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Exploring the links between personality and immune function

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ABSTRACT

Decades of research finds associations between personality traits and health. In recent years, it has become clear that the activities of the immune system play a key role in linking these variables. In the current work, we add to this research by exploring the relationship between Big Five personality traits and (Study 1) polymorphisms known to impact cytokine release and (Study 2) immunological parameters measured *in vivo* (differential white blood cell counts, plasma proinflammatory cytokine levels) and *in vitro* (proinflammatory cytokine release by peripheral blood mononuclear cells, *S. aureus* growth in plasma). Results provide insights into potential mechanistic drivers of the links between personality and immune function and the possibility that, in some cases, relationships between personality and immune function may be sex differentiated.

1. Exploring the links between personality and immune function

Researchers find robust relationships between people's Big Five personality traits and their health (e.g., Bogg & Roberts, 2004; Lahey, 2009). For example, Shipley et al. (2007) find that individuals high in neuroticism have a higher mortality rate from cardiovascular disease (CVD) than those low in neuroticism. Although it was long assumed that the links between personality and health emerge in response to different behavioral tendencies that characterize different personality traits, recent research suggests that the relationship between these variables may be bidirectional. That is, in addition to personality being predictive of behavioral tendencies that impact health, research indicates that health – as mediated through the functionally multifaceted effects of the immune system – may contribute to the development of distinct personality traits (D'Acquisto, 2017; Luchetti et al., 2014; Segerstrom, 2000; Sutin et al., 2010).

Here, we sought to expand upon this growing body of work by examining novel links between the activities of the immune system and personality traits in three ways. First, we sought to better understand how each of the Big Five personality traits is related to genetic polymorphisms that impact levels of inflammation. Inflammation is a key component of the body's defenses against pathogens and damage, but is itself a potent risk factor for chronic disease (Ridker et al., 1997). Because variability in Big Five personality traits cannot cause an individual to possess different genes, demonstrating a link between one's genotype and their personality traits will provide a first step towards untangling the directionality of the relationships between personality and immune function.

Additionally, we also sought to extend previous research by investigating relationships between Big Five personality traits and multiple immune measures, measured *in vivo* and *in vitro*. Beyond assessing plasma proinflammatory cytokine levels, we assessed five-part differential white blood cell (WBC) counts, inflammation in response to immunological challenge, and performed additional functional immune assays. By widening the scope of investigation of immune measures that may be related to personality traits, we aim to better understand the complex relationships between one's Big Five personality traits and immune function.

Finally, we explored sex differences in relationships between Big Five personality traits and immune function. Much research investigating links between personality traits and immune function have not tested whether these relationships differ between the sexes. As men and women tend to differ in their personalities (e.g., Schmitt et al., 2008) and immune function (e.g., Fish, 2008; Klein et al., 2015), we report results of the current research separately for each sex.

1.1. The Big Five personality traits and health

Much research has investigated relationships between personality and both health outcomes and immune function using the Big Five personality traits described by the Five Factor Model of Personality, the

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gold standard in personality research (see Table 1 for a description of the traits; Buss & Cantor, 2012; McCrae & Costa, 1987; McCrae & John, 1992; Widiger & Costa Jr, 2013). Individuals have various levels of each of these five traits, which are found to be relatively stable across time and situations (Cobb-Clark & Schurer, 2012; Sanderman & Ranchor, 1994) and associated with many health outcomes (e.g., Hagger-Johnson et al., 2012; Miller et al., 1999). For instance, individuals high in neuroticism, compared to those low in neuroticism, have been found to be at a higher risk for diseases associated with elevated inflammation, including CVD, asthma, and irritable bowel syndrome (for review see Lahey, 2009).

1.2. Bi-directional relationships between personality and immune function

Recently, researchers have proposed that relationships between personality and health may be mediated through the activities of the immune system (D'Acquisto, 2017; Luchetti et al., 2014; Segerstrom, 2000; Sutin et al., 2010) with inflammation hypothesized as the mechanistic driver of these effects. In addition to being one pathway through which stress influences health (Rohleder, 2014; Slavich & Irwin, 2014), inflammation is known to predict a variety of health conditions, including metabolic disorders, CVD, mental health issues, and greater all-cause mortality risk (e.g., Bonaccio et al., 2016; Esser et al., 2014; Savitz & Harrison, 2018; Yeun et al., 2000; Ziegler, 2005).

Consistent with the hypothesis that inflammation and personality are linked, several studies have identified relationships between personality traits and markers of inflammation. For example, research finds that low levels of traits like conscientiousness and openness are associated with heightened levels of C-reactive protein (CRP), a protein made by the liver in response to inflammation (Allen & Laborde, 2017; Armon et al., 2013; Luchetti et al., 2014; Sutin et al., 2010), and interleukin-6 (IL-6), a proinflammatory cytokine (Chapman et al., 2011; Luchetti et al., 2014). Similar patterns emerge for agreeableness, extraversion, and neuroticism, with high levels of these traits being linked to heightened CRP levels (Allen & Laborde, 2017; Armon et al., 2013; Sutin et al., 2010) and in the case of neuroticism, elevated IL-6 (Sutin et al., 2010). Because one's personality influences health practices (e.g., someone high in conscientiousness is likely to eat a healthy diet and exercise [Raynor & Levine, 2009]) and pathogen exposure (e.g., someone low in openness may encounter few pathogens due to rigidity of their routines), it is generally reasoned that personality is the causal factor linking personality and health. Although personality traits certainly impact one's health via differences in stress and pathogen exposure, recent research proposes that the immune system may also influence personality (Gassen & Hill, 2019; Lopes, 2017), suggesting a bidirectional relationship between personality and health.

The activities of the immune system are coordinated by signaling proteins called cytokines. Cytokines can be either pro- or anti-inflammatory in nature. Pro-inflammatory cytokines, such as IL-6 and IL-1β, promote inflammation and initiate innate immune mechanisms involved in combatting pathogens, while anti-inflammatory cytokines, such as IL-10, inhibit inflammatory activity, stimulate antibody production, and promote tissue repair. Beyond their influence on the immune system, these proteins also influence the activities of the nervous system, regulating behavior, both in sickness and in health (e.g., Dantzer, 2001; Eisenberger et al., 2010; Moieni & Eisenberger, 2018). For example, cytokines play an important role in regulating sleep (Jewett & Krueger, 2012), learning (Goshen et al., 2007), mood (Reichenberg et al., 2001), reward processing (Gassen, Makhanova, et al., 2019; Gassen, Prokosch, et al., 2019; Treadway et al., 2019), and even social behavior (Hennessy et al., 2014; Lisboa et al., 2018; Yim et al., 2017). Inflammatory activity, therefore, may promote behavioral tendencies that are consistent with different personality traits.

Consistent with this perspective, research finds that healthy adults with higher levels of proinflammatory cytokines exhibit increased impulsivity and a diminished ability to delay gratification compared to those with lower levels of these cytokines (Gassen, Makhanova, et al., 2019; Gassen, Prokosch, et al., 2019). Given that those with higher levels of impulsivity also tend to be higher in extraversion (Smith, 2013) and neuroticism (Costa Jr & McCrae, 1992), and lower in conscientiousness (Hair & Hampson, 2006), it is possible that personality plays an intermediary role in this relationship. Others find that experimentally induced inflammatory activity produces a constellation of behavioral changes including anhedonia, fatigue, and diminished social interest, collectively referred to as inflammation-induced sickness behavior (for review, see Dantzer & Kelley, 2007). These shifts, while transient, demonstrate the powerful role of inflammation in shaping behavior. Others yet find links between inflammation and activity in regions of the brain known to play a role in shaping personality traits. For example, experimentally inducing inflammation enhances activity in brain regions involved in processing fear, anxiety, and social rejection (Inagaki et al., 2012; Muscatell et al., 2015; Slavich et al., 2010), providing insight into neural mechanisms that contribute to the relationship between inflammation and neuroticism (Lahey, 2009).

Together, this research suggests a bidirectional link between personality and health, with personality impacting physiological and behavioral systems in ways that impact health (Allen et al., 2017; Armon et al., 2013; Luchetti et al., 2014; Sutin et al., 2010) and health impacting how individuals interact with their social and physical environments (e.g., Dantzer, 2001; Gassen & Hill, 2019; Hennessy et al., 2014; Lisboa et al., 2018; Yim et al., 2017).

1.3. The current research

Here, we sought to build on previous research investigating relationships between personality, immune function, and health. Specifically, we examined the relationship between Big Five personality traits and (a) four polymorphisms known to impact the activity of leukocytes (Study 1) and (b) multiple *in vivo* (i.e., tested directly from a participant's blood sample) and *in vitro* (i.e., tested by plating a participant's blood sample with an immunological stimulant) measures of inflammatory activity and immune function (Study 2). The results of the current research will extend what is known about relationships between personality and immune function by investigating a wider range of immune measures than has been explored in previous research and by investigating sex differences in these relationships.

Table 1
Big Five personality traits.

Personality trait	Description of trait
Agreeableness	kind, altruistic, sympathetic
Conscientiousness	self-disciplined, organized, efficient
Neuroticism	anxious, irrational, self-conscious
Extraversion	outgoing, social, energetic
Openness to Experience	curious, inventive, flexible

(Buss & Cantor, 2012; McCrae & John, 1992)

2. Study 1: cytokine genotypes and personality

Study 1 was designed to assess the relationship between Big 5 personality traits and polymorphisms, or genetic variation, known to impact the release of pro- and anti-inflammatory cytokines (IL-6 [−174], tumor necrosis factor alpha [TNF-α; −308], IL-10 [−1082, −819, −592], and interferon gamma [IFN-γ; +874]). These polymorphisms were chosen as they specifically regulate release of cytokines that have been found to be related to personality traits (Chapman et al., 2011; Sutin et al., 2010) or have been theorized to be related to personality traits (Lopes, 2017; MacMurray et al., 2014). It should be noted that while this study is exploratory in nature, we are able to make predictions based upon the results of previous research. Generally, IL-6, TNF-α, and IFN-γ are considered to be pro-inflammatory cytokines,

while IL-10 is considered to be an anti-inflammatory cytokine (see Cavaillon, 2001 for a more nuanced discussion). We expect to find that polymorphisms linked to elevated release of proinflammatory cytokines will be positively related to personality traits associated with inflammation in previous research (including agreeableness, extraversion, and neuroticism) and negatively related to traits found to be negatively related to inflammation (including conscientiousness and openness). Further, we expect the opposite pattern of results for IL-10 polymorphisms, as IL-10 is an anti-inflammatory cytokine.

While Study 1 utilizes cross-sectional data, preventing the ability to draw causal conclusions from the outcomes, it is unlikely that personality facets would have influenced one's genotype (as one's genotype is established at conception). As such, any relationships which emerge between personality traits and genotypes would suggest that immunological parameters influence personality (rather than the opposite), or that these relationships covary as a result of mutual influence or influence by a third, unmeasured variable. Understanding the unique ways in which one's genotype predicts personality will provide a first step in untangling the directionality of the relationships between personality and immune function.

2.1. Method

The data used in this study were made available by the Common Cold Project (CCP). The CCP was conducted by the Laboratory for the Study of Stress, Immunity, and Disease at Carnegie Mellon University under the directorship of Sheldon Cohen, PhD. Deidentified data were accessed via the CCP website (www.commoncoldproject.com; grant number NCCIH AT006694). We used data from the Pittsburgh Cold Study 3, a dataset that includes measures bearing on both personality and immunologically relevant genetic polymorphisms. See Supplemental Materials for more information about participants, materials and procedures, and potential covariates.

2.1.1. Participants

A total of 213[1] participants completed the study (123 men, 90 women; M_{age} = 30.13 years, SD = 10.85). Full characteristics of the sample have been published elsewhere (e.g., Cohen et al., 2012; Doyle et al., 2010).

2.1.2. Materials and procedure

Detailed information about study design is available on the CCP website (www.commoncoldproject.com). Participants entered the lab and completed a number of demographic questionnaires and self-report measures, including the target dependent personality measure. A buccal swab was collected from participants for DNA isolation and analysis. As part of a larger study, additional measures were later collected.

2.1.3. Personality measures

Participants completed the International Personality Item Pool (IPIP) Big Five Factors scale (Goldberg, 1999; Goldberg et al., 2006) to assess extraversion (α = 0.87, 0.89), conscientiousness (α = 0.83), neuroticism (emotional stability reverse-scored; see e.g., Ypofanti et al., 2015) (α = 0.88), agreeableness (α = 0.84, 0.87), and openness to experience (α = 0.82). Descriptive statistics are displayed in Table 2. The extraversion and agreeableness subscales were administered twice, thus averages of the participants' two responses to each subscale were used in analysis. The remaining subscales were only administered once.

2.1.4. Potential covariates

We tested the following variables as covariates: sex, race, age, body mass index (BMI), childhood socioeconomic status (SES), and adult SES.

[1] As this data was collected as a part of a larger study, the sample size is smaller than would be ideal and analyses may be somewhat underpowered to detect relationships between personality traits and polymorphisms assessed.

Table 2
Descriptive statistics for personality traits (Study 1).

Personality Trait	M(SD)	Range
Agreeableness	38.97 (6.03)	22.00–49.50
Conscientiousness	35.99 (6.71)	18.00–55.00
Emotional Stability/Neuroticism[a]	34.88 (7.56)	16.00–50.00
Extraversion	32.83 (7.20)	10.50–48.50
Openness to Experience	38.57 (5.89)	24.00–50.00

[a] Personality measured using International Personality Item Pool (IPIP) Big Five Factors scale (Goldberg, 1999; Goldberg et al., 2006).

2.2. Data analytic plan

Per convention (see e.g., Doyle et al., 2010; Gentile et al., 2003), each genotype was assigned to one of three phenotypic categories based on observed differences in levels of cytokine release, in vitro, by those with each genotype. These assignments categorized genotypes as being "high-producing", "intermediate-producing", or "low-producing" phenotypes (see Supplemental Materials for more information and Table 3 for phenotype assignments). Cytokine phenotypes were dummy-coded in analyses such that low-producers were coded as the reference group (i.e., "0"). To test the final comparison between intermediate- and high-producers for three-level predictors (i.e., IL-10, IL-6, and IFN-γ phenotypes), additional dummy variables were created with high-producers coded as the reference group.

All models were built using MPlus statistical software (Version 8, Muthén & Muthén, 1998–2017), and missing data were handled using full information likelihood estimation. We assessed model fit using four fit indices: χ^2 test of model fit, the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). Good model fit was indicated by a non-significant χ^2 value ($p > .05$), a CFI value >0.95, an RMSEA value <0.08, and an SRMR statistic <0.08. We first regressed each personality factor on all candidate covariates; covariates that significantly predicted a personality outcome were retained in all subsequent models (i.e., $p < .05$; see supplemental materials for significant covariates in each

Table 3
Phenotype assignments for cytokine genotypes/haplotype (Study 1).

Genotype/Haplotype	Phenotype	Sample Frequency
TNF-α (−308)		
A/A	High-producing	1.4%
G/A	High-producing	20.5%
G/G	Low-producing	78.1%
IL-10 (−1082, −819, −592)		
GCC/GCC	High-producing	17.6%
GCC/ACC	Intermediate-producing	25.7%
GCC/ATA	Intermediate-producing	21.0%
ACC/ACC	Low-producing	5.2%
ACC/ATA	Low-producing	19.5%
ATA/ATA	Low-producing	11.0%
IL-6 (−174)		
G/G	High-producing	51.0%
G/C	Intermediate-producing	35.7%
C/C	Low-producing	13.3%
IFN-γ (+874)		
T/T	High-producing	21.9%
T/A	Intermediate-producing	41.9%
A/A	Low-producing	36.2%

Note. These classifications determined by previous work using in vitro lymphocyte stimulation assays (Fishman et al., 1998; Heesen et al., 2003; Hoffmann et al., 2001; Karjalainen et al., 2003; Kilpinen et al., 2002 & Rivera-Chavez et al., 2003). The categories for cytokine phenotypes were determined from three possible combinations from a single nucleotide polymorphism (SNP) of the IL-6 gene, TNF-α gene, and the IFN-γ gene and six possible combinations based on three SNPs of the IL-10 gene.

model). Next, we utilized multivariate multiple regression in MPlus to examine relationships between cytokine phenotypes and personality factors, while controlling for the effects of other cytokine phenotypes. Finally, we used Wald tests of parameter constraints (see Gourieroux et al., 1982; Kline, 2016; Muthén & Muthén, 2018) to test for sex differences.

2.3. Study 1 results

Results are summarized in Table 4 and fully reported in the Supplemental Materials. All model fit indices indicated good model fit (see Table S1 for model fit statistics).

2.3.1. Agreeableness

Intermediate IFN-γ producers were low in agreeableness compared to both low-, $p = .001$, and high-, $p = .048$. producers of IFN-γ.

2.3.2. Conscientiousness

Intermediate IFN-γ producers were low in conscientiousness compared to low-producers, $p = .04$.

2.3.3. Neuroticism

Intermediate IFN-γ producers were high in neuroticism compared to both low-, $p = .001$, and high-, $p = .03$ producers of IFN-γ.

2.3.4. Extraversion

Low IFN-γ producers were high in extraversion compared to intermediate-producers, $p = .03$. Additionally, high TNF-α producers were more extraverted than were low-producers ($p = .04$).

In contrast to the relationship found between TNF-α phenotype and extraversion, the opposite pattern of results emerged between IL-6 phenotype and extraversion in men, where men who were either high-producers of IL-6 ($p = .008$), or intermediate-producers ($p = .02$), were found to be less extraverted than men who were low-producers. There was no relationship between IL-6 phenotype and extraversion in women ($ps > .78$). These results suggest that these pro-inflammatory cytokines may relate to extraversion in different ways, and that IL-6 phenotypes, specifically, might be related to extraversion in men, but not in women.

2.3.5. Openness

Individuals with high ($p = .01$) and intermediate ($p = .03$) producing IL-10 phenotypes were high in openness compared to those with low-producing IL-10 phenotypes.

2.4. Study 1 discussion

Together, the results of Study 1 revealed complex relationships between Big Five traits and cytokine gene polymorphisms. All personality traits, excluding openness, were related to IFN-γ phenotypes. Specifically, intermediate IFN-γ producers were low in agreeableness (compared to both high and low producers), conscientiousness (compared to low producers), and extraversion (compared to low producers), and high in neuroticism (compared to both high and low producers). Based on previous research, it is unclear why intermediate producers of this pro-inflammatory cytokine would be more likely to possess this constellation of personality traits. However, one previous study in women with metabolic syndrome found that the intermediate IFN-γ phenotype was related to higher levels of serum kynurenine (compared to high and low phenotypes), suggesting that this phenotype may be associated with altered tryptophan metabolism (Szkup et al., 2019), which could alter serotonin levels as tryptophan is a precursor to serotonin. Indeed, research finds that inflammation-driven changes in tryptophan metabolism such as these negatively impact mood and may increase anxiety (Kim & Jeon, 2018; Young & Leyton, 2002).

Openness was related to IL-10 phenotypes, with both high and intermediate IL-10 producers being more open to experience than low IL-10 producers. This finding is consistent with animal research finding that IL-10 administration increases exploratory behavior and reduces anxiety-like behavior (Bluthé et al., 1999; Munshi et al., 2019; Nava et al., 1997). Further, levels of extraversion were found to be related to TNF-α and IL-6 phenotypes (along with IFN-γ phenotypes, as previously mentioned). Consistent with previous research finding positive relationships between extraversion and inflammation (e.g., Wagner et al., 2019), high TNF-α producers were more extraverted than low TNF-α producers. Additionally, the present research found that intermediate IFN-γ producers were less extraverted than low IFN-γ producers, and, in men, high and intermediate producers of IL-6 were less extraverted than low producers of IL-6. Thus, while several relationships between extraversion and pro-inflammatory cytokine genes were found, the direction and sex specificity of these relationships differed across the SNPs examined.

3. Study 2: personality and multiple measures of immune function

In Study 2, we sought to build on the results of Study 1 by examining relationships between Big Five personality traits and 1) *Staphylococcus aureus* (*S. aureus*) growth in participant plasma, 2) peripheral blood mononuclear cell (PBMC) release of proinflammatory cytokines in response to lipopolysaccharide (LPS) stimulation, 3) plasma levels of proinflammatory cytokines, and 4) WBC count and composition. The first two measures of immune function were chosen to explore how people's immune responses to immunological challenges or threats (such as the presence of bacteria or LPS) were related to their personality traits. The third measure of immune function, plasma levels of proinflammatory cytokines, was chosen to replicate previous work investigating the relationships between personality and *in vivo* inflammation. We further included WBC composition (i.e., counts of neutrophils, eosinophils, basophils, lymphocytes, and monocytes) to better understand the relationships between personality traits and additional measures of immune function that have not yet been explored in the context of personality but are nonetheless related to many facets of immunity (e.g., Th1 vs. Th2 skew; Sokol et al., 2009; Spencer & Weller, 2010).

Based on the results of Study 1 and previous research, we predict that extraversion will be related to higher plasma levels of proinflammatory cytokines and a greater release of proinflammatory cytokines in response to stimulation, although these relationships may differ by cytokine and sex. Previous research also suggests that agreeableness and neuroticism should follow a similar pattern, while conscientiousness and openness should be related to lower plasma levels of proinflammatory cytokines and decreased release of proinflammatory cytokines in response to stimulation.

3.1. Method

3.1.1. Participants

A total of 159[2] participants completed the study (80 men, 79 women; $M_{age} = 20.17$ years, $SD = 2.75$). Participants were recruited from a university in the southern United States and the nearby community and received partial course credit or a $50 gift card as compensation for participation.

3.1.2. Materials and procedure

Prior to their session, participants completed the target personality

[2] As this data was collected as a part of a larger study, the sample size is smaller than would be ideal and analyses may be somewhat underpowered to detect relationships between personality traits and immune function. More information about participant inclusion criteria, materials and procedures, and covariates can be found in the Supplemental Materials.

Table 4
Summary of significant findings for Study 1.

Predictor	Agreeableness	Conscientious-ness	Neuroticism	Extraversion	Openness to Experience
TNF-α					
Phenotype	–	–	–	high > low	–
IL-10					
Phenotype	–	–	–	–	high > low; intermediate > low
IL-6 Phenotype	–	–	–	men: high < low; intermediate < low	–
IFN-γ	intermediate < low; intermediate	intermediate <	intermediate > low; intermediate		
Phenotype	< high	low	> high	intermediate < low	–

Note. TNF-α = tumor necrosis factor-alpha, IL-10 = interleukin-10, IL-6 = interleukin-6; IFN-γ = interferon-gamma. High = high-producer, intermediate = intermediate-producer, low = low-producer.

measure – and additional questionnaires – online using Qualtrics experimental software (Qualtrics, Provo, UT). During their laboratory session, participants first completed survey measures and tasks before being led into a biological collection laboratory where 85 mL of blood was collected via venipuncture into heparinized and EDTA-lined Vacutainer® collection tubes (Becton-Dickinson, Franklin Lakes, NJ). Participants were then thanked, debriefed, and compensated.

3.1.3. Personality questionnaires

Participants completed the Ten-Item Personality Inventory (TIPI) (Gosling et al., 2003) to assess their levels of the Big Five personality traits. Each question consists of two descriptors (e.g., "Extraverted, enthusiastic", "Disorganized, careless"), and participants are asked to respond to how much they see themselves as each pair of adjectives. Each of the 10 items was rated on a 7-point scale (endpoints: 1 = disagree strongly, 7 = agree strongly). The appropriate items were reversed-scored, and a composite score was calculated for each of the five traits (extraversion: α = 0.82, neuroticism: α = 0.62, agreeableness: α = 0.44, conscientiousness: α = 0.69, openness to experience: α = 0.35; see supplemental materials for more information about reliabilities). Descriptive statistics are displayed in Table 5.

3.1.4. Biological measures

Details of biological assays and measures (*S. aureus* growth assay, stimulated proinflammatory cytokine release assays, plasma cytokine level assays, and differential WBC counts), as well as references to descriptive statistics for these measures can be found in the Supplemental Materials.[3]

3.1.5. Potential covariates

We tested the following variables as covariates in each model: sex, race, age, exercise, sleep, BMI, childhood and adult SES, stress, loneliness, recent illness, and day length.

Table 5
Descriptive statistics for personality traits (Study 2).

Personality Trait	M(SD)	Range
Agreeableness	4.97 (1.24)	1.50–7.00
Conscientiousness	5.36 (1.34)	1.50–7.00
Neuroticism	3.06 (1.33)	1.00–6.00
Extraversion	4.43 (1.66)	1.00–7.00
Openness to Experience	5.28 (1.07)	2.00–7.00

Note. Personality measured using the Ten-Item Personality Inventory (Gosling et al., 2003).

[3] See Supplemental Materials for extended procedures, methods, and results for Study 2, including relationships between personality traits and cellular proliferation, phagocytosis, and natural killer cell cytotoxicity. As these immune measures were unrelated to personality traits, these results are not discussed in the main text.

3.2. Data analytic plan

Data were examined for normality prior to model testing. Outliers across immunological measures were excluded prior to analysis (> 3SD above the mean of that measure; <2.8% of values for any given measure: two WBC count values and 12 *S. aureus* growth values [across all time points]). Values for total WBC count, plasma IL-6 levels, plasma TNF-α levels, and PBMC release of cytokines in vitro were positively skewed. These variables were each natural log-transformed, after which the distribution of each variable approximated normality. As in Study 1, all models were estimated using MPlus statistical software (Version 8, Muthén & Muthén, 2018), and missing data were handled using full information likelihood estimation. We assessed model fit using the same indices as in Study 1.

For each model, we first regressed each dependent measure on each candidate covariate. As in Study 1, covariates that significantly predicted that outcome were retained in all subsequent models (i.e., $p < .07$; see supplemental materials for significant covariates in each model). Next, we simultaneously regressed each immune measure on each personality trait, to estimate the effects of each trait on the immune measure while controlling for the effects of other personality traits and covariates. Sex differences were again examined with Wald tests.

Data for *S. aureus* growth (time: 1–8 h, 12 h, 24 h), and stimulated proinflammatory cytokine release (time: 2, 24, 48, and 72 h) each contained nested structures. Thus, we used multilevel modeling to account for dependencies in the data. These models yielded a random intercept at level 2 representing average levels of the dependent measures across time points (i.e., *S. aureus* growth). To assess the influence the rate of *S. aureus* growth over time (i.e., in addition to total levels across time points), we also included a random slope term for time in this model.

3.3. Study 2 results

Summaries of the results are displayed in Tables 6–7. Full results are found in the Supplemental Materials. Fit indices indicated good model fit for all models (see Table S1 for model fit statistics).

3.3.1. Agreeableness

Higher levels of agreeableness predicted increased *S. aureus* growth for women in the current sample ($p = .005$).

3.3.2. Conscientiousness

Higher levels of conscientiousness predicted decreased levels of plasma IL-6 (*in vivo;* $p = .01$), decreased levels of plasma TNF-α (*in vivo*) in men ($p = .04$), and decreased stimulated proinflammatory cytokine release (*in vitro*) in women ($p = .005$). Higher levels of conscientiousness also predicted decreased monocyte counts in men ($p = .03$).

Table 6
Relationships between Personality Traits and Immune Measures in Study 2.

Immune Measure	Agreeableness	Conscientiousness	Neuroticism	Extraversion	Openness
in vivo					
Plasma IL-6					
Men	–	↓	–	↑†	–
Women	–	↓	–	↑†	–
Plasma TNF-α					
Men	–	↓	–	–	–
Women	–	–	–	–	–
in vitro					
Stimulated Proinflammatory Cytokine Release					
Men	–	–	–	↑	–
Women	–	↓	–	↑	–
S. aureus Growth					
Men	–	–	–	↑	–
Women	↑	–	–	↑	–

Note. IL-6 = interleukin-6, TNF-α = tumor necrosis factor-alpha; proinflammatory cytokine release = lipopolysaccharide-stimulated release of interleukin-1beta, IL-6, and TNF-α by peripheral blood mononuclear cells in vitro, modeled as a latent factor. ↑ = significant positive relationship ($p < .05$); ↓ = significant negative relationship ($p < .05$). ↑† = marginally significant positive relationship ($p < .07$).

Table 7
Relationships between Personality Traits and Differential White Blood Cell Count in Study 2.

White Blood Cells	Agreeableness	Conscientiousness	Neuroticism	Extraversion	Openness
Eosinophils					
Men	–	–	↓	↓	–
Women	–	–	↓	↓	–
Basophils					
Men	–	–	–	–	–
Women	–	–	–	↓	–
Neutrophils					
Men	–	–	–	–	–
Women	–	–	–	–	–
Monocytes					
Men	–	↓	↓	↑	–
Women	–	–	↓	–	–
Lymphocytes					
Men	–	–	–	–	–
Women	–	–	–	–	–

Note. ↑ = significant positive relationship ($p < .05$); ↓ = significant negative relationship ($p < .05$).

3.3.3. Neuroticism

Higher levels of neuroticism predicted decreased counts of both eosinophils ($p = .004$) and monocytes ($p = .002$).

3.3.4. Extraversion

Higher levels of extraversion predicted marginally higher levels of plasma IL-6 (*in vivo;* $p = .053$), and an increased rate of *S. aureus* growth ($p = .03$), along with increased stimulated proinflammatory cytokine release (*in vitro;* $p = .04$). Further, increased levels of extraversion predicted decreased eosinophil counts for both sexes ($p = .02$), decreased basophil counts in women ($p = .04$), and increased monocyte counts in men ($p = .049$).

3.3.5. Openness

No relationships between openness and any immune measures emerged ($ps > .08$).

3.4. Study 2 discussion

Results of Study 2 revealed several relationships between personality and immune function. Consistent with previous research, those high in conscientiousness had decreased markers of inflammatory activity (Allen & Laborde, 2017; Luchetti et al., 2014; Sutin et al., 2010), and those high in extraversion had increased markers of inflammatory activity (Armon et al., 2013). However, we did not find, as others have, that levels of agreeableness, neuroticism, or openness were related to inflammatory markers in our sample (e.g., Allen & Laborde, 2017; Armon et al., 2013). While we do not find evidence a relationship between neuroticism and inflammatory markers, neuroticism scores of the current sample were somewhat low (see Table 4), and, as such, these results should be interpreted with caution.

As we assessed proinflammatory cytokines levels and release, future research should extend this work by exploring levels of anti-inflammatory cytokines as well, particularly in relation to agreeableness and openness. Many sex differences also emerged in the relationships between personality traits and immune measures, indicating that the relationships between personality and health may be influenced by immune function differently between men and women.

4. General discussion

Results of the current research provide continued support for links between personality traits and immune function (e.g., Allen & Laborde, 2017; Armon et al., 2013; D'Acquisto, 2017; Lopes, 2017; Segerstrom, 2000), some of which differed by sex. For example, results of Study 1 revealed that high TNF-α producers were more extraverted than low-producers and that men who were high IL-6 producers were less extraverted than low-producers, suggesting that the links between health-relevant variables and personality may be sex-, context-, and cytokine-dependent. Study 1 also revealed that high IL-10 producers were more open to experience than low-producers. This is consistent with animal research that finds IL-10 may have anxiolytic properties (Martinez et al., 2018; Mesquita et al., 2008; Munshi et al., 2019; Nava et al., 1997).

One particularly striking result from Study 1 was the regularity with

which intermediate IFN-γ producers were found to differ from high- and low-producers across personality traits. Intermediate-producers, overall, reported being less agreeable, more neurotic, and, compared low-producers only, less conscientiousness and less extraverted. While we did not predict these results *a priori*, it is possible that this relationship could have emerged in response to these individuals' heightened risk for infectious disease. Researchers find that intermediate IFN-γ producers have an increased risk of certain infectious diseases relative to high- or low-producers (e.g., leishmaniasis: Kalani et al., 2019; tuberculosis: Amim et al., 2008). Accordingly, although the participants in the current study are unlikely to have come into contact with these infectious agents, it is possible that genetic predisposition to disease risk influences the development of personality traits (e.g., Bilbo & Schwarz, 2009). Additionally, separate research suggests that women with metabolic syndrome who are intermediate-producers of IFN-γ exhibit altered tryptophan metabolism compared to high- or low-producers (Szkup et al., 2019), which may influence personality traits. Although these interpretations are speculative, they raise interesting possibilities for future research.

Study 2 revealed additional associations between personality and immune measures. For example, higher extraversion was related to greater LPS-induced proinflammatory cytokine release by PBMCs *in vitro*, while higher conscientiousness was associated with lower levels of plasma IL-6, a result that is consistent with the results of previous research (e.g., Sutin et al., 2010). While similar results were found for the effect of conscientiousness on the remaining measures of inflammation, these effects were sex-differentiated with higher conscientiousness predicting lower levels of plasma TNF-α and diminished proinflammatory cytokine release by PBMCs in men and women, respectively. Results also revealed that higher levels of extraversion were associated with lower numbers of eosinophils and basophils (the latter in women only), potentially suggesting a skew towards Th1 over Th2 immunity in individuals high on this trait (Sokol et al., 2009; Spencer & Weller, 2010). This possibility is further supported by the finding that men high in extraversion had higher counts of monocytes than did men low in extraversion. Th1 immunity is primarily involved in the body's response to intracellular pathogens, like viruses, while Th2-biased responses are typically observed during macroparasite infection, such as with helminths, and also play a role in allergies (Romagnani, 2000). Interestingly, due to growing population density and urbanization, most modern human populations are exposed to much higher numbers of viruses than parasitic worms (Amoroso & Nunn, 2021). Accordingly, the heightened sociality associated with high extraversion likely increases one's exposure to viruses, specifically, which may lead to a Th1 skew.

Additionally, high levels of extraversion, and for women, high levels of agreeableness, were found to predict increased *S. aureus* growth in plasma *in vitro*. Additional research is needed to determine the exact differences in plasma composition that contribute to differences in rates of *S. aureus* growth (e.g., minerals: Cross et al., 2015, complement proteins: Walport, 2001); however, previous research has found lower *S. aureus* growth in the plasma of individuals whose PBMCs exhibit greater proliferation in response to antigen stimulation (Gassen, Leyva, et al., 2019), suggesting that this measure is related to well-characterized immunological parameters.

The current research finds certain personality traits are more consistently related to aspects of immune function than others. Across studies, conscientiousness and extraversion appear to be reliably related to levels of inflammation (although the directions of these relationships sometimes differ, e.g., Allen & Laborde, 2017; Armon et al., 2013; Sutin et al., 2010), while agreeableness is not. For example, the current research finds conscientiousness to be negatively related to plasma IL-6 levels, a pattern which is also reliably observed in others' work (e.g., Chapman et al., 2011; Luchetti et al., 2014; Sutin et al., 2010). Repeated replication of this result suggests that these two variables are likely interconnected in a meaningful way. For example, one possibility is that those with low IL-6 levels tend to utilize behavioral strategies, such as avoiding individuals who may be sick, visiting the doctor regularly for check-ups, washing hands often, etc., to compensate for their low levels of inflammation by avoiding pathogens in their environments. In this way, aspects of conscientiousness may develop as a strategy for managing infectious disease risk in a state of low inflammation or lack of immunological preparedness. Alternatively, it is also possible that the relationship between inflammation and conscientiousness primarily operates in the other direction. That is, individuals high in conscientiousness (compared to those lower in conscientiousness) may be more careful with their health and avoid circumstances that elicit inflammatory responses, such as eating unhealthy food or engaging in unsafe sexual practices. Future research is needed to test these, as well as other, hypotheses about the causal links between these variables.

The consistent relationships observed between inflammation and extraversion, both in the current work and in the work of others, further underscore that individual differences in human tendencies for behavior may be shaped by one's immunological vulnerabilities. For example, over human history, levels of extraversion would have been reliably linked to exposure to infectious diseases. That is, because humans are vectors for transmissible disease, increased sociality would have increased one's likelihood of coming in to contact with pathogens; however, elevated inflammation could be protective, rather than reactive, in this context, preventing an individual from becoming ill after encountering pathogens. Based on the results of Study 1, in which extraversion was associated with being a high-producer of TNF-α, our results suggest that differences in extraversion may be borne out of different immunological profiles, rather than the differences in levels of inflammation being exclusively the result of greater contact with others. Future research should explore this possibility, along with the threshold of inflammatory levels extraverted individuals must experience before exhibiting social withdrawal, one facet of inflammation-induced sickness behavior (Dantzer, 2001; Dantzer & Kelley, 2007), in response to elevated inflammation. While the levels of elevated inflammation explored in the current work are likely lower than what would be necessary to induce intense sickness behavior, it is possible that those high in extraversion require a larger release of proinflammatory cytokines before exhibiting social avoidance in response to inflammation compared to those lower in extraversion, given the potential for generally elevated inflammation and heightened stimulated proinflammatory cytokine release to buffer those high in extraversion from the somatic costs of elevated sociality. Identifying these thresholds would yield novel insights into the dynamic relationship between cytokines and the motivation to socially engage and withdraw.

The current work makes an important contribution to the literature by taking a step towards disentangling the directionality relationships between personality and immune function (Study 1), examining relationships between personality and novel measures of immunological functioning (Study 2), and examining sex differences in these effects (Studies 1 & 2). While Study 1 was cross-sectional, preventing us from drawing strong conclusions regarding causal directions, it is far more likely that one's genotype would predict their personality than vice versa. Relationships observed between cytokine genotypes and personality therefore provide initial support for the idea that immunological variables may impact aspects of personality in addition to personality having an impact on immune function, specifically in the case of extraversion. Further, Study 2 assessed the relationship between personality measures and novel measures of immunological functioning, including bacterial growth in plasma and stimulated proinflammatory cytokine release in PBMCs, both of which measure immune responses in the face of an immunological challenge. A better understanding of how personality relates to immunological responses to overt challenges will be informative for understanding how personality relates to immune function in the context of disease. Finally, this work also stands out from existing studies examining links between personality and immune function by reporting sex differences in these relationships. Much of the

extant personality and health literature has not investigated sex differences, which may be important to consider as men and women consistently exhibit differences in immune function (e.g., Fish, 2008; Klein et al., 2015) and personality (e.g., Schmitt et al., 2008). This study was the first – to our knowledge – to investigate sex differences in relationships between personality traits and a comprehensive set of immune measures (e.g., bacterial growth in plasma, stimulated cytokine release, WBC composition, etc.).

The current studies do, however, have limitations to consider. First, the sample of participants in Study 2 was relatively homogenous and small, limiting the generalization of these results to all populations. Additionally, the measure used to assess personality was brief, and while validated in previous research (Gosling et al., 2003), the TIPI is not the most comprehensive measure of personality available. In light of these limitations, further research should include larger, more diverse samples of participants and administer a more comprehensive personality questionnaire, while also including a wide variety of immune measures capturing facets of immunity not assayed in the current research (e.g., adaptive immunity). A larger sample size would also allow for greater power to test for interactions between personality traits, sex, and immune function.

Furthermore, despite the hypothesized bi-directional nature of relationships between personality and health, in Study 1, we utilized genomic measures, and as such, investigated the impact of TNF-α, IL-10, IL-6, and IFN-γ genotypes on personality traits. In Study 2, we limited our analyses to the impact of personality on immune function to preserve power and limit the number of analyses ran. While this allowed us to test for relationships in both directions, we are nevertheless limited in the causal claims that can be made about the relationships found. Future longitudinal or experimental studies are warranted to provide a stronger test of directionality in relationships between personality and immunity.

Despite limitations, the current studies provide important data bearing on relationships between personality and immune function. The present results lend support for the growing body of theory and research suggesting covariation between psychological traits, like personality, and immunity. This research lays the foundation for future work that may provide groundbreaking insights into complex relationships between health, immune function, and behavior.

CRediT authorship contribution statement

J. Gassen and S. E. Hill developed the study concept, study design, and collected data. J. Gassen and S. Mengelkoch prepared datasets and performed statistical analysis. J. Gassen and E. Corrigan processed biological samples. All authors drafted the manuscript, provided critical feedback, and approved the final version of the manuscript for publication.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.paid.2021.111179.

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