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Childhood socioeconomic status and genetic risk for poorer cognition in later life

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ABSTRACT

The ε4 allele of the APOE gene is associated with poorer cognition in later life. This study aimed to advance understanding of how environments potentially moderate this genetic risk by focusing on childhood socioeconomic status (SES). Previous research across diverse national contexts has found that older adults from higher-SES families in childhood demonstrate better cognitive functioning than their lower-SES counterparts. Nevertheless, few studies have examined whether higher childhood SES might also promote later life cognition by mitigating the effects of ε4 carrier status. To address this gap, we used data from 3017 participants in the Wisconsin Longitudinal Study, which has followed a random sample of people who graduated from Wisconsin high schools in 1957. Childhood SES included parents' educational attainment, father's occupational status, and household income in adolescence. We constructed measures of memory and of language/executive functioning using scores from neurocognitive tests administered when participants were approximately ages 65 and 72. APOE ε4 status was measured through saliva samples. Results from cross-controlled multilevel models indicated that APOE ε4 status—and not childhood SES—independently predicted memory, whereas childhood SES—and not APOE ε4 status—independently predicted language/executive functioning. Moreover, a statistical interaction between APOE ε4 status and childhood SES for memory indicated that at baseline, higher childhood SES protected against the risk of APOE ε4 status, whereas lower childhood SES exacerbated the risk of APOE ε4 status. However, by follow-up, these moderating effects dissipated, and APOE ε4 status alone was associated with memory. We interpret these results in light of theorizing on differential susceptibility for poorer cognition across the life course.

1. Introduction

Cholesterol contributes to neurophysiological development—including myelin growth, synapse formation, and neuronal remodeling—which is instrumental to learning, memory formation, and other cognitive processes (Leduc et al., 2010). Proteins produced by the apolipoprotein E (APOE) gene transport cholesterol within and between the organs of the body, particularly the central nervous system. APOE has three isoforms, each of which metabolizes cholesterol somewhat differently due to its biochemical structure (Huang and Mahley, 2014). Accordingly, carrying one or two copies of the ε4 allele is associated with a 3- and 12-fold increase in risk, respectively, of Alzheimer's disease (AD) in later life, as well as with developing AD younger than persons who carry only ε2 or ε3 alleles (Corder et al., 1993; Saunders et al., 1993). The ε4 allele is not only associated with AD, but also with other neuropsychiatric disorders and memory deficits from approximately age 60 onward (Forero et al., 2016).

Although this genetic risk has been well established for more than 25 years, research also has demonstrated that carrying APOE ε4 does not guarantee cognitive problems in later life. Environmental factors can potentially reduce or neutralize the effects of the gene's protein on cognitive functioning (Reynolds et al., 2014). Most studies of gene-by-environment interactions have investigated behaviors and environments exclusively in adulthood. Yet there is growing consensus among researchers and clinicians that circumstances as early as infancy have potential implications for later life cognitive health and that neurophysiological abnormalities manifest decades before the onset of cognitive impairment (Ritchie et al., 2015). A large and growing body of empirical evidence indicates that childhood socioeconomic (SES)—as indicated by conditions such as parents' occupation, education, and income—is associated with individuals' cognition decades later (Anderson et al., 2017; Rogers et al., 2009). Integrating this literature

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with theorizing on gene-by-environment interactions and differential susceptibility (Belsky et al., 2007), we used data from the Wisconsin Longitudinal Study (WLS), which is one of the longest-running cohort studies in the U.S., to examine the extent to which childhood SES modifies associations between genetic risk from APOE ε4 and later life cognition.

1.1. Dual risk and differential susceptibility models of gene-by-environment interaction

Much of the prior research on the confluence of environmental and genetic effects on later life conditions has adopted a "diathesis-stress," "double jeopardy," or "dual risk" perspective (Ellis et al., 2011). This perspective focuses on mechanisms of vulnerability whereby risks are cumulative and heighten the likelihood of developmental problems. A study by Petkus et al. (2012) demonstrates this idea within the field of cognitive aging. Using data from the Rancho Bernardo Study of Healthy Aging, they found that carriers of the APOE ε4 allele who had also experienced sexual assault were at a multiplicatively higher level of risk for both earlier and faster decline in executive functioning than those with experience of sexual assault alone. The authors interpreted this finding in line with the idea that people who both carry genetic risk factors and face social adversity realize the poorest outcomes throughout compounded vulnerability.

More recent theorizing on gene-by-environment interactions, however, suggests other processes through which genetics and environments jointly contribute to developmental outcomes. One such perspective has been articulated by Belsky and colleagues as the differential susceptibility perspective (Belsky et al., 2009). This perspective suggests that individuals with particular genotypes are more susceptible to social-environmental influences—for better or for worse (Mitchell et al., 2013). Accordingly, certain alleles render people more likely to be jeopardized by disadvantageous environments—but also more likely to benefit from advantageous environments. Non-carriers, by contrast, are less responsive or entirely non-responsive to environmental conditions.

APOE may be among these "plasticity" genes. At the cellular level, ε4 carriers show impaired neural plasticity compared to non-carriers (Chen et al., 2010). That is, the ε2 and ε3 variants of APOE help the brain to develop and change in response to environmental stimuli, whereas the ε4 variant does not. This finding would suggest that carriers of ε2 and ε3 might demonstrate greater susceptibility to environments, while carriers of ε4 would demonstrate less (Reynolds et al., 2014). There is some empirical evidence to support this hypothesis. For example, studies have found that carriers of ε2 and ε3 are more susceptible to a range of environments from dietary fat intake (T. L. Huang et al., 2005) to cognitive stimulation (Runge et al., 2014). However, many gene-by-environment interaction studies find the opposite: ε4 carriers are most responsive to environments, while environmental effects are much less pronounced or not significant for non-carriers. These studies also cover a range of environments from obesity (Rajan et al., 2014) to educational attainment (Cook and Fletcher, 2015). Despite inconsistent findings, the evidence is nonetheless suggestive that environments interact with APOE.

Notably, the bulk of APOE-by-environment studies examine environments in midlife or older adulthood. Yet new evidence suggests that the neurological effects of APOE may first manifest in young adulthood (Forero et al., 2016), and that indeed, early-life environments might continue to have effects on cognitive aging (Reynolds et al., 2014). Accordingly, a new body of studies has begun to examine childhood environments as potential moderators of association between APOE ε4 and later life cognition (e.g., Petkus et al., 2012). Below, we focus our review on studies that have focused specifically on childhood SES as a moderator of associations between APOE ε4 and later life cognition.

1.2. Childhood socioeconomic status (SES) and later life cognition

Child development research is increasingly recognizing that SES is a critical context for lifelong neurocognitive development (Richards and Wadsworth, 2004). Childhood SES is a multi-faceted construct that includes characteristics such as parental education, occupational status, and income. Scholars have theorized that higher SES affords children developmental assets, such as more cognitively complex environments, better nutrition, and higher quality schools. Lower SES, in contrast, can pose developmental liabilities, such as environmental toxins and greater chronic stress (Duncan and Magnuson, 2012). Consistent with this theorizing, studies have found that from infancy, children from higher SES families demonstrate better cognitive outcomes, on average, than children from less advantaged families (Tomalski et al., 2013).

Cognitive advantages from having high SES in childhood extend throughout childhood and into young adulthood, middle, and later life (Richards and Wadsworth, 2004). Much of this research has been based on cohort studies from diverse national contexts, including the United Kingdom, New Zealand, Sweden, China, as well as Central and Eastern Europe (Beck et al., 2018; Ericsson et al., 2017; Wang et al., 2017). Other studies have used data from large social surveys that incorporate retrospective measures of childhood SES (Moceri et al., 2000; Zhang et al., 2016). Many of these studies have found that SES in adulthood, at least in part, helps to explain why higher childhood SES is associated with better cognition: Children from wealthy, well-educated families are more likely to become wealthy and well-educated themselves, which helps to promote later life cognition. Yet most studies find that associations between childhood SES and later life cognition persist after accounting for adult SES, indicating that childhood SES might have more direct and long-lasting effects on individuals' neurophysiological development (Rogers et al., 2009).

Studies have begun to examine how childhood SES and APOE ε4 interact in their association with later life cognition. Four studies have focused on SES in childhood, with two concluding that ε4 carriers are most disadvantaged by lower childhood SES, and two finding no differences in associations between APOE and later life cognition by childhood SES. A pair of studies examined a sample of about 500 members of a Seattle-area HMO (Moceri et al., 2001, 2000). The 2000 study, using self- or proxy-reports of childhood background (including area of residence and sibship size), found no differences in associations by APOE ε4 status. The 2001 study, which drew SES information from the U.S. Census, identified an interaction such that individuals from low SES families (i.e., father held a manual occupation; household size of seven or more persons) who carried ε4 had the highest odds of developing AD. A third study used the Aging, Demographics, and Memory Study subsample of the Health and Retirement Study (Rogers et al., 2009). Similar to the study by Moceri et al. (2001), ε4 carriers whose parents had low educational attainment had nearly four times the odds of dementia of non-carriers whose parents were highly educated. Finally, a recent study examined community-dwelling Swedes aged 75 and older, and estimated structural equation models to examine associations between cognitive reserve variables in childhood, middle adulthood, and later life within a nine-year prospective study of dementia (Wang et al., 2017). Results indicated associations between cognitive reserve in each life stage and risk of dementia, with no differences between APOE ε4 carriers and non-carriers.

1.3. Focus of the current study

Our study aimed to advance understanding of childhood SES as a potential modifier of the association between carrying the APOE ε4 allele and later life cognition by using data from the Wisconsin Longitudinal Study (WLS). The WLS affords both methodological and conceptual advantages. Most notably, the WLS has measures of household income, parental occupational status, and parental education collected when participants were in adolescence. This feature