Chapter 4
The Relationship Between Neuroticism and Inflammatory Markers: A Twin Study

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The Relationship Between Neuroticism and Inflammatory Markers: A Twin Study

Arthur A. Sas, Frühling V. Rijsdijk, Johan Ormel, Harold Snieder, and Harriette Riese

Introduction: Neuroticism is an important marker of vulnerability for both mental and physical disorders. Its link with multiple aetiopathological pathways has been studied before. Inflammatory markers have been demonstrated to predict similar mental and physical disorders as neuroticism. However, currently no study has focused on the shared genetic background of neuroticism and inflammatory markers. In the present study we will focus on the phenotypic and genetic relationship between neuroticism and three commonly used inflammatory markers: C-reactive protein (CRP), fibrinogen and Immunoglobulin G (IgG).

Material and Methods: The study was conducted in 125 Dutch female twin pairs. For each participant, four different neuroticism scores were available to calculate a neuroticism composite score that was used in the statistical analyses. Blood samples for inflammatory marker determination were taken after an overnight fast. Heritabilities, phenotypic and genetic correlations were estimated using bivariate structural equation modeling. Reactive-Heritabilities are fair for neuroticism (0.55), CRP (0.52) and Fibrinogen (0.67) and moderate for IgG (0.48). No significant phenotypic or genetic correlations were found between neuroticism and the inflammatory markers. Interaction models yielded no moderation of the genetic and environmental pathways in the regulation of inflammatory markers by neuroticism. Conclusion: Substantial heritabilities were observed for all variables. No correlation was found for shared environmental (or moderate to high genetic or environmental pathways underlying neuroticism and inflammatory status.

Keywords: neuroticism, twins, heritability, C-reactive protein, fibrinogen, immunoglobulin G

Neuroticism refers to a relatively stable personality trait that is characterized by a tendency to respond with negative emotions to threat, frustration or loss (Costa & McCrae, 1992; Hoekstra et al., 1996). It is characterized by a tendency to respond with negative emotions to threat, frustration or loss (Costa & McCrae, 1992). Neuroticism refers to a relatively stable personality trait that is characterized by a tendency to respond with negative emotions to threat, frustration or loss (Costa & McCrae, 1992; Hoekstra et al., 1996). Neuroticism has been linked to a variety of mental and physical disorders such as anxiety and depression (Ormel et al., 2013a; McManus, 2013), Su et al., 2008, 2009). In order to assess these potentially shared genetic influences, in the present study we will investigate the phenotypic relationship between neuroticism and three commonly used inflammatory markers: C-reactive protein, fibrinogen, and Immunoglobulin G (IgG). Using a classical twin study design, we hypothesize that the markers are heritable, and that they may share their genetic influences with neuroticism.

Material and Methods

Participants

This study is part of the Twin Interdisciplinary Neuroticism Study (TWINS) in which the genetic and environmental origins of neuroticism are studied. For this purpose, in 2002 (T1) the Groningen Twin Registry (GTR) was established. A full description of the sample selection and procedures has been published before (Rijsdijk et al., 2015). In short, in 2002 (T1), 1,067 participants of the GTR participated in a survey. The survey included, among others, a neuroticism questionnaire. From the GTR, neuroticism data of 206 female twins were used in the statistical analyses of the current study. As gender differences in both mean level as well as variance of neuroticism are well established, including both men and women in our experimental situations would have implied that gender needed to be included as a covariate in our statistical analyses, or statistical analysis had to be stratified for gender. Both statistical procedures would have resulted in less power in our statistical analyses. Therefore, a priori decided to only include female twin pairs in our experimental situations and (repeated) the measurement of our core variable neuroticism multiple times. A subsample of 125 female twin pairs between 18 and 30 years from the GTR participated in TWINS in 2005/2006 (T2). TWINS participants did not differ from the other eligible women of the GTR, in age or neuroticism as assessed at T1. At T2, the subgroup of 125 twin pairs participated in a laboratory experiment in which additional neuroticism measures, CRP, fibrinogen and IgG-data, information about smoking habits and oral contraceptive use were collected and body weight and height were assessed. All participants reported to be in good physical and mental health at T2. Zygosity was assessed by questionnaire (Nicholls & Bilbos, 1996), and DNA samples. The study was approved by the Ethics Committee of the University Medical Center Groningen, and all participants gave written consent prior to participation.

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The inflammatory markers CRP, IL-6 and fibrinogen (Millar et al., 2013). Thus, the literature on the relationship between neuroticism and inflammatory markers is inconsistent. To the best of our knowledge, no study has examined the shared genetic background of neuroticism and baseline level of inflammatory markers, although neuroticism scores and the majority of commonly used immunological markers are both found to be substantially heritable (Health et al., 1989; Su et al., 2008, 2009). In order to assess these potentially shared genetic influences, in the present study we will investigate the phenotypic relationship between neuroticism and three commonly used inflammatory markers: C-reactive protein, fibrinogen, and Immunoglobulin G (IgG). Using a classical twin study design, we hypothesize that the markers are heritable, and that they may share their genetic influences with neuroticism.

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0.16 for these missing values gave slightly lower point estimates for variance components and correlations as reported in the results section, but did not result in different
conclusions as presented in the current study. For 22 sub-
jects CRF values were above 10 mg/L. These values are
assumed to reflect clinical inflammation and were therefore
excluded from the final analysis (Rahman et al., 2009; Su
et al., 2008). Fibrinogen and IgG measurements were also
excluded for these subjects, leaving data of 214 participants
for the final statistical analyses.

Preparation of the Data

Data distributions were checked prior analyses in SPSS
(SSPS for Windows, Version 16.0. Chicago, USA). CRF and
database were log-transformed to obtain a bet-
\text{er approximation of a normal distribution. Linear regress-
ion analysis was used to create residual scores adjusted for
potential confounding influences on inflammatory mark-
ers. Residual scores were used in the twin modeling anal-
yses. General Estimating Equations analyses were used to
test for significant differences in Ncomp-score, inflamma-
tory markers, age, BMI, smoking and oral contraceptive (OC)
use between MZ and DZ twin pairs.

Statistical Analyses

Twin modeling. The classical twin model allows estimation of the effects of (latent) genetic and environmental fac-
tors on the variance of an observed trait. The power to estimate these variance components is derived by the dif-
fert predictions of the covariance (or correlation) of the
trait among MZ and DZ twin pairs. MZ pairs correlate 1
and DZ twins experience the same degree of similarity
in their environments, a higher MZ than DZ twin correla-
tion is expected if there is significant heritability. MZ
pairs are always of the same age. Third, prior modeling,
which are in line with previous findings in the literature
implications for the interpretation and expectation of re-

\text{Table 3; all confidence intervals included the value zero).}

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However, the MZ cross-twin correlations of the inflammatory markers can be considered as a lower bound of the measurement reliability within the same individual. As all markers showed reasonably large correlations (>0.60) it is unlikely that instability of the measurements would have had a major effect. On the other hand, it is plausible that the present findings are real. Prior studies with null findings may not have been published, possibly due to publication bias. This is supported by a study in a population sample of 666 men and women that found no relationship between neuroticism and the inflammatory markers, CRP and fibrinogen (Billings et al., 2013). An alternative explanation is that a relationship between neuroticism and inflammatory markers is only present in individuals in the acute phase of a mental disorder. This view is in line with findings in a large sample of persons (18–65 years) with current and remitted anxiety disorders (a disorder closely related to high neuroticism) and healthy controls (Vogelzangs et al., 2013). In this study, men with a current anxiety disorder had somewhat increased levels of CRP. Moreover, elevated inflammation in particular was found in those men and women with a late onset of an anxiety disorder (between ages 50–65).

In the present study, only data of healthy premenopausal women were assessed. The benefit of this homogeneous sample is that the results cannot be confounded by gender or a wide age range, since these covariates have previously been shown to have significant effects (Suin et al., 2010). A limitation of this strategy, however, is that our conclusions are not generalizable to men, older subjects or subjects with somatic or mental disorders.

The present study shows that in healthy young women there is no evidence for a shared (genetic) predisposition or the presence of possible pleiotropic effects of neuroticism on the inflammatory markers CRP, fibrinogen and IL6, meaning that although high neuroticism and plasma levels of the studied inflammatory markers can lead to similar unfavourable health outcomes, the underlying pathways for these two risk markers should be considered as independent of each other.

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References


