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Research Article

Personality and Cognition: The Mediating Role of Inflammatory Markers

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Abstract

Objectives: Five-Factor Model personality traits are associated consistently with cognition. Inflammation has been hypothesized as a biological pathway in this association, but this assumption has yet to be tested. The present study tested inflammatory markers as mediators between personality traits and cognition.

Methods: Participants were from the Health and Retirement Study (HRS; *N* = 4,364; 60% women; mean age = 64.48 years, standard deviation = 8.79). Personality traits and demographic factors were assessed in 2010/2012. Data on inflammatory markers (high-sensitivity C-reactive protein [hsCRP], interleukin-6 [IL-6], soluble tumor necrosis factor 1 (sTNFR1), interleukin-10 [IL-10], interleukin-1 receptor antagonist [IL-1Ra], and transforming growth factor [TGF]-β1) were obtained in 2016 from the HRS Venuous Blood Study. Cognition was assessed in 2020 using the modified Telephone Interview for Cognitive Status.

Results: Higher neuroticism was related to lower cognition at follow-up, whereas higher extraversion, openness, agreeableness, and conscientiousness were associated with better cognition. Higher extraversion and higher conscientiousness were related to lower hsCRP, IL-6, IL-10, IL-1Ra, and sTNFR1, and higher openness was associated with lower IL-10, IL-1Ra, and sTNFR1 and to higher soluble TGF-β1. Lower sTNFR1 partially mediated the associations between conscientiousness, extraversion, and openness and cognition at follow-up, explaining an estimated 4%–12% of these associations. The mediating role of sTNFR1 persisted when physical activity and depressive symptoms were included as additional mediators.

Discussion: The present study provides new evidence on personality and inflammatory markers. Consistent with the inflammation hypothesis, the sTNFR1 finding supports a potential biological pathway between personality and cognition.

Keywords: Cognition, Inflammation, Longitudinal, Personality

There is consistent evidence that personality traits (i.e., relatively enduring patterns of emotion, cognition, and behavior) are associated with cognition across adulthood. Among the traits defined by Five-Factor Model personality traits (McCrae & John, 1992), higher neuroticism (the tendency toward negative emotionality and vulnerability to stress) is related to worse cognitive performance and higher risk of cognitive impairment (Aschwanden et al., 2021; Chapman et al., 2017; Graham et al., 2021; Sutin et al., 2023), whereas higher conscientiousness (the tendency to be responsible, disciplined, and organized) is associated with better cognitive function and lower risk of cognitive impairment (Aschwanden et al., 2021; Chapman et al., 2017; Sutin et al., 2022). In addition to their association with objective cognitive performance, neuroticism and conscientiousness have similar associations with subjective (e.g., self-rated memory; Stephan et al., 2023a) and informant-rated cognition (Best et al., 2021; Stephan et al., 2023a; Sutin et al., 2019b, 2022). Some studies also found openness (the tendency to be imaginative, curious, and creative) associated with better cognition and lower risk of dementia, but findings are less consistent across samples (Aschwanden et al., 2021; Graham et al., 2021; Sutin et al., 2023). In contrast, there is less consistent evidence that extraversion (the tendency to be sociable, energetic, and to experience positive emotions) and agreeableness (the tendency to be trusting, cooperative, and friendly) are associated with cognition across adulthood (Aschwanden et al., 2021; Graham et al., 2021; Sutin et al., 2023).

Given the replicable evidence that personality traits are associated with cognitive functioning and impairment, there is growing interest on the mechanisms that explain these associations. Conceptually, the association between personality and cognition is thought to operate through several behavioral, psychological, and health-related pathways. Recent studies that have conducted formal tests of mediation provide some evidence to support these theoretical assumptions. For

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example, higher neuroticism has been found to relate to worse cognition because of its association with greater sedentary behavior (Allen et al., 2019), lower engagement in cognitive activities (Sutin et al., 2020), higher perceived stress (Da Silva Coelho et al., 2021; Montoliu et al., 2022), lower subjective health (Sutin et al., 2020), and worse physical performance (Stephan et al., 2023a). Mediation analyses have also found that higher conscientiousness and higher openness are associated with better cognition in part through their association with greater engagement in cognitive activities (Hogan et al., 2012; Jackson et al., 2020; Mercuri & Holtzer, 2021; Sutin et al., 2020), better subjective health (Sutin et al., 2020), and better physical performance (Stephan et al., 2023a). Higher conscientiousness has further been related to better cognitive performance through its association with less sedentary behaviors and more frequent physical activity (Allen et al., 2019), and its industriousness facet has been associated with better cognitive function in part through lower negative affect (Sutin et al., 2022) in mediation analyses.

The research on pathways linking personality to cognition has focused primarily on behavioral, psychological, and health-related mediators. Less is known about the potential biological pathways through which personality is associated with cognition. One recent study that tested mediation found that higher neuroticism, lower extraversion, and lower conscientiousness were associated with lower memory performance in part through their relations with lower Vitamin D (Stephan et al., 2023b). The biological pathways between personality and cognition, however, remain relatively unaddressed. According to the inflammation hypothesis, inflammatory markers have been proposed as a potential biological pathway that explains the association between personality and cognition (Luchetti et al., 2016; Sutin et al., 2019a; Terracciano et al., 2017, 2022b). However, no research has yet formally tested this hypothesis, even though there is evidence that personality is associated with inflammation and inflammation is associated with cognition.

Personality has been associated with inflammatory markers. Indeed, higher neuroticism, lower conscientiousness, and lower openness have been related to both higher systemic inflammation, indexed by higher C-reactive protein (CRP), and pro-inflammatory marker such as higher interleukin-6 (IL-6; Chapman et al., 2011; Graham et al., 2018; Luchetti et al., 2014; Wright et al., 2022). These associations are not surprising given that personality traits are related to behavioral, psychological, and clinical factors that are implicated in inflammation. For example, higher neuroticism, lower openness, and lower conscientiousness are related to smoking (Hakulinen et al., 2015), higher stress (Luo et al., 2023), and higher body mass index (BMI; Sutin & Terracciano, 2016), which are in turn associated with higher risk of inflammation (Kalaoja et al., 2021; Khan et al., 2020; Marsland et al., 2017). Furthermore, inflammatory markers have been associated with cognitive function across adulthood. For example, higher CRP, IL-6, and pro-inflammatory marker such as tumor necrosis factor 1 (TNFR1) have been related to worse cognition (Gross et al., 2019; Kipinoinen et al., 2022; Noble et al., 2010; West et al., 2020) and higher risk of dementia (Darweesh et al., 2018; Zhao et al., 2020). These inflammatory markers are also associated with reduced hippocampal (Schmidt et al., 2016; Walker et al., 2017) and white matter volume (O'Donovan et al., 2021), lower regional cerebral blood flow (Warren et al., 2018), and amyloid beta (Aβ) plaques deposition (Oberlin et al., 2021). Furthermore, anti-inflammatory cytokines such as interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1Ra) have also been associated with lower cognitive performance (Serre-Miranda et al., 2020; Tegeler et al., 2016). Although another anti-inflammatory cytokine, the transforming growth factor (TGF)-β1, plays a neuroprotective role (Cao et al., 2020), little is known about its association with measures of cognitive function.

Additional evidence that supports the mediational model tested in this study comes from recent findings that inflammatory markers mediate the association between personality and a range of health-related outcomes. Specifically, higher conscientiousness has been associated with lower mortality risk in part through its link with lower IL-6 (O'Súilleabháin et al., 2021). Higher neuroticism and lower conscientiousness have been related to physical health-related quality of life, chronic disease burden, and higher BMI through their association with higher IL-6 (Wright et al., 2022). Finally, higher conscientiousness has been linked to higher grip strength in part through its association with lower CRP (Stephan et al., 2022). To our knowledge, no research has yet tested whether inflammatory markers mediate the association between personality and cognition.

Based upon a large longitudinal sample of older adults, the present study examined the mediating role of inflammatory markers in the relationship between personality and cognition. This study adopted a comprehensive approach by simultaneously examining a broad range of markers, including markers of systemic inflammation (CRP), as well as pro-(IL-6, TNFR1) and anti-(IL-10, IL-6Ra, TGF-β1) inflammatory cytokines. It was hypothesized that higher neuroticism would be related to lower cognition through higher systemic inflammation and pro- and anti-inflammatory cytokines. In contrast, it was expected that lower systemic inflammation and pro- and anti-inflammatory cytokines would mediate the link between conscientiousness and openness and higher cognition. Additional analysis tested whether inflammation is an independent pathway in the association between personality and cognition by including behavioral (physical activity) and psychological (depressive symptoms) factors as additional mediators.

Method

Participants

Data were from the Health and Retirement Study (HRS), a nationally representative longitudinal study of adults living in the United States aged 50 years and older and their spouses. The University of Michigan's Institutional Review Board approved the HRS. All participants provided written informed consent. HRS data are publicly available at: https://hrs.isr.umich.edu/data-products/access-to-public-data.

Personality and demographic data were obtained from a random half of the sample in 2010 and from the other half in 2012. With both waves combined, complete baseline personality and demographic data were available from 13,023 participants. Data on inflammatory markers were from the HRS 2016 Venuous Blood Study. Data on cognition were obtained in 2020. Of the baseline sample, 6,726 individuals were excluded because they did not have data on cognition in 2020, resulting in a sample of 6,297 participants. A total of 1,933 participants without complete data on inflammatory

markers in 2016 or extreme values on these markers (see below) were excluded. The final analyzed sample included 4,364 individuals aged from 50 to 93 years (60% women, mean = 64.48, standard deviation = 8.79). Participants with complete data at follow-up were younger (d = 0.42), had more years of education (d = 0.07), were more likely to be Hispanic and female and scored higher on extraversion (d = 0.10), openness (d = 0.11), agreeableness (d = 0.10), conscientiousness (d = 0.10) than those with incomplete data. There were no differences in race or neuroticism.

Measures

Personality

The five personality traits were measured with the 26-item Midlife Development Inventory (Zimprich et al., 2012). Participants rated how well adjectives that assessed neuroticism (moody), extraversion (outgoing), openness (curious), agreeableness (caring), and conscientiousness (responsible) described them on a scale from 1 (*not at all*) to 4 (*a lot*). Cronbach alphas were 0.72 (neuroticism), 0.76 (extraversion), 0.78 (openness), 0.77 (agreeableness), and 0.65 (conscientiousness).

Inflammatory markers

Inflammatory markers were measured in serum from blood samples collected in 2016 (see Crimmins et al., 2017, 2020). A latex-particle-enhanced immunoturbidimetric assay kit (Roche Diagnostics, Indianapolis, IN) was used to measure high-sensitivity CRP (hsCRP). The laboratory interassay coefficient of variation (CV) was 5.1% at a concentration of 1.05 mg/L and 6.7% at a concentration of 3.12 mg/L (Crimmins et al., 2017). An enzyme-linked immunosorbent assay technique was used to measure pro- and anti-inflammatory cytokines (Crimmins et al., 2020). IL-1Ra was assessed using the Human Interleukin 1 receptor antagonist Simple Plex Assay on the ELLA System from Protein Simple (San Jose, CA). At a concentration of 27.2 pg/ml, manufacturer interassay CV was 7.4%, and was 5% at a concentration of 1390 pg/ml (Crimmins et al., 2020). The Human Interleukin 6 Simple Plex Assay on the ELLA System from Protein Simple (San Jose, CA) was used for IL-6. Manufacturer interassay CV was 8.3% at a concentration of 41.5 pg/ml and 7.1% at a concentration of 1,800 pg/ml (Crimmins et al., 2020). IL-10 was measured using the Human Interleukin 10 Simple Plex Assay on the ELLA System from Protein Simple (San Jose, CA). At a concentration of 33.2 pg/ml, manufacturer interassay CV was 7.1%, and it was 7.1% at a concentration of 1681 pg/ml (Crimmins et al., 2020). The Human Transforming Growth Factor beta 1 Simple Plex Assay on the ELLA System from Protein Simple (San Jose, CA) was used to assess soluble TGF-β1 (sTGF-β1). Manufacturer interassay CV was 6.9% at a concentration of 89.9 pg/ml and 6.9% at a concentration of 5,109 pg/ml (Crimmins et al., 2020). Soluble TNFR1 (sTNFR1) was assessed using the Human Tumor Necrosis Factor Receptor 1 Simple Plex Assay on the ELLA System from Protein Simple (San Jose, CA). Manufacturer interassay CV was 11.8% at a concentration of 19.5 pg/ml and 10% at a concentration of 971 pg/ml (Crimmins et al., 2020). In line with Crimmins et al. (2020), participants with sTGF-β1 data >300,000 (N = 1), IL-10 >300 (N = 2), IL-6 >1,000 (N = 3), and sTNFR1 >40,000 (N = 1) were excluded. The six inflammatory markers were natural log-transformed. Correlations between log-transformed inflammatory markers ranged from −0.15 to 0.40.

Cognition

Cognition was measured with the modified Telephone Interview for Cognitive Status (TICSm; Crimmins et al., 2011). A 27-point TICSm score was computed as the sum of performance on three tasks: immediate and delayed recall of 10 words that assessed memory (range: 0–20), serial 7 subtraction that assessed working memory (range: 0–5), and backward counting that assessed attention and processing speed (range: 0–2). A higher score on the TICSm indicated better cognition.

Covariates

Age, sex, education, race, and ethnicity were included as covariates. Age and education were measured in years, sex was coded as 1 for female and 0 for male, race was coded as 1 for African American and 0 for other, and ethnicity was coded as 1 for Hispanic and 0 for not Hispanic. Year of personality assessment was also controlled and coded as 1 for 2010 and 0 for 2012.

Physical activity and depressive symptoms assessed in 2016 (the same year as the inflammatory markers) were examined as additional mediators in supplementary analysis. Two items asked participants to indicate their frequency of vigorous and moderate activities using a scale from 1 (*hardly ever or never*) to 4 (*more than once a week*). The two items were averaged, with higher scores indicating greater physical activity. The eight-item version of the Center for Epidemiological Studies—Depression scale (Wallace et al., 2000) was used to assess depressive symptoms. Eight items asked participants whether they experienced specific symptoms for much of the past week (1 = yes, 0 = no). Items were summed, with higher scores indicating more depressive symptoms (α = 0.81).

Data Analysis

The PROCESS macro (Hayes, 2018) was used because the present study aimed to test whether inflammatory markers mediated the association between personality and cognition. We consider only significant total effects, and thus a prerequisite was a significant total effect of personality on cognition. Mediation was considered significant when 0 was not included in the 95% confidence intervals (CIs). The mediation analysis used 5,000 bootstrapped samples and 95% bias-corrected CIs. Personality traits were examined in separate analyses. The six inflammatory markers were first entered in separate analyses, and then simultaneously for each trait. Demographic factors and wave of personality assessment were included as covariates. Follow-up analyses were conducted with baseline cognition as an additional covariate. Supplementary analyses included physical activity and depressive symptoms as additional mediators. In addition, serial mediation was tested in two analyses. The first analysis tested a model in which personality was related to physical activity, which in turn was related to inflammation, which was ultimately associated with cognition. The second model tested whether personality was associated with depression, which was related to inflammation, and then to cognition. Sensitivity analyses excluded individuals with dementia at baseline (TICSm score ≤6; Crimmins et al., 2011) to evaluate whether the results were driven by participants who had significant cognitive impairment. Finally, separate analyses were

conducted with memory, serial 7, and backward count scores as the dependent variables.

Results

Descriptive statistics are in Table 1. The mediation analyses are in Table 2. Higher neuroticism was related to lower cognition at follow-up, whereas higher extraversion, openness, agreeableness, and conscientiousness were associated with better cognition. Furthermore, higher extraversion and higher conscientiousness were related to lower hsCRP, IL-6, IL-10, IL-1Ra, and sTNFR1. Higher openness was associated with lower IL-10, IL-1Ra, and sTNFR1 and higher sTGF-β1. Neuroticism and agreeableness were unrelated to inflammatory markers.

Bootstrap analyses conducted with each mediator entered separately indicated that lower sTNFR1 mediated the association between extraversion (estimate: 0.055; 95% CI: 0.0292; 0.0863), openness (estimate: 0.037; 95% CI: 0.0149; 0.0644), and conscientiousness (estimate: 0.042; 95% CI: 0.0165; 0.0749) and cognition. Furthermore, lower IL-6 partially mediated the association between extraversion (estimate: 0.014; 95% CI: 0.0018; 0.0329) and conscientiousness (estimate: 0.015; 95% CI: 0.0006; 0.0371) and cognition. Finally, the association between extraversion and cognition was mediated in part by lower IL-10 (estimate: 0.012, 95% CI: 0.0002; 0.0280). Bootstrap analyses that included all inflammatory markers simultaneously indicated that the association between conscientiousness and openness and cognition at follow-up was mediated in part by sTNFR1. No other inflammatory markers independently mediated these associations. Unexpectedly, sTNFR1 also mediated the association between extraversion and cognition (Table 2). These results suggest that higher conscientiousness, higher openness, and higher extraversion are related to higher cognition in part because they are associated with lower sTNFR1. The proportion mediated by sTNFR1 was an estimated 4%, 6%, and 12% for the associations of conscientiousness, openness, and extraversion with cognition at follow-up, respectively.

Additional analyses indicated that the overall pattern of mediation was the same when baseline cognition was included as a covariate. Furthermore, the mediating role of sTNFR1 persisted when physical activity and depressive symptoms were included as additional mediators (Supplementary Table S1). Lower sTNFR1, higher physical activity, and lower depressive symptoms significantly mediated the association between conscientiousness, openness, and extraversion and higher cognition. sTNFR1 explained around an estimated 3%–9% of the association between the three traits and cognition, whereas physical activity and depressive symptoms explained around an estimated 10%–27% of these associations. Physical activity and depressive symptoms partially mediated the association between neuroticism and agreeableness and cognition (Supplementary Table S1). Additional serial mediation analysis indicated that extraversion (estimate: 0.013; 95% CI: 0.0056; 0.0218), openness (estimate: 0.011; 95% CI: 0.0046; 0.0181), and conscientiousness (estimate: 0.013; 95% CI: 0.0053; 0.0215) were related to higher cognition in part because these traits were related to higher physical activity, which in turn was related to lower sTNFR1, which was associated with better cognition. A second analysis further indicated that higher extraversion (estimate: 0.006; 95% CI: 0.0023; 0.0099), openness (estimate: 0.003; 95% CI: 0.0013; 0.0064), and conscientiousness (estimate: 0.009; 95% CI: 0.0038; 0.0161) were associated with lower depression, which in turn was associated with lower sTNFR1, which was related to better cognition. Finally, sensitivity analysis indicated that sTNFR1 remained a significant mediator between conscientiousness (estimate: 0.042; 95% CI: 0.0157; 0.0793), openness (estimate: 0.037; 95% CI: 0.0134; 0.0670), extraversion (estimate: 0.054; 95% CI: 0.0247; 0.0899), and cognition when individuals with dementia at baseline were excluded (N = 55). Furthermore, additional mediation analyses with the subscores of the TICSm as dependent variables indicated that sTNFR1 was a significant mediator of the association between extraversion (estimate: 0.034; 95% CI: 0.0122; 0.0601), openness (estimate: 0.023; 95% CI: 0.0075; 0.0462), and conscientiousness (estimate: 0.028; 95% CI: 0.0087; 0.0544) and memory; sTNFR1 also significantly mediated the link between conscientiousness and the serial 7 score (estimate: 0.015; 95% CI: 0.0054; 0.0283). No other inflammatory markers significantly mediated these associations.

Table 1. Descriptive Statistics

Variable	*M*/%	*SD*
Age (years)	64.48	8.79
Sex (% women)	60%	—
Race (% African American)	15%	—
Ethnicity (% Hispanic)	11%	—
Education	13.20	2.79
sTGF-β1 (pg/ml)	47,803.83	13,917.85
IL-10 (pg/ml)	3.90	3.84
IL-1Ra (pg/ml)	599.22	418.15
IL-6 (pg/ml)	6.79	20.95
sTNFR1 (pg/ml)	1,807.70	1,281.03
hsCRP (mg/L)	4.26	8.34
Neuroticism	2.01	0.61
Extraversion	3.21	0.56
Openness	2.97	0.54
Agreeableness	3.54	0.47
Conscientiousness	3.41	0.46
Cognition	15.38	4.62

Notes: N = 4,364. hsCRP = high-sensitivity C-reactive protein; IL-1Ra = interleukin-1 receptor antagonist; IL-6 = interleukin-6; IL-10 = interleukin-10; *SD* = standard deviation; sTGF-β1 = soluble transforming growth factor-β1; sTNFR1 = soluble tumor necrosis factor 1.

Discussion

The present study examined whether the association between personality and cognition was mediated by inflammatory markers. Consistent with the hypothesis, lower sTNFR1 was found to partially mediate the association between higher conscientiousness and openness and higher cognition at follow-up. Unexpectedly, the association between higher extraversion and higher cognition was explained in part by lower sTNFR1. In contrast to the hypothesis, none of the inflammatory markers mediated the association between neuroticism and cognition. Notably, the pathway through sTNFR1 was found even after accounting for and in part because of behavioral

Table 2. Indirect Effects of Personality on Cognition Through Inflammatory Markers

Variables	Personality to mediators	Mediators to cognition	Indirect effect	Total effect	Direct effect
	B (*SE*)	*B* (*SE*)	Estimate (95% CI)	*B* (*SE*)	*B* (*SE*)
Neuroticism				−0.625*** (0.10)	−0.617*** (0.10)
sTGF-β1	−0.011 (0.007)	−0.20 (0.21)	0.002 (−0.0031; 0.0095)		
IL-10	0.010 (0.01)	−0.035 (0.17)	−0.0004 (−0.0060; 0.0045)		
IL-1Ra	0.009 (0.01)	0.053 (0.14)	0.000 (−0.0040; 0.0065)		
IL-6	−0.010 (0.02)	−0.146 (0.09)	0.001 (−0.0050; 0.0095)		
sTNFR1	0.015 (0.009)	−0.933*** (0.21)	−0.014 (−0.0328; 0.0022)		
hsCRP	0.022 (0.025)	0.099 (0.07)	0.002 (−0.0034; 0.0104)		
Extraversion				0.468*** (0.11)	0.412*** (0.11)
sTGF-β1	0.010 (0.008)	−0.181 (0.21)	−0.002 (−0.0098; 0.0034)		
IL-10	−0.039*** (0.01)	−0.036 (0.17)	0.001 (−0.0124; 0.0154)		
IL-1Ra	−0.055*** (0.01)	0.057 (0.14)	−0.003 (−0.0209; 0.0128)		
IL-6	−0.073*** (0.02)	−0.128 (0.09)	0.009 (−0.0041; 0.0273)		
sTNFR1	−0.062*** (0.009)	−0.900*** (0.21)	0.056 (0.0264; 0.0917)		
hsCRP	−0.064* (0.03)	0.093 (0.07)	−0.006 (−0.0197; 0.0029)		
Openness				0.666*** (0.12)	0.630*** (0.12)
sTGF-β1	0.018* (0.009)	−0.199 (0.21)	−0.003 (−0.0141; 0.0040)		
IL-10	−0.028*** (0.01)	−0.031 (0.17)	0.000 (−0.0098; 0.0121)		
IL-1Ra	−0.031*** (0.01)	0.057 (0.14)	−0.002 (−0.0136; 0.0080)		
IL-6	−0.031 (0.02)	−0.132 (0.09)	0.004 (−0.0026; 0.0161)		
sTNFR1	−0.042*** (0.01)	−0.903*** (0.21)	0.037 (0.0145; 0.0692)		
hsCRP	−0.012 (0.03)	0.088 (0.07)	−0.001 (−0.0092; 0.0053)		
Agreeableness				0.562*** (0.14)	0.552*** (0.14)
sTGF-β1	0.007 (0.01)	−0.177 (0.21)	−0.001 (−0.0089; 0.0042)		
IL-10	−0.012 (0.01)	−0.035 (0.17)	0.000 (−0.0064; 0.0079)		
IL-1Ra	0.009 (0.01)	0.039 (0.14)	0.000 (−0.0057; 0.0076)		
IL-6	0.006 (0.03)	−0.137 (0.09)	−0.000 (−0.0110; 0.0078)		
sTNFR1	−0.013 (0.01)	−0.943*** (0.21)	0.012 (−0.0110; 0.0413)		
hsCRP	−0.016 (0.03)	0.096 (0.07)	−0.002 (−0.0120; 0.0061)		
Conscientiousness				1.24*** (0.14)	1.21*** (0.14)
sTGF-β1	−0.003 (0.01)	−0.163 (0.21)	0.000 (−0.0057; 0.0070)		
IL-10	−0.045*** (0.01)	−0.015 (0.17)	0.000 (−0.0148; 0.0163)		
IL-1Ra	−0.057*** (0.02)	0.059 (0.14)	−0.003 (−0.0225; 0.0133)		
IL-6	−0.086*** (0.03)	−0.122 (0.09)	0.010 (−0.0053; 0.0328)		
sTNFR1	−0.049*** (0.01)	−0.894*** (0.21)	0.044 (0.0163; 0.0808)		
hsCRP	−0.127*** (0.03)	0.111 (0.07)	−0.014 (−0.0378; 0.0042)		

Notes: *N* = 4,364; Age, sex, education, ethnicity, race, and wave of personality assessment were controlled. CI = confidence interval; hsCRP = high-sensitivity C-reactive protein; IL-1Ra = interleukin-1 receptor antagonist; IL-6 = interleukin-6; IL-10 = interleukin-10; *SE* = standard error; sTGF-β1 = soluble transforming growth factor-β1; sTNFR1 = soluble tumor necrosis factor 1.
*$p < .05$. **$p < .01$. ***$p < .001$.

(physical activity) and psychological (depressive symptoms) pathways between personality and cognition.

Consistent with existing research (Graham et al., 2021; Sutin et al., 2019a), lower neuroticism and higher openness and conscientiousness were prospectively related to higher cognition. Furthermore, higher extraversion and agreeableness were also associated with better cognition. Higher conscientiousness, openness, and extraversion were related to lower inflammation, which in part mediated their association with cognitive function. The findings are broadly consistent with the literature that links conscientiousness and lower IL-6 and CRP (Luchetti et al., 2014; Wright et al., 2022), and extends this association to lower levels of the pro-inflammatory cytokine sTNFR1 as well as lower anti-inflammatory cytokines such as IL-10, IL-R1a. In contrast to past findings (Luchetti et al., 2014), openness was unrelated to IL-6 and hsCRP but was associated with lower IL-10, IL-1Ra, and sTNFR1 and higher sTGF-β1. The relationship between extraversion and lower inflammation across a range of markers adds to the mixed evidence for this trait, with some studies that find a positive association with IL-6 (Wagner et al., 2019) and other studies that find no association with IL-6 or CRP (Allen & Laborde, 2017; Luchetti et al., 2014; Wright et al., 2022). Unexpectedly, neuroticism was unrelated to the inflammatory markers. This finding contrasts with previous research that found higher neuroticism related

to higher Il-6 and CRP (Sutin et al., 2010; Wright et al., 2022) but consistent with other research that found no association (Luchetti et al., 2014; Wagner et al., 2019).

Among the set of inflammatory markers, sTNFR1 was the marker that was the most strongly related to cognition at follow-up. This finding is in line with one study that reported an association between higher sTNFR1 and steeper cognitive decline, whereas none of the other markers, including IL-6, was associated with decline (Gross et al., 2019). Furthermore, sTNFR1 has been found to be a stronger predictor of other outcomes, such as mortality, than other inflammatory markers (Varadhan et al., 2014). Higher sTNFR1 promotes neurotoxicity (Papazian et al., 2021) and is involved in neuropathological processes, such as Aβ-induced neuronal death (Li et al., 2004), and tau pathology (Zhao et al., 2020) and has been associated with a higher risk of dementia (Buchhave et al., 2010; Diniz et al., 2010). Higher sTNFR1 is also related to a higher risk of cardiovascular disease (Carlsson et al., 2018), which is implicated in cognitive impairment (Stewart et al., 2019). These neuropathological and cardiovascular implications may explain in part the stronger link between sTNFR1 and cognition observed in the present study compared with other markers.

Mediation analysis indicated that lower sTNFR1 partially explained the prospective association between conscientiousness, extraversion, and openness and cognition at follow-up. The lower level of sTNFR1 associated with these traits may promote better brain health and reduce pathophysiological processes and vascular damage that ultimately supports better cognitive function. This finding supports the inflammation hypothesis suggested in past research as a potential explanation of the personality–cognition relationship (Luchetti et al., 2014; Sutin et al., 2019a; Terracciano et al., 2017, 2022b). However, past studies have focused mainly on CRP and IL-6, and these two markers were not significant mediators; sTNFR1 was the only significant mediator among the immunity markers. The mediation through sTNFR1 persisted when physical activity and depressive symptoms were included as additional mediators. Although sTNFR1 explained less of the association than both physical activity and depressive symptoms, this finding indicates that it is an independent biological pathway that links personality and cognition.

In contrast with the hypothesis, inflammatory markers did not mediate the association between neuroticism and cognition. This null finding is consistent with recent research providing little evidence for a biological pathway through hypothalamic–pituitary–adrenal axis dysregulation (Montoliu et al., 2022), but contrasts with another research finding of a significant mediation through Vitamin D (Stephan et al., 2023b). More consistent evidence has been found for a mediating role of behavioral (e.g., sedentary behavior; Allen et al., 2019) and psychological (e.g., higher perceived stress; Da Silva Coelho et al., 2021; Montoliu et al., 2022) factors and physical performance measures, such as slower gait speed (Stephan et al., 2023a). In this study, additional analysis supported these findings by showing that less physical activity and more depressive symptoms significantly mediated the link between higher neuroticism and lower cognition. Therefore, it is likely that the association between neuroticism and cognition may be mostly explained by such factors.

The present findings contribute more broadly to models and research on the association between personality and cognition. First, this study extends existing research that focused primarily on behavioral, psychological, and health-related pathways (Allen et al., 2019; Hogan et al., 2012; Jackson et al., 2020; Mercuri & Holtzer, 2021; Stephan et al., 2023a; Sutin et al., 2020, 2022) by providing novel evidence for a biological pathway linking personality to cognition. Furthermore, existing studies on behavioral, psychological, and biological mediators of the association between personality and cognition have been conducted separately. Therefore, the present study provides evidence that personality is associated with cognition through the simultaneous mediation of several distinct biological, behavioral, and psychological factors. In addition, the results of this study may inform existing knowledge about the association between personality and dementia. For example, the association of lower conscientiousness with sTNFR1 suggests the presence of neuroinflammatory processes that may increase vulnerability to amyloid and tau neuropathology (Terracciano et al., 2022a), as well as measures of astrogliosis and neuronal injury (Terracciano et al., 2023), and a higher risk of incident dementia (Aschwanden et al., 2021). Indeed, higher sTNFR1 is implicated in Alzheimer's disease (AD) neuropathology and incident AD (Diniz et al., 2010; Zhao et al., 2020). Therefore, the sTNFR1 mediation between conscientiousness and cognition may extend to AD-related neuropathology and incident dementia, a hypothesis that future studies should test. From a practical perspective, personality assessments may facilitate identification of individuals at risk of poor cognition that may benefit from cognition-focused intervention efforts. It is also possible that intervention tailored to specific personality traits could increase adherence and increase effectiveness (Chapman et al., 2014; Newton et al., 2022). Furthermore, interventions may be directed toward changing risky personality traits such as low conscientiousness (Stieger et al., 2021), which may lead to better biological functioning and ultimately to better cognition.

The present study has several strengths, including the broad set of inflammatory markers, all five major personality traits, the large sample of older adults, and the longitudinal design with three waves of assessment over an 8-year follow-up. There are also several limitations. Causal interpretations are limited by the observational design of the study. In particular, reciprocal relationships between personality, inflammatory markers, and cognition are likely to exist. Future longitudinal research with repeated assessments is needed to disentangle these reciprocal associations. Furthermore, there was only one available assessment of inflammatory markers in the HRS, and it was not possible to test whether personality was related to changes in these markers and whether these changes mediated the link between personality and cognition. Future research may also include medication known to influence inflammation to test for the robustness of the effects. The results are specific to a sample of U.S. older adults, and further research is needed to test whether they may generalize to samples from other cultures.

In sum, the present study finds that inflammation mediates the association between personality and cognition. Higher conscientiousness, extraversion, and openness were related to higher cognition in part through their link with lower sTNFR1. More research is needed to replicate the mediational role of inflammation in the association between personality and cognition.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of Interest

None.

Data Availability

The HRS is funded by the National Institute on Aging (NIAU01AG009740) and conducted by the University of Michigan. HRS data are available for registered users at: https://hrs.isr.umich.edu/data-products/access-to-public-data. This study was not preregistered.

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