Retirement Study (n = 7,493). A tertile variable was constructed that classified each participant into groups of equal size representing those living in low, moderate, and high poverty areas.