


ORIGINAL ARTICLE

Associations between loneliness and personality are mostly driven by a genetic association with Neuroticism

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Abstract

Objective: Loneliness is an aversive response to a discrepancy between desired and actual social relationships and correlates with personality. We investigate the relationship of loneliness and personality in twin family and molecular genetic data.

Method: Phenotypic correlations between loneliness and the Big Five personality traits were estimated in 29,625 adults, and in a group with genome-wide genotype data ($N=4,222$), genetic correlations were obtained. We explored whether genetic correlations may reflect causal relationships by investigating within monozygotic twin pair differences ($N_{\text{pairs}}=2,662$), by longitudinal within-subject changes in personality and loneliness ($N=4,260-9,238$ longitudinal comparisons), and by longitudinal cross-lagged panel analyses ($N=15,628$). Finally, we tested whether genetic correlations were due to cross-trait assortative mating ($N_{\text{spouse pairs}}=4,436$).

Results: The strongest correlations with loneliness were observed for Neuroticism ($r=.55$) and Extraversion ($r=-.33$). Only Neuroticism showed a high correlation with loneliness independent of other personality traits ($r=.50$), so follow-up analyses focused on Neuroticism. The genetic correlation between loneliness and Neuroticism from genotyped variants was .71; a significant reciprocal causal relationship and nonsignificant cross-trait assortative mating imply that this is at least partly due to mediated pleiotropy.

Conclusions: We show that the relationship between loneliness and personality is largely explained by its relationship with Neuroticism, which is substantially genetic in nature.

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1 | INTRODUCTION

As a social species, humans tend to have a strong need for social connection. There are individual differences, however, in how socially connected one needs to be to feel fulfilled (Eysenck, 1947) and in how aversive the threat or loss of important social bonds is (J. T. Cacioppo & Patrick, 2008). The negative emotions one experiences when one's needs for social connection, either quantitatively or qualitatively, are not met (e.g., sadness, frustration, sorrow, shame, desperation) are referred to as loneliness. There are conditions under which facing loneliness may be advantageous, and hence genetic polymorphisms influencing loneliness are maintained in the population (J. T. Cacioppo, Cacioppo, & Boomsma, 2014). Loneliness is an aversive signal that likely evolved to motivate humans and other social animals to seek and improve the salutary social connections needed to help them survive and reproduce (J. T. Cacioppo, Cacioppo, et al., 2014). In contemporary society, chronic loneliness can have detrimental consequences for one's physical and mental health. Lonely individuals are at an increased risk for psychiatric disorders, substance abuse, elevated activation of the hypothalamic–pituitary–adrenal (HPA) axis, cardiovascular health problems, impaired immune functioning, fragmented sleep, increased prepotent behavior, and early mortality in general (J. T. Cacioppo & Cacioppo, 2014; J. T. Cacioppo, Cacioppo, Capitano, & Cole, 2015a; J. T. Cacioppo & Hawkey, 2009; S. Cacioppo, Capitano, & Cacioppo, 2014; Cole et al., 2015; Hawkey & Cacioppo, 2010; Heinrich & Gullone, 2006; Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015). Not everyone is equally susceptible to loneliness given similar levels of objective social isolation; loneliness reflects a discrepancy between the desired and actual relationships, both of which may be influenced by personality (Asendorpf & Wilpers, 1998). In this article, we focus on the relationship between individual differences in loneliness and personality.

The Big Five personality framework is one of the robust models for personality structure describing characteristic patterns of human behavior, cognition, and emotion (McCrae & John, 1992). Like loneliness, the Big Five dimensions (Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism) are significantly associated with physical and mental health outcomes, with Neuroticism showing the strongest associations (Christensen et al., 2002; Goodwin & Friedman, 2006; Kotov, Gamez, Schmidt, & Watson, 2010), which are in part genetic (Gale et al., 2016). Across studies on the relationship between loneliness and the Big Five, all five personality dimensions have been reported to significantly correlate with loneliness in at least one of the studies (Atak, 2009; J. T. Cacioppo et al., 2006; Lopes, Salovey, & Straus, 2003; Mund & Neyer, 2016; Teppers et al., 2013; Vanhalst et al., 2012), but there are no studies that investigate whether a dimension is significantly associated with loneliness

independently from the other four personality dimensions. Higher-order personality factors may cause the Big Five dimensions to intercorrelate (DeYoung, 2006; Digman, 1997; Musek, 2007; Van der Linden, te Nijenhuis, & Bakker, 2010), which may bias the interpretation of the relationship between personality and loneliness (or any other trait). Overall, previous studies report the strongest associations between loneliness and either Extraversion or Neuroticism (Atak, 2009; J. T. Cacioppo et al., 2006; Lopes et al., 2003; Mund & Neyer, 2016; Stephan, Fäth, & Lamm, 1988; Teppers et al., 2013; Vanhalst et al., 2012), which is theoretically plausible. In behavioral and neuroimaging research, loneliness is characterized by an implicit sensitivity to negative social stimuli (J. T. Cacioppo et al., 2014; J. T. Cacioppo, Norris, Decety, Monteleone, & Nusbaum, 2009; S. Cacioppo, Balogh, & Cacioppo, 2015; S. Cacioppo et al., 2015; Duck, Pond, & Leatham, 1994) and a decreased sensitivity to positive social stimuli (J. T. Cacioppo et al., 2009; J. T. Cacioppo & Patrick, 2008). Neuroticism is characterized by a heightened sensitivity to negative stimuli overall, whereas Extraversion is characterized by a heightened sensitivity to especially social positive stimuli (Larsen & Ketelaar, 1989, 1991; Rusting & Larsen, 1997). Hence, scoring high on Neuroticism or low on Extraversion may increase the propensity to feel lonely and vice versa.

The strength of the association between loneliness and personality dimensions such as Neuroticism, with correlations ranging from $\sim.28$ to $\sim.40$ (Atak, 2009; J. T. Cacioppo et al., 2006; Stephan et al., 1988; Vanhalst et al., 2012), may raise questions about their conceptual overlap. J. T. Cacioppo et al. (2006) addressed the possible conceptual overlap between loneliness and personality dimensions by showing that effects attributed to loneliness (higher depressed affect, negative mood, anxiety, and anger, and lower optimism, self-esteem, and social support) were independent from the association between loneliness and personality dimensions such as Extraversion, Neuroticism, Agreeableness, Conscientiousness, shyness, and sociability. Hawkey, Burleson, Berntson, and Cacioppo (2003) provide additional evidence of the functional independence between loneliness and Neuroticism—Neuroticism cannot explain the association they found between loneliness and the peripheral resistance levels found in undergraduates during the course of a normal day.

1.1 | The present study

We first estimated the phenotypic associations between loneliness and the Big Five personality dimensions in 29,625 Dutch adults and investigated whether the associations are independent from the other four Big Five dimensions.

Next, we assessed to what extent this relationship is explained by genetic correlations based on genome-wide single

nucleotide polymorphisms (SNPs). An SNP is a difference between people in a single nucleotide in the DNA sequence and represents a common type of genetic variation in humans. Because of their abundance throughout the human genome, common SNPs capture the large majority of human genetic variation and thus can be used to approximate the heritability of complex human traits (Yang et al., 2010). Genetic influences on loneliness and personality have been confirmed previously, mostly in twin and family studies, and imply a heritable biological basis for these traits. The Big Five personality dimensions consistently show heritability estimates ranging from 35 to 57% (Bouchard & McGue, 2003; Johnson, Vernon, & Feiler, 2008; Loehlin, McCrae, Costa, & John, 1998; Polderman et al., 2015), and SNP-based heritability estimates ranging from 0 to 18% for Extraversion, 0 to 9% for Agreeableness and Conscientiousness, 12 to 15% for Neuroticism, and 11 to 21% for Openness (De Moor et al., 2015; Lo et al., 2017; Power & Pluess, 2015; Van Den Berg et al., 2015). For loneliness, heritability estimates are around 40% in adults (Distel et al., 2010; Goossens et al., 2015). We estimated heritability and genetic correlations from SNP data in 4,375 Dutch adults from 2,405 families (4,222 individuals with both loneliness and the Big Five personality dimensions). These were estimated by modeling in distantly and closely related individuals, which allowed us to distinguish between correlations due to genetic factors captured by measured common SNPs (the so-called “SNP” heritability) and residual genetic factors (which we call “residual” heritability), which together add up to the narrow-sense heritability as derived from family-based approaches (Zaitlen et al., 2013).

We next investigated the evidence for a causal relationship between loneliness and personality by (a) testing in genetically identical twins whether within-twin pair differences in personality were associated with within-twin pair differences in loneliness (De Moor, Boomsma, Stubbe, Willemsen, & De Geus, 2008), (b) testing whether longitudinal within-subject changes in personality led to parallel within-subject changes in loneliness (De Moor et al., 2008), and (c) conducting a longitudinal cross-lagged panel analysis (J. T. Cacioppo, Hawkley, & Thisted, 2010; Curran, 2000).

We tested whether a correlation could be explained by the presence of cross-trait assortative mating, whereby genes for loneliness and personality are passed down and inherited together, based on data from 4,436 spouse pairs. When, for example, mothers high on loneliness select partners high in Neuroticism, the genetic variants for both traits are passed on to their offspring, inducing a genetic correlation between the two traits.

In short, we aim to characterize to what extent genetics influences loneliness and its relation with personality, and to what extent these relationships can be directly captured with common SNPs.

2 | METHOD

2.1 | Data sets

2.1.1 | Participants

The data were collected from twins and family members from across the Netherlands who were registered at the Netherlands Twin Register (NTR; based on ~40% of multiples born since 1987; Boomsma et al., 2006; Willemsen et al., 2010, 2013). Loneliness was measured at one, two, or three time points between 2004 and 2014 for 30,995 adult subjects. For nonlongitudinal analyses, the last measurement was chosen (age range = 18–98; $M_{\text{age}} = 40.42$, $SD = 16.31$). The Big Five personality dimensions were measured with the NEO scale for 29,625 of these subjects at the same time as loneliness. A total of 4,375 subjects with loneliness data were genotyped with the Affymetrix Human Genome-Wide SNP 6.0 Array (Affymetrix, Santa Clara, CA, USA). We selected only individuals with Dutch ancestry based on principal components (PCs) projected from the 1000 Genomes data set and with additional help of the birth country of the parents (Abdellaoui, Hottenga, De Knijff, et al., 2013).

2.1.2 | Phenotypes

Loneliness was measured by the short scale for assessing loneliness in large epidemiological studies, developed by Hughes, Waite, Hawkley, and Cacioppo (2004), containing three items from the Revised UCLA Loneliness Scale (Russel, Peplau, & Cutrona, 1980): (a) “How often do you feel left out?” (b) “How often do you feel isolated from others?” (c) “How often do you feel that you lack companionship?” Response categories were (a) *hardly ever*, (b) *some of the time*, and (c) *often*. This scale has been shown to be measurement invariant across age and gender in the data set we use for the current study (Distel et al., 2010). Using the same analyses as Distel et al. (2010), we confirmed that the scale is also measurement invariant across the three measurement points used here (metric invariance: CFI = 1, TLI = .999, RMSEA = .027; strong factorial invariance: CFI = .999, TLI = .999, RMSEA = .029; strict factorial invariance: CFI = .998, TLI = .999, RMSEA = .032). The three responses were summed to obtain the loneliness score, with higher scores indicating more loneliness. Because of a skewed distribution (skewness = 1.45, $SE = .014$; kurtosis = 1.85, $SE = .028$), the loneliness score was log-transformed for all analyses (log-transformed measure had a skewness of .93, $SE = .014$, and a kurtosis of $-.16$, $SE = .028$). The Big Five personality dimensions were measured with the NEO Five-Factor Inventory (NEO-FFI; Costa & MacCrae, 1992; Hoekstra, Ormel, & De Fruyt, 1996) with 60 items (i.e., 12 for each of the five

dimensions: Openness to Experience, Conscientiousness, Extraversion, Agreeableness, and Neuroticism), which have been shown to be measurement invariant across different cultural and cognitive groups and different ages (Allemand, Zimprich, & Hertzog, 2007; Marsh, Nagengast, & Morin, 2013; Waiyavutti, Johnson, & Deary, 2012). Since the Neuroticism scale contains an item that directly asks the participants about loneliness (“I rarely feel lonely or blue”), we repeated analyses with positive results using the Neuroticism score recomputed without this item (i.e., 11 instead of 12 items) to account for the possible conceptual overlap between loneliness and Neuroticism (results not shown). The correlation between the Neuroticism measure with and without this item is greater than .95 at each measurement wave, and not surprisingly, all analyses produced nearly identical outcomes regardless of the Neuroticism measure that was used.

For longitudinal analyses, three measurement points were used from questionnaires that were sent out in 2004 (response ranged from 2004 to 2010; $N=13,585$; $M_{\text{age}}=41.88$, $SD=15.23$), 2009 (response ranged from 2009 to 2013; $N=20,377$; $M_{\text{age}}=40.42$, $SD=16.33$), and 2013 (response ranged from 2013 to 2014; $N=19,022$; $M_{\text{age}}=43.44$, $SD=17.09$). The average number of years between the first and the second measurement was 4.08 ($SD=1.43$), and 4.18 ($SD=0.67$) between the second and the third.

2.1.3 | Genotyping, quality control (QC), and PCA

Blood and buccal swab collection, genomic DNA extraction, genotyping, and QC have been described previously (Abdellaoui, Hottenga, De Knijff, et al., 2013; Abdellaoui et al., 2015; Abdellaoui, Hottenga, Xiao, et al., 2013). Genotyping was performed on the Affymetrix Human Genome-Wide SNP 6.0 Array according to the manufacturer's protocol. Only autosomal SNPs were included in analyses. SNPs were excluded if they (a) had probes that mapped suboptimally against NCBI Build 37/UCSC hg19 (i.e., to a “random” region, to > 1 region, or to 0 regions); (b) showed a minor allele frequency (MAF) smaller than 5%; (c) had a missing rate greater than 5%; or (d) deviated from Hardy–Weinberg equilibrium (HWE) with a p value smaller than .001. After QC, 498,592 SNPs remained. Individuals were removed if they (a) showed a contrast $QC < 0.4$ (CQC, a quality metric from Affymetrix representing how well allele intensities separate into clusters); (b) fell outside of the main cluster of a PC, reflecting a batch effect (Abdellaoui, Hottenga, De Knijff, et al., 2013); (c) had a missing rate greater than 5%; (d) had excess genome-wide heterozygosity/inbreeding levels (F , as calculated in PLINK [Purcell et al., 2007] on a linkage disequilibrium [LD]-pruned set, must be greater than -0.10 and smaller than 0.10); (e) had non-European/non-Dutch

ancestry (Abdellaoui Hottenga, De Knijff, et al., 2013); or (f) had genotypes with inconsistencies regarding reported gender or reported relatedness within families.

Ancestry-informative PCs were computed on 5,166 unrelated subjects and were projected onto the rest of the subjects using EIGENSTRAT (Price et al., 2006). The first three PCs correlated significantly with geography in the Netherlands: PC1 = North–South PC, PC2 = East–West PC, PC3 = middle-band PC. The procedure for the Principal Component Analysis (PCA) and the three ancestry-informative PCs are described in detail elsewhere (Abdellaoui Hottenga, De Knijff, et al., 2013).

2.2 | Statistical analyses

2.2.1 | Phenotypic associations between loneliness and personality dimensions

The association between loneliness and the five personality dimensions was tested using generalized estimation equations (GEE) in SPSS 22.0. GEE has been shown to adequately account for the dependence of genetically identical individuals (monozygotic [MZ] twins) without affecting the Type I error rate (Minică, Dolan, Kampert, Boomsma, & Vink, 2014). The GEE approach uses an exchangeable conditional covariance matrix to account for relatedness (i.e., we allowed for correlated residuals between members of the same family) and uses a robust sandwich correction for the standard errors, which produces correct Type I error rates, regardless of misspecification (Minică et al., 2014). By standardizing loneliness and the personality dimensions, the reported effect sizes are equivalent to correlations. Correlations were computed for males and females separately while correcting for age, for males and females simultaneously while correcting for age and gender, and for males and females simultaneously while correcting for age, gender, and the remaining four personality dimensions. Sample sizes for each analysis are reported in Table 4. Subsequent analyses focus on loneliness and Neuroticism, since this was the only personality dimension that showed a considerable association with loneliness after accounting for the rest of the personality dimensions.

2.2.2 | Heritability and genetic correlations

A total of 4,375 adult subjects were genotyped and had loneliness measured, and 4,230 had the Big Five assessed (overlap with loneliness = 4,222). The heritability of and the genetic correlation between loneliness and Neuroticism were estimated by genomic-relatedness-based restricted maximum likelihood (GREML) in Genome-wide Complex Trait Analysis (GCTA) (Yang, Lee, Goddard, & Visscher, 2011), with an adjustment developed by Zaitlen et al. (2013) that allows for the simultaneous estimation of the narrow-sense

heritability (h^2 ; i.e., the aggregate of all additive genetic effects) and the heritability explained by genotyped SNPs (h_g^2), by including both closely and distantly related pairs of individuals. Two advantages of this method are that (a) by taking into account both closely and distantly related individuals, the statistical power increases, causing the standard error of the estimate to decrease, while avoiding the upward bias that can result from including closely related pairs; and (b) it produces both estimates of heritability (h^2 and h_g^2) in the same population sample, making the two estimates directly comparable. The heritability estimates are computed by fitting two genetic relationship matrices (GRMs) jointly, namely, the full GRM \mathbf{K}_{IBS} , including the genetic relatedness estimate based on genome-wide SNPs for all pairs of individuals, and $\mathbf{K}_{IBS>0.05}$, which only contains the genetic relatedness estimates for closely related pairs of individuals (Zaitlen et al., 2013). The p values were computed by the likelihood ratio test that is implemented in GCTA (Yang et al., 2011). We corrected for ancestry-informative PCs, CQC, genotyping batch, age, gender, and year of birth.

2.2.3 | Causal relationships between loneliness and Neuroticism

If there is a causal effect between loneliness and Neuroticism, this should cause lonelier twins within genetically identical twin pairs to also show higher levels of Neuroticism. In addition, a causal effect would also cause an increase in Neuroticism over time when loneliness increases (De Moor et al., 2008). The presence of these within-twin pair and across-time associations does not prove a causal relationship, but the absence of these associations would falsify it. The correlation between the difference in Neuroticism between MZ twin 1 and MZ twin 2 and the difference in loneliness between MZ twin 1 and MZ twin 2, and the correlation between the difference in Neuroticism between different measurement points and the difference in loneliness between different measurement points were computed with the GEE analysis described above.

To further investigate the presence of a causal relationship between loneliness and Neuroticism and its direction, analyses were conducted using an autoregressive cross-lagged panel model approach (Curran, 2000). The analyses were conducted with MPlus version 7.4 (Muthén & Muthén, 2007) on 15,878 participants (15,628 twins, whereas the rest consists of triplets, quadruplets, and quintets; it was computationally infeasible to include additional family members while simultaneously taking into account age and relatedness). The computation of standard errors and tests for model fits were adjusted to take into account the clustering nature of the current data structure (twins within families). The model contained loneliness, Neuroticism, and two basic demographic covariates: age and gender. The model was specified such that the cross-lagged relationships between different

measurement points (between 2004 and 2009; between 2009 and 2013) were set to be the same for each variable of interest. This stationarity specification treated the residual influences of both the loneliness level on Neuroticism and the Neuroticism level on loneliness to be stable across years. Standardized regression coefficients, standard errors, and 95% confidence intervals were reported. The degree of model fit was assessed using the root mean square error of approximation (RMSEA), the comparative fit index (CFI), and the Tucker-Lewis Index (TLI). RMSEA values less than .05, CFI values greater than .95, and TLI values greater than .95 indicate a good model fit.

2.2.4 | Cross-trait assortative mating

When there is significant cross-trait assortative mating between two traits (i.e., individuals with certain trait values for trait 1 select mates with certain trait values for trait 2), the two traits will show significant genetic correlations in subsequent generations because causal genes for both traits are being transmitted to the offspring simultaneously. Cross-trait assortative mating was evaluated for 4,436 spouse pairs by estimating the correlations for loneliness and personality within pairs of spouses and the cross-trait correlations. Correlations were obtained by maximum likelihood estimation in Mx (Neale, Boker, Xie, & Maes, 1997) in a conditional path model (Carey, 1986). The observed matrix of spouse correlations was decomposed into the matrix of correlations between loneliness and Neuroticism within husbands (\mathbf{R}_h), the correlations between loneliness and Neuroticism within wives (\mathbf{R}_w), and the matrix of the within- and cross-trait correlations for loneliness and Neuroticism between husbands and wives (\mathbf{D} ; Maes et al., 1998; Phillips, Fulker, Carey, & Nagoshi, 1988; Van Grootheest, Van den Berg, Cath, Willemsen, & Boomsma, 2008). This gave estimates for the direct assortment effects—that is, the spouse correlations for loneliness and Neuroticism, the within-person correlations for husbands and wives, and the cross-trait correlations between husbands and wives. In matrix notation, the model is specified as follows: $\mathbf{M} = (\mathbf{R}_h) \times \mathbf{D} \times (\mathbf{R}_w)$, or

$$\mathbf{M} = \begin{pmatrix} 1 & h \\ h & 1 \end{pmatrix} \times \begin{pmatrix} d11 & d12 \\ d21 & d22 \end{pmatrix} \times \begin{pmatrix} 1 & w \\ w & 1 \end{pmatrix} = \begin{pmatrix} d11 + hd21 + d12w + hd22w & d11w + hd21w + d12 + hd22 \\ hd11 + d21 + hd12w + d22w & whd11 + d21w + hd12 + d22 \end{pmatrix}$$

The diagonal of matrix \mathbf{M} (2×2) has the within-trait spouse correlations on the diagonal, which are a function of the direct assortment for loneliness, the direct assortment for Neuroticism, and the direct assortment across loneliness and Neuroticism. Matrix \mathbf{D} contains the *direct* assortment effects—that is, the spouse correlations for loneliness and

TABLE 1 Cronbach's alpha for loneliness and the Big Five for the three measurement points

	Measurement 1 (2004–2010)	Measurement 2 (2009–2013)	Measurement 3 (2013–2014)
Loneliness	.73	.76	.75
Openness	.55	.56	.58
Conscientiousness	.68	.76	.77
Extraversion	.39	.76	.75
Agreeableness	.68	.70	.36
Neuroticism	.66	.68	.68

Neuroticism after the correlations due to assortment for other correlated variables have been partialled out. We estimated D and tested whether spouse correlations within and across loneliness and Neuroticism were significantly different from zero with likelihood ratio tests, comparing the more restricted model to a less restricted model.

3 | RESULTS

3.1 | Phenotypic correlation between loneliness and personality dimensions

Loneliness and the Big Five showed high Cronbach's alphas, as displayed in Table 1. The measurements were relatively stable over time, as can be seen from the longitudinal correlations (Table 2). In order to increase sample size, we analyzed the strength of associations between loneliness and the Big Five for the last available measurement. The Big Five personality dimensions showed significant correlations with each other (all correlations were significant, except the correlation between Openness to Experience and Conscientiousness; Table 3). Loneliness showed significant associations with all personality dimensions, with similar estimates for males and females (Table 4). Neuroticism showed the strongest association, with an effect size equivalent to a correlation of .55. Extraversion showed a negative correlation with loneliness of $-.33$. When correcting for the remaining four personality dimensions, four out of five associations with loneliness become considerably weaker

(with Conscientiousness becoming the weakest association with a correlation of .005, not significantly different from zero). Neuroticism is the only personality dimension whose correlation with loneliness remains high after this correction ($r = .50$, i.e., 25% explained variance), whereas the rest of the personality dimensions drop to a correlation below .10 (i.e., less than 1% explained variance). The correlations with Openness, Conscientiousness, Extraversion, and Agreeableness also drop below .10 when accounting for Neuroticism only (Table 4). Because the association between loneliness and each of the Big Five personality dimensions is mostly driven by Neuroticism, subsequent analyses will only focus on the relationship between loneliness and Neuroticism.

3.2 | SNP heritability and genetic correlations for loneliness and Neuroticism

Genomic-relatedness-based restricted maximum likelihood (GREML) was used in GCTA (Yang et al., 2011) including closely and distantly related individuals, which allows for the simultaneous estimation of the heritability explained by measured SNPs and the residual heritability, which both add up to the narrow-sense heritability (Zaitlen et al., 2013). About 14% of the individual differences in loneliness can be explained by genotyped common SNPs ($h_g^2 = .14$, $p = .04$), a little over half of the narrow-sense heritability of 26%. Neuroticism has an estimated narrow-sense heritability of 43% (which is very similar to the

TABLE 2 Pearson correlations between the different measurements

	Correlation between Measurements 1 and 2	Correlation between Measurements 2 and 3	Correlation between Measurements 3 and 4
Loneliness	.55	.54	.48
Openness	.76	.71	.68
Conscientiousness	.70	.69	.63
Extraversion	.77	.73	.69
Agreeableness	.69	.61	.57
Neuroticism	.75	.73	.68

TABLE 3 Standardized betas (equivalent to correlations) of the association between the Big Five personality dimensions as estimated by generalized estimation equations

	Openness to Experience	Conscientiousness	Extraversion	Agreeableness	Neuroticism
Openness to Experience	1				
Conscientiousness	-.01*	1			
Extraversion	.09**	.365**	1		
Agreeableness	.08**	.258**	.252**	1	
Neuroticism	.04**	-.405**	-.49**	-.279**	1

Note. $N=30,202$.

* $p < .05$. ** $p < .001$.

estimates reported by twin studies; Bouchard & McGue, 2003; Johnson et al., 2008), of which a little over half can be explained by the genotyped SNPs ($h_g^2 = .22$, $p = .005$). The variation captured by the narrow-sense heritability shows a strong and significant correlation between loneliness and Neuroticism (.83). The SNP heritability of loneliness ($h_g^2 = .14$) and of Neuroticism ($h_g^2 = .22$) can be largely assigned to the same SNPs with a genetic correlation of .71 ($p = .007$).

3.3 | Causal relationships between loneliness and Neuroticism

A causal effect of Neuroticism on loneliness (or vice versa) would predict that within genetically identical twin pairs, the twin who has higher levels of Neuroticism should feel lonelier (or vice versa); a causal effect would also predict that an increase in Neuroticism over time leads to an increase in loneliness (or vice versa; De Moor et al., 2008). An absence

of these effects would falsify a causal relationship, which is not the case in our data set. In 2,662 identical twin pairs, the difference in Neuroticism between twin 1 and twin 2 correlated significantly with the difference in loneliness between twin 1 and twin 2 ($r = .46$, $SE = .019$). The difference in Neuroticism between measurement points 1 and 2 correlated significantly with the difference in loneliness between measurement points 1 and 2 ($r = .24$, $SE = .013$; $N = 7,127$), as did the differences between measurement points 2 and 3 ($r = .28$, $SE = .012$; $N = 9,238$) and the differences between measurement points 1 and 3 ($r = .32$, $SE = .017$; $N = 4,268$).

We specified autoregressive cross-lagged panel models to further investigate the possibility of a (reciprocal) causal relationship between Neuroticism and loneliness over a 10-year period. In Figure 1, autoregressive effects are represented as single-headed arrows running from a given variable at one point in time to the same variable at the next point in time. Diagonal single-headed arrows indicate how well loneliness prospectively predicts Neuroticism, and how well

TABLE 4 Standardized betas (equivalent to correlations) of the association between loneliness and the Big Five personality dimensions as estimated by generalized estimation equations

	Males (corrected for age)	Females (corrected for age)	Pooled (corrected for age and gender)	Pooled (corrected for age, gender, and remaining four personality dimensions)	Pooled (corrected for age, gender, and Neuroticism)
Openness to Experience	.07 ($SE = .009$)	.07 ($SE = .008$)	.07 ($SE = .006$)	.06 ($SE = .005$)	.05 ($SE = .005$)
Conscientiousness	-.22 ($SE = .009$)	-.23 ($SE = .008$)	-.22 ($SE = .006$)	.005 ($SE = .006$)	-.02 ($SE = .006$)
Extraversion	-.29 ($SE = .009$)	-.35 ($SE = .008$)	-.33 ($SE = .006$)	-.09 ($SE = .006$)	-.08 ($SE = .006$)
Agreeableness	-.14 ($SE = .009$)	-.22 ($SE = .008$)	-.18 ($SE = .006$)	-.03 ($SE = .006$)	-.03 ($SE = .006$)
Neuroticism	.51 ($SE = .009$)	.57 ($SE = .007$)	.55 ($SE = .005$)	.50 ($SE = .006$)	NA

Note. $N_{\text{males}} = 11,321$; $N_{\text{females}} = 18,474$; $N_{\text{total}} = 29,795$.

Neuroticism prospectively predicts loneliness over a measurement interval (i.e., cross-lagged effects). We assumed that the prospective effects of the covariates modeled on loneliness and Neuroticism did not differ as a function of measurement interval, and equality constraints were therefore applied to each of these covariates over the three measurement periods. The effects of covariates are illustrated by diagonal single-headed arrows. Correlations between variables at a given measurement interval are illustrated by dashed lines and double-headed arrows.

The results for the model summarized in Figure 1 support the stationary process assumption and fit the data adequately, $\chi^2(4)=163.6$, $p<.001$, RMSEA=.04, CFI=.98, TLI=.96. There was a significant association between age and loneliness, with older participants reporting higher levels of loneliness ($\beta=.26$, $SE=.042$, $p<.001$). In addition, there was a significant association between gender and Neuroticism, with females scoring higher on Neuroticism than males ($\beta=.29$, $SE=.026$, $p<.001$). The results show significant cross-lagged effects of loneliness on Neuroticism, $\beta=.09$, 95% CI [.07, .11], and of Neuroticism on loneliness, $\beta=.21$, 95% CI [.18, .25], which are not attributable to differences in age or gender.

3.4 | No cross-trait assortative mating between loneliness and Neuroticism

We tested for the presence of cross-trait assortative mating between loneliness and Neuroticism in 4,436 spouse pairs. We first tested whether there are gender differences

in cross-trait assortment (i.e., whether the correlation between Neuroticism in husbands and loneliness in wives is equal to the correlation between loneliness in husbands and Neuroticism in wives). The model with equal cross-trait assortment for both genders did not result in a significant deterioration of model fit, $\chi^2(1)=.258$, $p=.61$. Subsequently, we tested whether the cross-trait assortment parameters ($r=-.03$) could be constrained to zero without a significant loss of fit, which was the case, $\chi^2(2)=4.93$, $p=.09$. The within-trait correlations between spouses could not be constrained to zero (Neuroticism: $r=.11$, $p<.001$; loneliness: $r=.13$, $p<.001$). To conclude, there was significant assortative mating for both loneliness and Neuroticism, but no significant cross-trait assortative mating.

4 | DISCUSSION

Consistent with previous studies on loneliness and the Big Five, the strongest Big Five correlates for loneliness in our study are Neuroticism and Extraversion (Atak, 2009; J. T. Cacioppo et al., 2006; Lopes et al., 2003; Mund & Neyer, 2016; Teppers et al., 2013; Vanhalst et al., 2012). The largest correlation is observed between loneliness and Neuroticism ($r=.55$), which decreases only slightly when correcting for the other four personality dimensions ($r=.50$). Extraversion shows the second largest correlation with loneliness ($r=-.33$), which decreases substantially to less than 1% explained variance when correcting for Neuroticism. Thus, the relatively strong negative relationship between loneliness

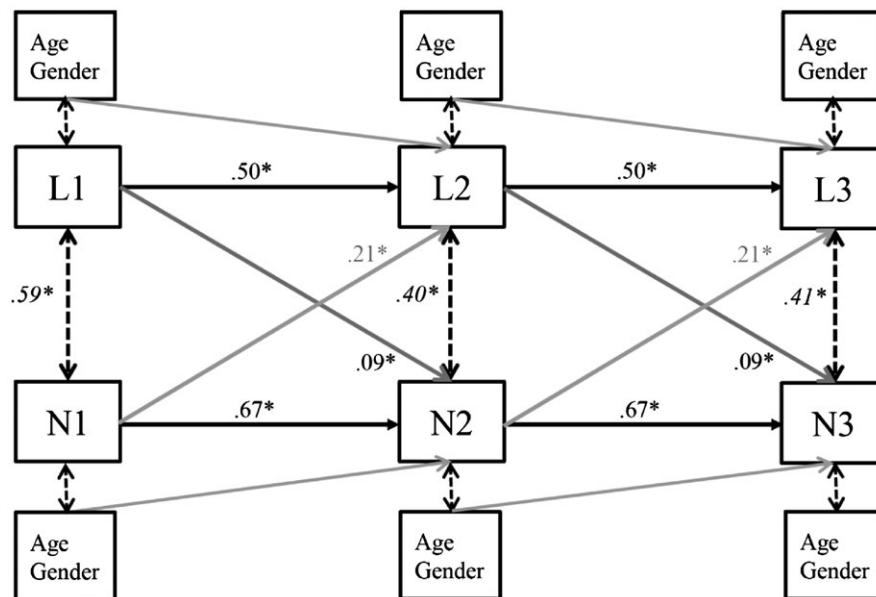


FIGURE 1 Cross-lagged panel model showing that loneliness predicts increases in Neuroticism, and Neuroticism predicts increases in loneliness, independent of age and gender. Regression weights are standardized. Covariances (italicized) are also standardized (i.e., equivalent to correlations). L=loneliness, N=Neuroticism. Numbers refer to measurement period. * $p < .001$.

and Extraversion can be largely explained by the negative relationship between Extraversion and Neuroticism. The fact that loneliness shows such a stronger association with Neuroticism than with Extraversion suggests that the propensity to make social connections (which highly extraverted people have) contributes less to the feelings of loneliness than the sensitivity to negative emotions that may arise when one's needs for social connections are not met. In practice, this means that Extraversion correlates with loneliness largely because introverted people may on average be more neurotic; less neurotic introverted individuals are not much more likely to feel lonely than extraverted people with the same level of Neuroticism. Previous studies showed Neuroticism to be the strongest correlate of the Big Five when it comes to mood disorders (Kotov et al., 2010), which are strongly associated with loneliness as well (J. T. Cacioppo et al., 2010, Jones, Rose, & Russell, 1990). Neuroticism has also been reported to act as a moderator for the relationship between loneliness and depressive symptoms; their bidirectional association is only observed in subjects scoring relatively high on Neuroticism (Vanhalst et al., 2012).

Loneliness and Neuroticism show a considerably high genetic correlation. The genetic correlation between loneliness and Neuroticism based on the narrow-sense heritability is .83, and when only considering the heritability explained by genome-wide measured common SNPs, the genetic correlation is .71. The strong genetic correlation we observe implies that the genes influencing loneliness and Neuroticism fall through the family tree in the same way. This relationship can arise when there is pleiotropy, when there is a causal relationship between the two traits (mediated pleiotropy), and when there is cross-trait assortative mating between loneliness and Neuroticism. Cross-trait assortative mating has been reported between several psychiatric disorders (Maes et al., 1998; Plomin, Krapohl, & O'Reilly, 2016; Van Grootheest et al., 2008), but it was not significantly different from zero between loneliness and Neuroticism in a relatively large sample, making this an unlikely explanation for the genetic correlation. The results of the longitudinal cross-lagged analyses suggest that a causal relationship may be present, which is likely to explain at least part of the strong genetic correlation between loneliness and Neuroticism. The presence of a causal relationship is also in line with (a) a significant correlation between loneliness and Neuroticism differences within genetically identical twin pairs, and (b) significant correlations between longitudinal within-subject differences in loneliness and Neuroticism (De Moor et al., 2008). A possible biological relationship between loneliness and Neuroticism is suggested by the finding that Neuroticism mediates the positive association between loneliness and gray matter volume of the dorsolateral prefrontal cortex (Kong et al., 2015), one of the most recently evolved structures of the human brain and implicated in social cognition (Miller & Cummings, 2007).

The autoregressive cross-lagged panel model showed a reciprocal relationship between loneliness and Neuroticism. There was a significantly stronger effect of Neuroticism on loneliness than vice versa (i.e., Neuroticism increases loneliness more than loneliness increases Neuroticism). This is in line with a recently published study on the longitudinal relationship between personality, loneliness, and health, where it was found that loneliness and Neuroticism are predictive of each other longitudinally, with a stronger effect of Neuroticism on loneliness than vice versa (Mund & Neyer, 2016). This may be related to the fact that loneliness leads to a stronger sensitivity to *social* negative stimuli (J. T. Cacioppo et al., 2009; S. Cacioppo, Balogh, et al., 2015), whereas Neuroticism reflects a sensitivity to *all* negative stimuli. The larger effect of Neuroticism may also explain how a smaller study ($N = 132$) found personality to have an influence on the quality of relationships, but it could not detect whether relationship qualities had an effect on personality (Asendorpf & Wilpers, 1998). Personality traits are considered to account for consistencies in thoughts, feelings, and behaviors across different situations (Kandler, 2012), an idea that may have to be attenuated given that a less stable feature like loneliness can change Neuroticism levels over time. The cross-lagged model showed that loneliness could explain variance in Neuroticism at time $n + 1$ that was not explained by Neuroticism at time n , and inversely, there was variance that Neuroticism could explain in loneliness at time $n + 1$ that was not explained by loneliness at time n . This confirms that loneliness is conceptually and empirically distinct from Neuroticism. Nevertheless, the two traits showed a considerable genetic overlap in analyses using both measured genetic variants and familial relationships.

5 | LIMITATIONS

There are a number of limitations that should be considered when interpreting this study. A causal relationship is difficult to prove in an epidemiological setting, which is why our results should be interpreted as a failure to falsify the presence of a causal relationship rather than direct proof of presence of a causal relationship. We cannot fully exclude a third underlying factor that influences both Neuroticism and loneliness. It has been posited that the cross-lagged panel model does not fully account for stable, trait-like individual differences, which may lead to biased regression coefficients (Hamaker, Kuiper, & Grasman, 2015), and the Big Five personality dimensions are usually considered to be trait-like. Our longitudinal correlations show that the Big Five measurements are not fully stable over time, albeit more stable than a state-like variable such as loneliness (Table 2).

6 | CONCLUSIONS

Neuroticism explains ~25% of the individual differences in loneliness independent of the other four dimensions of the Big Five. Common SNPs explain a significant amount of individual differences in both loneliness and Neuroticism and capture a strong genetic relationship between them. The relationship with Neuroticism is reciprocal and is likely due to a large set of genes that operate on biological processes that influence both of these traits either directly or indirectly. The co-heritability likely represents biological processes underlying negative affect, but it is unclear what the uncorrelated genetics represent. The negativity in loneliness is specific to social stimuli, whereas it is not in Neuroticism. Further study is needed to determine whether this distinction is genetic in nature and, if so, what biological faculties are regulated by genes that differentiate these constructs.

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CONFLICT OF INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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SUPPORTING INFORMATION

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