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Polygenic Score for Alzheimer Disease and Cognition: The Mediating Role of Personality

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Abstract

Alzheimer's disease (AD) polygenic risk score (PGS) is associated with lower cognitive functioning even among older individuals without dementia. We tested the hypothesis that personality traits mediate the association between AD genetic risk and cognitive functioning. Participants (N >7,000, aged 50 to 99 years old) from the Health and Retirement Study were genotyped and completed personality and cognition tests at baseline. Cognition was assessed again four years later. Bootstrap analysis revealed that a higher AD polygenic risk score was associated with lower cognitive scores at baseline through higher neuroticism, lower conscientiousness, and lower levels of the industriousness facet of conscientiousness. In addition, a higher polygenic score for AD was associated with decline in cognition over four years in part through higher neuroticism and lower conscientiousness. The findings support the hypothesis that the genetic vulnerability for AD contributes to cognitive functioning in part through its association with personality traits.

Keywords

Polygenic risk; personality; cognition; facets

1. Introduction

Higher genetic risk of Alzheimer's disease (AD) is associated with lower cognitive functioning among non-demented older individuals (Adams et al., 2015; Andrews et al., 2016; Verhaaren et al., 2013). However, little is known about the potential mechanistic pathways of this association. Among a set of potential factors, personality traits may act as mediators of the association between the genetic vulnerability to AD and cognitive functioning. In particular, conscientiousness, which refers to the propensity to be self-disciplined and organized, and neuroticism, which reflects a tendency to experience negative emotions, are promising mediators because lower conscientiousness and higher neuroticism predict a higher risk of incident AD in prospective studies (Terracciano et al., 2014). In

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addition, lower conscientiousness and higher neuroticism are consistently related to lower concurrent cognitive performance and to steeper cognitive decline (Caselli et al., 2016; Luchetti, Terracciano, Stephan, & Sutin, 2015). The hypothesis that personality traits may function as a potential mediator is further supported by the partial genetic overlap between personality and risk for AD. Indeed, findings from the largest genome wide association study to date suggest that there is a genetic correlation (r = .10) between risk of AD and neuroticism (Luciano et al., 2018). Past research has mostly considered personality traits as moderators of the association between APOE genetic variant and cognitive outcomes, with mixed results (Chapman et al., 2018; Terracciano et al., 2014).

The present study examined whether personality mediates the association between the genetic propensity to AD and cognitive functioning in a large cohort of cognitively normal older adults. Based upon the evidence described above, it was hypothesized that a higher polygenic score for AD is related to lower concurrent cognitive functioning and steeper cognitive decline in part through its association with higher neuroticism and lower conscientiousness. In addition, recent research provided evidence of a link between facets of conscientiousness and lower cognitive function (Sutin, Stephan, & Terracciano, 2018). Therefore, additional analyses tested whether the facets of conscientiousness mediated the association between the genetic risk for AD and cognitive functioning. Finally, in line with Mõttus et al. (2018), supplemental analysis tested whether a personality poly-item score, which represents a personality propensity to cognition, also mediated the link between PGS for AD and cognition.

2. Method

2.1. Participants

Participants were drawn from the Health and Retirement Study (HRS), a nationally representative longitudinal study of Americans aged 50 years and older, assessed every two years (grant number NIA U01AG009740). The HRS was approved by the Institutional Review Boards at the University of Michigan and the National Institute on Aging. All participants provided written informed consent at enrollment.

In 2006, HRS started an enhanced face-to-face interview with collection of saliva samples. A self-report questionnaire including personality measures was also administered for a random half the sample in 2006 and the other half in 2008. Cognition was assessed at each wave. Complete data at baseline (2006–2008) were obtained from a total of 7340 individuals of European Ancestry without cognitive impairment (58% female, Mean age= 67.90, SD= 9.39). Among these participants, 6429 individuals provided cognitive measure four years later, in 2010 (for participants from the 2006 wave) or 2012 (for participants from the 2008 wave). Participant with complete data at follow-up were younger (d= .54), were more likely to be female, more extraverted (d=.15), open (d=.17), agreeable (d=.06), conscientious (d=. 22), and had better cognitive functioning (d= .38) than those without follow-up data.

Conscientiousness facets were first assessed in the 2008 wave for half of the sample, and in the 2010 wave for the other half of the sample. Therefore, the 2008 and 2010 waves were combined as the baseline measure for the conscientiousness facets. A total of 7130

individuals of European Ancestry without cognitive impairment provided complete facet, genetic, cognitive and demographic data at baseline (58% female, Mean age= 67.92, SD= 9.65). Follow-up cognition was obtained four years later from 6239 participants, in 2012 (for participants from the 2008 wave) or 2014 (for participants from the 2010 wave). Participant with complete data at follow-up were younger (d= .45), were more likely to be female, more industrious (d=.22), responsible (d=.16), and had better cognitive functioning (d= .39) than those without follow-up data. See Supplemental Material for a figure summarizing the timeline of data collection.

2.2. Personality

Personality traits were assessed using the Midlife Development Inventory (MIDI) (Zimprich, Allemand, & Lachman, 2012). Participants were asked to rate the extent to which 26 adjectives that assessed the personality traits of neuroticism (e.g. worrying), extraversion (e.g. active), openness (e.g. curious), agreeableness (e.g. warm) and conscientiousness (e.g. responsible) described themselves using a scale ranging from 1 (*not at all*) to 4 (*a lot*). Cronbach alphas ranged from .67 to. 79. In addition, six facets of conscientiousness were assessed using a 24-item measure with a scale from 1 (*strongly agree*) to 6 (*strongly disagree*) (Roberts, Chernyshenko, Strark, & Goldberg, 2005). These facets were self-control (e.g., " I rarely jump into something without first thinking about it"), order (e.g., " Every item in my home has its own particular place"), industriousness (e.g., " I make every effort to do more than what is expected of me"), traditionalism (e.g., " I support long-established rules and traditions"), virtue (e.g., " When I was in school, I would rather get a bad grade than copy someone else's homework"), and responsibility (e.g., "I carry out my obligations to the best of my ability"). Cronbach alphas ranged from .52 to. 65. Facets of other personality traits are not assessed in HRS.

2.3. Cognition

Cognitive functioning was assessed using the modified Telephone Interview for Cognitive Status (TICSm) (Crimmins, Kim, Langa, & Weir, 2011). A composite score ranging from 0 to 27 was computed from a test of immediate and delayed recall to assess short-term memory, a serial 7 subtraction test to assess working memory, and a backward counting test to assess mental processing speed. Based upon past validation studies (Crimmins et al., 2011), individuals with values equal to or lower than 11 were classified as cognitively impaired and were excluded from the analysis. The TICSm score has been used effectively to index dementia-related trends (Langa et al., 2017) and to predict the incidence of cognitive impairment and dementia (Terracciano, Stephan, Luchetti, Albanese, & Sutin, 2017).

2.4. Polygenic Score

The polygenic score for AD was based upon a recent genome-wide association study (GWAS) (Lambert et al., 2013). This GWAS meta-analysis was based on the results of 20 independent samples using two stages of discovery and replication samples. The polygenic score for AD included all available single-nucleotide polymorphisms (SNP) identified in this GWAS meta-analysis that overlapped with the SNPs in the HRS genetic database, resulting in 1,145,021 SNPs included. Different estimation methods were tested in the HRS for

computing polygenic scores, which revealed that including all available SNPs either demonstrated the largest predictive value of the polygenic score or produced a score that did not differ from scores with similar predictive power that used linkage disequilibrium trimming or a threshold for p-value (Ware, Schmitz, Gard, & Faul, 2018). Each SNP was weighted by the effect size from the GWAS, and weighted sums were used to compute the polygenic score (Ware et al., 2018).

2.5. Statistical Analysis

Bootstrap analysis using 5,000 bootstrapped samples and 95% bias-corrected confidence intervals were conducted using the PROCESS macro (Hayes, 2013). A first analysis was conducted with baseline cognition as the dependent variable, personality traits as mediators, and the polygenic score for AD as the predictor. The five personality traits were simultaneously included as mediators. A separate analysis was performed with the six conscientiousness facets as possible mediators of the association between the polygenic score for AD and cognition. Again, the six facets were simultaneously included. Age, sex, and ten ancestry-specific principal components were controlled. A second analysis predicted follow-up cognition from the polygenic score, with personality traits or conscientiousness facets as mediators, controlling for the same covariates and baseline cognition. Confidence intervals that did not include zero indicated a statistically significant indirect effect.

3. Results

The analysis revealed that a higher AD polygenic score was related to higher neuroticism and to lower conscientiousness, but not to extraversion, openness or agreeableness. Furthermore, consistent with the hypothesis, neuroticism and conscientiousness mediated the association between the polygenic risk of AD and cognition at baseline (see Table 1). In addition, higher AD polygenic score was associated with lower industriousness, which was a significant mediator of the link with lower cognition (see Table 1). Neuroticism, conscientiousness, and industriousness explained about 7%, 5%, and 7% of the association between AD PGS and cognition, respectively.

A higher polygenic score for AD was also related to decline in cognition, and this association was partially mediated by neuroticism and conscientiousness, but not by extraversion, openness, and agreeableness (see Table 2) or any of the facets of conscientiousness. Indeed, although a higher polygenic score was related to lower industriousness, this facet was not related to change in cognition (Table 2). The proportion of the effect mediated by neuroticism and conscientiousness was about 6% and 4%, respectively. Consistent with the main analysis, supplemental analysis revealed that higher genetic propensity to AD was related to lower cognitive functioning at baseline because it is associated with a reduced personality propensity to cognition (see supplementary material).

4. Discussion

The present study revealed that personality mediates the association between the genetic propensity to AD and concurrent cognition and cognitive decline. As hypothesized, higher polygenic risk of AD was associated with lower cognitive performance and a steeper

cognitive decline in part through lower conscientiousness, particularly lower industriousness, and higher neuroticism. These findings suggest that higher genetic propensity to AD may have detrimental effects on cognitive functioning in part through the tendency to experience more negative emotions, a lower striving to achieve, and fewer goal-directed behaviors. This association could illustrate a stress-related pathway connecting AD genetic risk to cognitive function. Indeed, high neuroticism, low conscientiousness and low industriousness are characterized by higher stress reactivity (Leger, Charles, Turiano, & Almeida, 2016; Luo & Roberts, 2015), which harms cognitive function (Aggarwal et al., 2014). Taken together, these findings indicate that a mediated pleiotropy (Solovieff et al., 2013) exists between the polygenic risk of AD, personality and cognition.

Past research has examined the association between polygenic risk of AD, personality and cognition separately. This is the first study to integrate these dimensions into a single explanatory model. Furthermore, the present study adds to existing report of a genetic correlation between AD and neuroticism (Luciano et al., 2018), by providing the first evidence of an association between polygenic risk of AD and conscientiousness, at the level of both the trait and facet. These findings closely mirror the phenotypic relationships found between low conscientiousness and higher neuroticism and incident AD (Terracciano et al., 2014) and between low industriousness and higher risk of dementia (Sutin et al., 2018). Consistent with past research (Luchetti et al., 2016), neuroticism and conscientiousness were the strongest personality predictors of cognition at baseline and of cognitive changes. This study extends these findings by indicating that these two traits may act as intermediate phenotypes between the genetic propensity to AD and worse cognitive functioning.

The study has several strengths including the examination of polygenic risk of AD, its association with cognition through personality factors, and the use of a large sample of older individuals. The longitudinal design is particularly valuable to examine mediation. However, there are also limitations to consider. Although the mediational model tested was theoretically and empirically supported, it is also likely that cognition may mediate the link between polygenic risk and personality traits and facets. Indeed, higher polygenic risk for AD may relate to lower cognitive functioning which may be reflected in a higher propensity to distress and lower self-discipline and organization. More broadly, the polygenic vulnerability to AD could shape brain structures, networks, or other physiological systems that have detrimental effects on both personality and cognition. While our analyses cannot rule out alternative interpretations, at minimum, our findings suggest that specific personality traits are part of the complex cascade from genetic vulnerability to cognitive functioning and decline. The present study used a performance-based measure of cognition. Future research is needed to test whether the findings replicate using clinical measures of cognitive impairment. In addition, the HRS did not include facets of neuroticism. Personality explains part of the association between polygenic scores and cognition, but further research is needed to identify additional mediating factors. Despite these limitations, this study provides novel evidence on mechanisms that mediate the link between AD genetic risk and cognition. Individuals with higher genetic risk of AD may have lower cognitive performance in part because they are less conscientious, less industrious, and more emotionally unstable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Summary of Bootstrap Analysis Predicting Baseline Cognition from Polygenic Score for AD

	Total Effect of PGS on Cognition [a]	MV	Effect of PGS on MV	Effect of MV on Cognition	Direct Effect of PGS on Cognition [b]	Indirect Effect of PGS on Cognition [c]
Trait-Level Analysis [d]						
	−0.08 *				−0.07 *	
		Neuroticism	0.02 **	−0.31 ***		−0.006(−.011;−.001)
		Extraversion	−0.002	−0.29 ***		0.0005(−.003;.004)
		Openness	−0.01	0.77 ***		−0.008(−.018;.001)
		Agreeableness	0.001	−0.32 ***		−0.000(−.004;.003)
		Conscientiousness	−0.01 *	0.33 ***		−0.004(−.009;−.0008)
Facet-Level Analysis [e]						
	−0.07 *				−0.06	
		Self-control	−0.01	0.24 ***		−0.003(−.009;.002)
		Order	−0.02	0.008		−0.00(−.002;.001)
		Industriousness	−0.03 *	0.17 ***		−0.005(−.010;−.0009)
		Traditionalism	0.005	−0.09 *		−0.00(−.003;.002)
		Virtue	−0.009	−0.04		0.00(−.0008;.002)
		Responsibility	−0.007	0.32 ***		−0.002(−.008;.003)

Note.

* p<.05

** p<.01

*** p< .001

PGS AD: Polygenic Score for Alzheimer Disease ; MV: mediating variable.

Coefficients are unstandardized coefficients

[a] Relationship between PGS AD and cognition, controlling for age, sex and ancestry-specific principal components

[b] Relationship between PGS AD and cognition, with mediators included in the model and controlling for age, sex and ancestry-specific principal components

[c] Bootstrap estimates and 95% bias-corrected confidence interval for indirect effects of PGS on cognition through mediators, controlling for age, sex and ancestry-specific principal components

[d] Analysis conducted with the five personality traits as mediators (N= 7340)

[e] Analysis conducted with the six conscientiousness facets as mediators (N=7130)

Table 2.

Summary of Bootstrap Analysis Predicting Follow up Cognition from Polygenic Score for AD

	Total Effect of PGS on Cognition [a]	MV	Effect of PGS on MV	Effect of MV on Cognition	Direct Effect of PGS on Cognition [b]	Indirect Effect of PGS on Cognition [c]
Trait-Level Analysis[d]						
	−.0.09 *				−0.07 *	
		Neuroticism	0.02 **	−0.25 ***		−0.005(−.010;−.001)
		Extraversion	0.000	−0.29 **		−0.00(−.004;.004)
		Openness	−0.01	0.34 ***		−0.003(−.008;.001)
		Agreeableness	0.000	−0.39 ***		−0.00(−.005;.004)
		Conscientiousness	−0.01 *	0.34 ***		−0.004(−.009;−.0002)
Facet-Level Analysis[e]						
	−.10 **				−.10 *	
		Self-control	−0.009	0.10 *		−0.001(−.004;.001)
		Order	−0.01	0.06		−0.001(−.004;.0007)
		Industriousness	−0.03 *	0.08		−0.003(−.007;.0002)
		Traditionalism	0.01	−0.07		−0.00(−.003;.001)
		Virtue	−0.006	0.03		−0.00(−.002;.001)
		Responsibility	−0.007	0.10		−0.00(−.003;.001)

Note.

* p<.05

** p<.01

*** p< .001

PGS AD: Polygenic Score for Alzheimer Disease ; MV: mediating variable.

Coefficients are unstandardized coefficients

[a] Relationship between PGS AD and follow-up cognition, controlling for age, sex, baseline cognition and ancestry-specific principal components

[b] Relationship between PGS AD and follow-up cognition, with mediators included in the model and controlling for age, sex, baseline cognition and ancestry-specific principal components

[c] Bootstrap estimates and 95% bias-corrected confidence interval for indirect effects of PGS on follow-up cognition through mediators, controlling for age, sex, baseline cognition and ancestry-specific principal components

[d] Analysis conducted with the five personality traits as mediators (N= 6429)

[e] Analysis conducted with the six conscientiousness facets as mediators (N=6239)