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Social disorder, APOE-E4 genotype, and change in cognitive function among older adults living in Chicago

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ABSTRACT

The goal of this paper is to describe the simultaneous influence of social and genetic risk factors on declines in cognitive functioning among older American adults. We use detailed information about the social characteristics of older adults' neighborhoods from the Chicago Health and Aging Project (n = 1655; ages 65+) in conjunction with information about respondent's APOE genotype to predict changes in cognitive function over time. Results indicate that the presence of the ε4 allele is associated with a significantly lower cognitive function score at baseline *and* greater declines in cognitive function compared to those without this risk allele. Importantly, we also show significant variation in the effect of the ε4 allele across neighborhoods and our results indicate that this genotype is more strongly associated with cognitive function for residents of neighborhoods with the lowest levels of social disorder. Our findings support the non-causal social push gene–environment interaction model.

Introduction

The ε4 allele is a polymorphism in the apolipoprotein E (APOE) gene that has been associated with the early onset of cognitive decline and is more prevalent among those with Alzheimer's disease compared to the rest of the population (Corder et al., 1993; Small, Rosnick, Fratiglioni, & Backman, 2004). Importantly, there is a great deal of variability in the magnitude of the effects of the ε4 allele across studies (Small et al., 2004), which has produced a fairly small average effect size (Williams, Plassman, Burke, Holsinger, & Benjamin, 2010). Although differences in effect size may reflect random variation, they could also allude to the influence of *variable environments* on the potency of APOE-E4 in relation to cognitive function; a gene–environment (G × E) interaction (Shanahan & Hofer, 2005; Raine, 2002). In this paper, we use data from a longitudinal study of older American adults from 20 census tracts in Chicago to examine differences in the effects of the allele for residents of neighborhoods that differ markedly from one another with respect to social disorder.

Gene–environment interaction and aging

There is an emerging interest in more precisely defining the role of APOE-E4 in cognitive function and cognitive decline in older populations. Specifically, researchers point to differences in the effect of this risk allele as a function of different behavioral and environmental factors (Lee, Glass, James, Bandeen-Roche, & Schwartz, 2011; Peavey et al., 2007). In one of the earliest studies in this area, Haan, Shemanski, Jagust, Manolio, and Kuller (1999) found that several biological risk factors for cardio-vascular disease were more strongly linked to cognitive decline for those with at least one ε4 allele compared to those without this risk allele. Similar results are shown in more recent studies in which the association between cognitive performance and biomarkers including beta-carotene (Hu et al., 2006), vitamin B-12 (Feng, Li, Yap, Kua, & Ng, 2009), estrogen (Yaffe, Haan, Byers, Tangen, & Kuller, 2000), and cortisol (Lee et al., 2008) are systematically different for carriers of the ε4 allele compared to others.

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These studies focus on proximal biological risk factors but similar results have started to emerge from studies that have focused on psychological and social characteristics that, from an etiological perspective, reflect a more distal relationship to the underlying disease process (Lee et al., 2011; Link & Phelan, 1995; Peavy et al., 2007). For example, using data from the Health and Retirement Study, a large study of older adults in the United States, McCardle and Prescott (2010) find no main effect of APOE-E4 on decline in episodic memory but they show steeper declines in memory for the ε4 carriers compared to the non-ε4 carriers among those with less than 8 years of education. This finding is in line with the "social trigger" G × E model in which particular environmental contexts trigger genetic risk factors (Shanahan & Hofer, 2005). In a thorough review of the literature, Reiss and Leve (2007) argue that there is wide support for the triggering perspective and state that "[i]n virtually all publications reporting positive results for this phenomenon, a substantial association between allele and behavior is observed under adverse environmental circumstances but not under favorable circumstances" (pp. 1006–7).

The social trigger approach assumes that the interactive relationships between genes and environments are causal; that is, G × E interactions are interpreted to mean that specific environmental conditions are required for a polymorphism to become expressed, leading to its differential associations with behavioral phenotypes or disease risk (Meaney, 2010). Although this model makes intuitive and biological sense, it is worth noting that statistical interactions between a measured E and a measured G may also be observed in the absence of a causal (interactive) relationship. For example, social contexts characterized by high levels of disadvantage may have such a dominant effect on the occurrence of specific behaviors or diseases that they may "overwhelm" the typically more subtle genetic effects on outcomes. Raine (2002) refers to this situation as a social push model, arguing that social environments may push certain phenotypes forward irrespective of the distribution of genetic risk factors; only when these adverse social conditions are minimized will the genetic influences become apparent, allowing "biology to shine through" (Raine, 2002: 13). Scarr (1993: 5) provides a similar perspective in which she elaborates on Hartmann's (1958) notion of the "average expectable environment." This general evolutionary perspective emphasizes "normal organisms in normal environments" and Scarr argues that "[e]nvironments that fall outside of the species-normal range will not promote normal developmental patterns" (Scarr, 1993:5). According to her perspective, forces related to genetic inheritance are not likely to cause individual differences in phenotype for organisms within environments that are atypical. This "social push" perspective is illustrated in Fig. 1.

In this paper, we turn our focus to psychosocial stress as an important environmental condition that may modify the relationship between genotype and cognitive outcomes in late-life to test causal and non-causal G × E models. Previous research has shown that markers of stressful life experiences may interact with specific polymorphisms in relation to behavioral and disease-related outcomes (Caspi et al., 2003) and more recent research is providing clues about the physiological mechanisms behind these complex interactions (Su et al., 2009). Such work has also begun to emerge for cognitive aging. In a small volunteer sample, Peavy and colleagues found that APOE-E4 positive older adults reporting high levels of stress had a substantially poorer performance on memory tasks than low stress persons, whose performance was similar to either high stress or low stress APOE-E4 negative persons (Peavy et al., 2007).

Much of the present work on psychosocial stress by gene interaction has emphasized individual-level stress exposures, often defined as experiences or perceptions of stressful life conditions. Very little is known about the degree to which stressful conditions in the actual environment such as work places or neighborhoods interact with genetic risk factors in producing specific behavioral or disease outcomes. A notable exception is a recent study that suggests that living in more hazardous neighborhoods is associated with worse executive functioning and processing speed among persons with an ε4 allele, but not in those without this allele (Lee et al., 2011). Another important limitation of present work on G × E interactions in relation to late-life cognitive function is that it has relied on cross-sectional cognitive function data. Such data do not permit solid inferences regarding the role of G × E interactions in aging-related disease processes, as they do not differentiate between early-life and life-course influences on cognition and aging-related disease effects on cognitive decline. Serial cognitive performance data are better suited to the establishment of aging-related declines in cognition associated with dementia, Alzheimer's disease and their pre-clinical, early stage manifestations.

The purpose of this study is to explore the G × E mechanism that may structure the relationship between APOE-E4, neighborhood social environment, and change in cognitive function in older age. The *social trigger model* represents a causal mechanism in which the association between APOE-E4 and cognitive decline is triggered by specific social circumstances, in our study represented by adverse

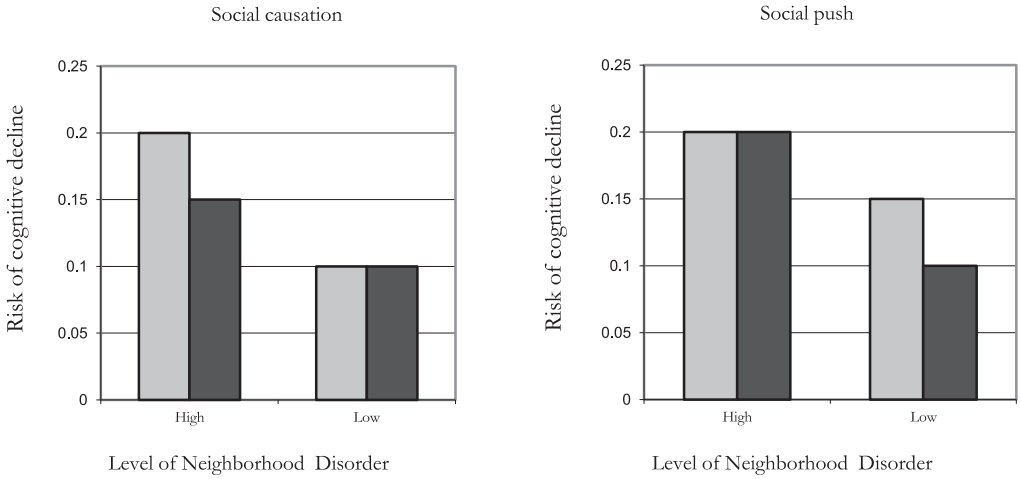

Fig. 1. Causal and non-causal gene-environment interaction models. Note: Models above denote conceptual examples of different G × E models. The light shaded bar indicates the risk of cognitive decline for those with a risky genotype and the dark shaded bar is the risk of cognitive decline for those without the risky genotype.