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Genetic and neural bases of the Neuroticism general factor

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Abstract

We applied structural equation modeling to conduct a genome-wide association study (GWAS) of the general factor measured by a Neuroticism questionnaire administered to ∼380,000 participants in the UK Biobank. We categorized significant genetic variants as acting either through the Neuroticism general factor, through other factors measured by the questionnaire, or through paths independent of any factor. Regardless of this categorization, however, significant variants tend to show concordant associations with all items. Bioinformatic analysis showed that the variants associated with the Neuroticism general factor disproportionately lie near or within genes expressed in the brain. Enriched gene sets point to an underlying biological basis associated with brain development, synaptic function, and behaviors in mice indicative of fear and anxiety. Psychologists have long asked whether psychometric common factors are merely a convenient summary of correlated variables or causal entities with a partial biological basis, and our results provide some support for the latter interpretation. Further research is needed to determine the extent to which causes resembling common factors operate alongside other mechanisms to generate the correlational structure of personality.

Keywords:

Neuroticism

genome-wide association study

factor analysis

construct validity

biology

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1 Introduction

The biological underpinnings of personality are far from being understood. Genome-wide association studies (GWAS) can provide insight into personality's biological etiology by indicating which genomic polymorphisms are significantly associated with a trait of interest. Most GWAS focus on single-nucleotide polymorphisms (SNPs), the most common type of genetic variation. GWAS results can be used to identify the protein-coding genes that encompass or lie near the significant SNPs. As many functions of genes and their tissue-specific patterns of expression have been experimentally elucidated or computationally predicted, researchers can then infer the biological processes that are likely to be responsible for variation in the trait. Unfortunately, GWAS of personality traits often lack sample sizes large enough to detect many significant loci (e.g., Lo et al., 2017).

Studies focusing on Neuroticism typically have been more successful (de Moor et al., 2015; Luciano et al., 2018; Nagel et al., 2018; Okbay et al., 2016a; Smith et al., 2016). Neuroticism is one of the factors in the Big Five model of personality. Individuals who score highly in Neuroticism tend to experience diverse and relatively more intense negative emotions. The largest GWAS meta-analysis of Neuroticism to date found 136 significant independent loci (Nagel et al., 2018). Neuroticism was measured using the Eysenck Personality Questionnaire–Revised Short Form (Eysenck, Eysenck, & Barrett, 1985). In the present study, we further investigated the genetics and biology of Neuroticism using the summary statistics of a companion study analyzing the individual items in the questionnaire (Nagel, Watanabe, Stringer, Posthuma, & van der Sluis, 2018).

We also examined whether the significant SNPs act in accordance with the common-factor model, which is an important tool in the psychology of individual differences. McDonald (2003) suggested that a common factor might be regarded as a mental property with a non-physicalist

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interpretation, which nevertheless can be acted upon by physical causes: "the external variable causes the common factor of the dependent variables, that is, acts to change the level of the psychological attribute common to them" (p. 221). Others have proposed that a common-factor model is merely a convenient summary of otherwise formidably high-dimensional data rather than a representation or approximation of a causal model (Cramer et al., 2012). Genetics now provides us with an unprecedented opportunity to test these ideas. If we could find candidate causal variables, such as SNPs in the human genome, that exert effects on the questionnaire items proportional to their factor loadings, then we would have powerful evidence that the common factor does indeed mediate biological causes and therefore cannot be dismissed as an artifact. That is, if the loadings of certain dependent variables on their common factor were λ_1, λ_2, and so forth, then a SNP with effects on those variables of $\beta\lambda_1$, $\beta\lambda_2$, and so forth would strongly suggest that the SNP has on effect of β on *something* very much like the common factor.

Conversely, if the effects of the SNPs failed to accord with the factor loadings, this would suggest looking toward proposals such as "bonds" (Thomson, 1951) or network models (Cramer et al., 2012) for a superior causal model explaining the item covariation. Either way, identification of the biological mechanisms mediating the effects of the SNPs can provide insight into the nature of the higher-level objects in the hierarchy of explanation—whether those objects are common factors, "bonds," networks, or something else entirely. A number of authors have previously tested a similar idea with general intelligence (g) (Cox, Ritchie, Fawns-Ritchie, Tucker-Drob, & Deary, 2019; Kievit et al., 2012; Lee, McGue, Iacono, Michael, & Chabris, 2019). Their results were consistent with brain size being one of multiple factors that affect a unitary g.

In this work we do not claim to resolve this issue conclusively. We claim merely that if we do find SNPs associated with all indicators to a degree corresponding roughly with their factor

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loadings, then we have evidence that common biological causes are one kind of mechanism contributing to the covariation "accounted for" by the common-factor model.

To conduct this analysis of the common factor Neuroticism, we turned to Genomic SEM, a software tool for applying factor and path models to genetic data (Grotzinger et al., 2019). We classified the GWAS-identified SNPs as working either through the general factor, the group factors that happen to be present in this questionnaire, or none of the above (i.e., through "independent pathways"). It is the SNPs in the latter category that might call into question the appropriateness of the common-factor model at a deeper biological level. We then used the bioinformatic software tool DEPICT (Pers et al., 2015) in an attempt to identify the tissues and biological mechanisms mediating the effects of the SNPs in these categories. In this way we not only tested the verisimilitude of the common-factor model at the genetic level, but also obtained mechanistic insight into the nature of the Neuroticism factor. Eysenck (1992) in particular stressed the importance of grounding the constructs of personality models genetically and biologically in order to further their validity.

2 Methods

2.1 Confirmatory factor analysis

We used the software tool Genomic SEM (Grotzinger et al., 2019) to calculate the genetic covariance matrix of the Neuroticism items in the Eysenck Personality Questionnaire–Revised Short Form, as administered to about 380,000 UK Biobank participants (Nagel, Watanabe, Stringer, Posthuma, & van der Sluis, 2018). The "genetic correlation" between two traits is the correlation between their heritable components. That is, if each trait is the sum of a genetic and environmental term, then the genetic correlation is the correlation between just the genetic terms. Genetic correlations tend to be close to their corresponding phenotypic correlations (Sodini, Kemper, Wray, & Trzaskowski, 2018), being slightly larger on average, and so should

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yield a similar factor-analytic solution (e.g., de la Fuente, Davies, Grotzinger, Tucker-Drob, & Deary, 2021). To calculate the genetic correlation between two binary traits, estimates of the population prevalences (pass rates) are required. We used the estimates previously published (Nagel, Watanabe, Stringer, Posthuma, & van der Sluis, 2018). Note that the genetic correlations are calculated over essentially all "common SNPs"—polymorphic sites where both alleles exceed a threshold frequency—regardless of statistical significance.

We adopted the three-factor model of the Neuroticism questionnaire used in the original Genomic SEM publication by Grotzinger et al. (2019). In this model the items *mood*, *misery*, *irritable*, *fed-up*, and *lonely* are indicators of a factor that we will call Depressed Affect, after the largely similar group of items identified by hierarchical cluster analysis Nagel, Watanabe, Stringer, Posthuma, and van der Sluis, 2018. The items *nervous*, *worry*, *tense*, and *nerves* are indicators of a factor that we will call Worry, also after a similar cluster identified in the previous analysis. The items *guilt*, *hurt*, and *embarrass* are indicators of a third factor that we leave unnamed, for reasons that we will later give. We introduced a Neuroticism general factor into this model by treating the three group factors as indicators of a hierarchical second-order factor.

The group factors Depressed Affect and Worry do not readily map onto aspects in the BFAS (DeYoung, Quilty, & Peterson, 2007), but do arguably map onto the respective facets Depression and Anxiety in the NEO (Costa & McCrae, 1992).

There is some evidence that participants in the UK Biobank differ in Neuroticism at least slightly from the rest of the population (Young et al., 2022). Such selection bias can distort the factor structure of the measurements (Lee, 2012; Meredith, 1993). Our conjecture is that psychological traits most affecting participation in research are those related to education and social class, and Neuroticism does not seem strongly related to such status markers (Demange et al., 2021; Poropat, 2009). When the association between personality and research participa-

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tion has been directly studied, no significant correlations with Neuroticism have been observed (Cheng, Zamarro, & Orriens, 2020; Marcus & Schütz, 2005). Therefore we expect any impact of selection bias on our results to be modest.

2.2 Path modeling of SNP effects

2.2.1 GWAS of the Neuroticism general factor

We performed a GWAS of the Neuroticism general factor by specifying, in Genomic SEM, a causal path from the tested SNP to the second-order general factor (Fig. 1a). Note that we use terms such as "causal" and "effect" loosely, because a SNP may often show an association with a trait not because it is causal but only because it is correlated with one or more true causal SNPs nearby in the genome (Lee & Chow, 2013). This is the likely to be the only major source of confounding in the GWAS; within-family GWAS of the Neuroticism sum score produced results very close to those of population GWAS (Howe et al., 2022; Young et al., 2022), showing that correlation with causal polymorphisms is the predominant contribution to SNP associations (Laird & Lange, 2006; Lee, 2012). We used the reference file supplied by Genomic SEM to retain only SNPs with a minor allele frequency (MAF) exceeding .005 in the 1000 Genomes European populations. This left more than 7 million SNPs in the GWAS.

Because they are often highly correlated, nearby SNPs may not not represent independent association signals. We attempted to identify independently significant SNPs by using the "clump" function of the software tool PLINK (Chang et al., 2015; Purcell et al., 2007). In essence, clumping picks out local minima of the p-value sequence along the genome. We used the clump settings of the bioinformatics tool DEPICT (Pers et al., 2015), which calls PLINK to identify lead SNPs. The most important of these settings is the threshold $p < 10^{-5}$ for the statistical significance of the association between SNP and trait. Although less stringent than the conventional GWAS significance threshold $p < 5 \times 10^{-8}$, this threshold is recommended by

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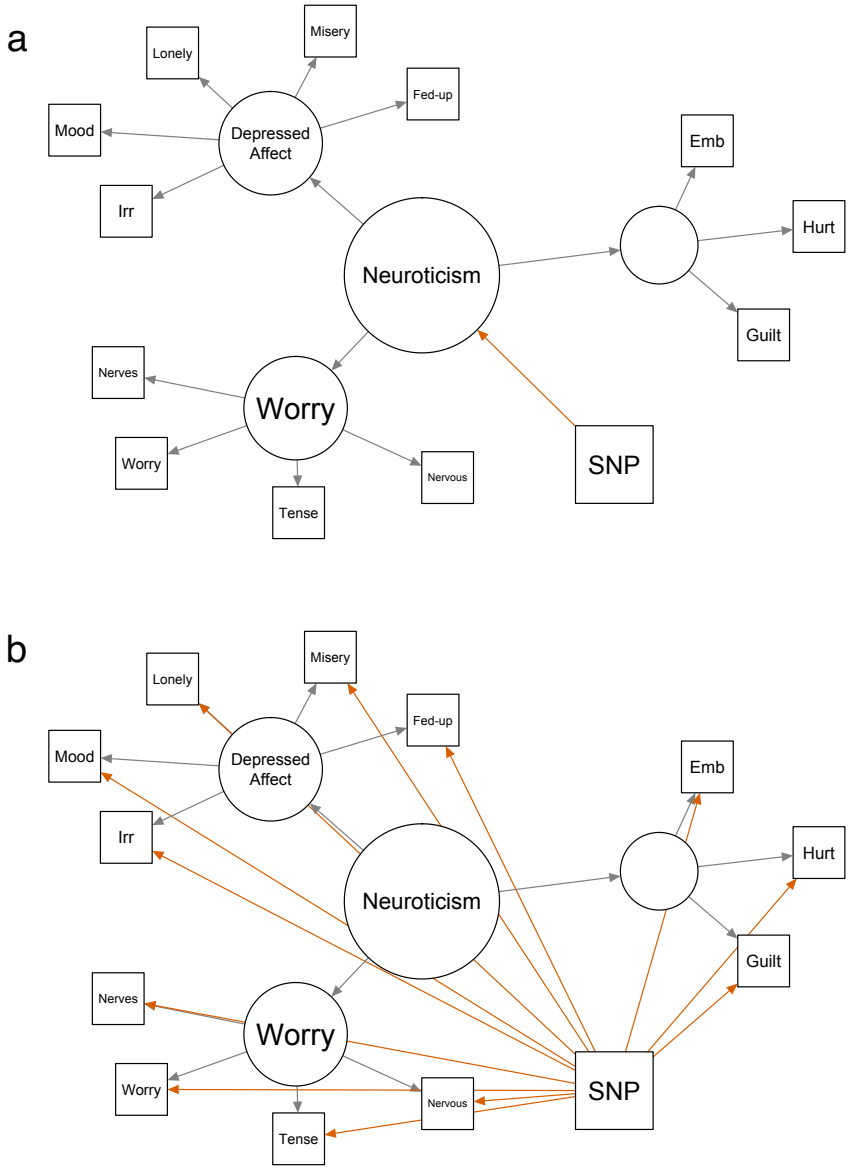

Figure 1: Path diagrams portraying how a single-nucleotide polymorphism (SNP) might be associated with the questionnaire items. A. The focal SNP (or a nearby highly correlated SNP) acts through the Neuroticism general factor. B. The focal SNP (or a nearby highly correlated SNP) acts on the 12 items through "independent pathways." Not shown is a model where the SNP's associations are with one or more of the three group factors.

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the DEPICT developers because the biological annotation provided by their tool (see below) is tolerant of false-positive SNPs.

Note that the conventional GWAS threshold aspires to prevent even a single false positive from appearing among the SNPs significantly associated with a single trait. Although there may be at least one false positive among the SNPs in the range $10^{-5} > p \geq 5 \times 10^{-8}$, many of these SNPs will be true positives in a well-powered GWAS with many SNPs reaching $p < 5 \times 10^{-8}$.

We subjected the candidate lead SNPs from the GWAS of the Neuroticism general factor to further tests. We ran a "group-factor" model in which the three first-order group factors were regressed on each of the candidate lead SNPs. This model thus requires three path coefficients in the place of the one required by the general-factor model. The general-factor model is nested within the group-factor model, the former being obtained from the latter by making the three SNP effects proportional to the loadings of the group factors on the general factor. We then ran an "independent-pathway" model regressing all 12 items on each candidate lead SNP (Fig. 1b). The independent-pathway model thus estimates 12 path coefficients in the place of the three required by the group-factor model; the latter is nested within the former.

The independent-pathway model is an operationalization of not only Thomson's bonds model, but also the network model (Cramer et al., 2012); our Fig. 1 contrasting the common-factor and independent-pathway models is exactly parallel to Figure 7 of Cramer et al. (2012). These authors proposed that support for the independent-pathway model over the common-factor model would count as support for their network perspective. Taking the most significant SNPs in the GWAS of Neuroticism sum scores published at that time, they carried out an analysis similar to ours and claimed to find some evidence for the SNPs acting on individual items rather than the general factor. The only SNP-item association of theirs that we could attempt to look up and replicate was the one between rs12509930 and *guilt*. In the UK Biobank sample of roughly 380,000 individuals, this association is not significant ($p = .70$). We should not be

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surprised by this replication failure, in light of the small sample sizes of the GWAS at that time, and the authors themselves avowed the tentative and exploratory nature of their analysis. The important point is that we can now carry out their proposal of pitting the common-factor and network models against each other to a much greater extent than was possible a decade ago.

To determine whether a candidate lead SNP identified in the GWAS of the Neuroticism general factor is better regarded as acting through factors or independent pathways, one can test the significance of the difference in χ^2 between more and less parsimonious models. The Genomic SEM developers call this difference Q_{SNP} (Genomic SEM tutorial, accessed October 2020). In one of their analyses, Grotzinger et al. (2019) used the threshold $p > .005$ for calling a Q_{SNP} value "low." Following the suggestion of a peer reviewer, however, we carried out model selection using Akaike weights (Wagenmakers & Farrell, 2004). The sum of the weights equals one by construction, making them analogous to probabilities. The ratio of two weights can be interpreted as the relative likelihood of the model corresponding to the numerator (Royall, 1997) times a factor penalizing that model if it has more estimated parameters. Such a penalty may be desirable if a sufficient increase in sample size will lead to the rejection of any simple model regardless of its qualitatively excellent fit. We treated any model with an Akaike weight exceeding $2/3$ as the "correct" model for a given SNP, as this means at least twice as much support as any alternative. It is possible for no model to obtain this large a weight, meaning that the SNP's associations with the items are not clearly fit best by any of the candidate models.

Since calculating the model χ^2 and AIC increases the computation time of a SNP association by roughly a factor of 10, we did not calculate these for all SNPs in the GWAS but rather only the lead SNPs, once for each of the three candidate models (general factor, group factor, independent pathway). Supplementary Fig. S1 provides an overview of our pipeline for the GWAS of the Neuroticism general factor and subsequent classification of lead SNPs.

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2.2.2 GWAS of additional factors

We also conducted GWAS of each group factor with nontrivial variance attributable to sources other than the Neuroticism general factor (i.e., Depressed Affect and Worry). The first step of our procedure was to conduct a GWAS with Genomic SEM, specifying directed edges from the SNP to all three group factors. We then examined each factor's association results satisfying $p < 10^{-5}$. Of the lead SNPs identified by the clumping procedure, we discarded any already assigned to either the general-factor or independent-pathway model in the GWAS of the Neuroticism general factor (Supplementary Fig. S1). Since we were particularly interested in SNPs associated solely with the focal group factor, we tested each remaining lead SNP for association with that factor while setting to zero the coefficients of its paths to the other two factors. We also ran the independent-pathway model for each of these lead SNPs (Fig. 1b). As before, we used an Akaike weight exceeding $2/3$ as the criterion for assigning a lead SNP to one of three competing models (all group factors, one group factor, independent pathways). Supplementary Fig. S2 provides an overview of our pipeline for the GWAS of the group factors and subsequent classification of lead SNPs.

To convey the difference between this GWAS and the one outlined in Supplementary Fig. S1, we will give an example of a SNP that would be ascertained as significant in the former but not in the latter. Suppose that a SNP acts solely through the residual of a group factor. This SNP might be ascertained in the GWAS of the group factors, through a combination of a relatively large effect size and favorable sampling variation. It might not be ascertained in the GWAS of the general factor, despite this GWAS containing a follow-up step checking for association with the group factors, because it is less likely to become a lead SNP in the first step. This difference in the ascertainment scheme can be important for certain inferences, a matter to which we return in the Discussion.

It is worthwhile to consider whether independent-pathway SNPs enrich any tissues or bio-

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logical pathways (see below), despite not acting through any common factors. To identify such SNPs, Grotzinger et al. (2019) conducted two GWAS, one of Neuroticism in their single-factor model and the other of independent pathways, and calculated a form of the Q_{SNP} statistic for each SNP in the GWAS. At the time of our own analysis, this procedure was beyond the computational resources available to us. As a compromise, we took forward to DEPICT the union of the lead SNPs from the GWAS of the common factors that qualified by virtue of their Akaike weights for the independent-pathway model.

2.3 Biological annotation

DEPICT (Data-driven Expression Prioritized Integration for Complex Traits) is a software tool that prioritizes likely causal genes affecting the trait, identifies tissues/cell types where the causal genes are highly expressed, and detects enrichment of gene sets. A "gene set" is a group of genes designated by database curators as sharing some common property, such as encoding proteins that participate in the same biological function. A gene set shows "enrichment" if SNPs significantly associated with the trait fall in or near the set's member genes more often than expected by chance. More complete descriptions of DEPICT can be found in previous publications (Okbay et al., 2016b; Pers et al., 2015).

Our path modeling with Genomic SEM placed each lead SNP into a collection (e.g., SNPs associated with the Neuroticism general factor). Each such collection of SNPs was supplied as input to DEPICT (https://github.com/perslab/DEPICT, release 194). DEPICT takes lead SNPs and merges them into loci potentially encompassing more than one lead SNP according to certain criteria (Pers et al., 2015). The genes overlapping these loci are the basis of the DEPICT analysis.

To run DEPICT, we edited and then executed the template configuration file. We left in place all default parameter values except those affecting how the results are printed in the output

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files. Many tissues/cell types and gene sets in the DEPICT inventory are in fact duplicates despite having different identifiers; we excluded duplicates using the criteria set out by Lee et al. (2018). We adopted the developer-recommended definition of statistical significance at the level of genes, tissues/cell types, and gene sets as a false discovery rate (FDR) below .05.

For a given trait and sample size, DEPICT will identify more gene sets as significantly enriched than other tools that have been used in some previous GWAS of Neuroticism (e.g., Nagel et al., 2018). One might argue that the statistical power of DEPICT cannot be compared to that of other methods because they are testing different hypotheses. To be specific, whereas other methods rely on the original discrete version of a given gene set, DEPICT uses a "reconstituted" version of that gene set with respect to which all genes are given a continuous membership score based on their co-expression with members of the original all-or-nothing gene set. Stratified LDSC is a standard method testing enrichment of discrete sets (Finucane et al., 2015; Kim et al., 2019), and one study found that the two methods give similar results when applied to years of education (Lee et al., 2018). If the results of this study can be generalized, then the greater number of significant results yielded by DEPICT correspond to genuine biological insight. Another convenient feature of DEPICT in our application is that its input can be limited to a subset of SNPs. A method like stratified LDSC, which relies on genome-wide summary statistics, is not straightforward to adapt if some SNPs in a GWAS of a common factor must be dropped for better fitting a more complex model (Fig. 1).

The reconstitution of the gene sets was motivated by a desire to compensate for the limitations of existing bioinformatic databases, which suffer from both false positives and false negatives. The reader can consult Supplementary Table 28 of Lee et al. (2018) for a demonstration of the reconstitution procedure's success in empowering detection of enrichment only in sets appropriate to the studied trait. The reconstitution procedure has also proven fruitful in other applications (Cvejic et al., 2013; Fehrmann et al., 2015).

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2.4 Genetic correlations

Genomic SEM calls LD Score regression (LDSC) to calculate genetic correlations, and this method is known to be unbiased under fairly general conditions (Bulik-Sullivan et al., 2015; Lee, McGue, Iacono, & Chow, 2018).

A finding of genetic correlations similar to those calculated in previous studies of Neuroticism observed scores would provide an affirmative quality-control check of our approach based on structural equation modeling. It would also support the validity of the common assumption that a correlation with an observed sum score primarily reflects a correlation with the scale's general factor. Supplementary Fig. S3 and Supplementary Table S1 present the results.

2.5 Departures from the analysis of Grotzinger et al. (2019)

Our work extends Grotzinger et al. (2019), in a manner that we now explain.

Supplementary Figure 4 of Grotzinger et al. shows what was done in that paper. The authors performed a GWAS specifying a single Neuroticism factor measured by all items. They also performed an independent-pathways GWAS and identified 69 SNPs fitting the independent-pathways model better than one where the SNP acts through the single factor, at the significance threshold $p < 5 \times 10^{-8}$. They then examined whether these 69 SNPs would continue to fit the independent-pathways model better if the more parsimonious model was one where the SNP acts through two or three factors.

The authors found that for each additional factor posited in the model, there was a reduction in the number of SNPs showing a significantly better fit to the independent-pathways model. This pattern by itself strongly suggests that a model of a SNP acting through common factors rather than independent pathways will tend to fit better as the fit of the factor model itself improves. Note that the SRMR dropped from .109 to .057 as the number of factors in the model went from one to three. In our view an SRMR exceeding .1 is indicative of a poor fit, which we

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confirmed by finding several large elements in the residual correlation matrix resulting from a one-factor model.

It is therefore clear that any attempt to pit common- and independent-pathway models against each other must take into account the multidimensional basis of the factor space. This was not the aim of Grotzinger et al.; that is, they did not specify a general factor (whether in a hierarchical or bifactor model) in addition to the group factors in their two- and three-factor models. The authors mentioned performing a GWAS of the two correlated factors and of the three correlated factors, but to our knowledge have not detailed or deposited these results anywhere. They did not perform biological annotation of their multiple-factor results. Even their biological annotation of their one-factor results was somewhat limited because they only provided $p < 5 \times 10^{-8}$ lead SNPs as input to DEPICT, whereas the developers of this tool recommend a more liberal threshold of $p < 10^{-5}$. As a result Grotzinger et al. found only one gene set to be significantly enriched.

In summary, we included a second-order general factor in our model of three first-order factors and followed up a GWAS based on this model with the bioinformatic tool DEPICT. The latter tool was set to the developer-recommended parameter values.

3 Results

3.1 Factor analysis of the Neuroticism questionnaire

We replicated the indices reported by Grotzinger et al. (2019) indicating a good fit of a model with three group factors (CFI $= .969$, SRMR $= .054$). We therefore regarded the three-factor model as satisfactory for purposes of SNP-level path modeling. The loading of the group factor defined by *guilt*, *hurt*, and *embarrass* on the Neuroticism general factor was estimated to be nearly one (.97) (Supplementary Table S2). These items seem to have very little genetic variance shared in common other than what is attributable to Neuroticism. For this reason we did not

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conduct a GWAS of this factor when trying to identify SNPs associated with group factors.

3.2 GWAS of the Neuroticism general factor

Our GWAS of the Neuroticism general factor identified 394 lead SNPs satisfying $p < 10^{-5}$, in 296 distinct DEPICT-defined loci. We examined these SNPs for an improvement in model fit upon increasing the number of paths. Thirty-five of the 394 SNPs were characterized by small negative values of the Q_{SNP} statistic when comparing the fit of the model where the SNP acts on the general factor (Fig. 1a) to that of the model where the SNP acts on the three group factors. Such negative values can arise as a result of a numerical problem in this version of Genomic SEM (October 2020) when the two models under comparison are distinguished by few degrees of freedom, and they indicate that the fit of the data to the more restrictive model is extremely good (A. Grotzinger, personal communication). Of the 394 lead SNPs, 139 qualified by virtue of their Akaike weights for the general-factor model, 81 for the group-factor model, and 63 for the independent-pathway model. One hundred eleven SNPs had no Akaike weight greater than $2/3$, precluding for now their assignment to any model. Of these 111 indeterminate SNPs, a plurality of 54 attained their largest Akaike weight in the general-factor model.

Supplementary Table S3 lists the 139 general-factor lead SNPs. Nineteen of these SNPs attained the strict genome-wide significance level $p < 5 \times 10^{-8}$, indicating reasonable statistical power in this GWAS. Information about all significant SNPs regardless of classification can be found in the Supplementary Data.

It is of interest to examine how the cutoffs defined by Akaike weights correspond to Q_{SNP} statistics. Upon treating any SNP with a negative Q_{SNP} statistic as having a p value of one, we found that the 139 SNPs assigned by their Akaike weights to the general-factor model were all characterized by $p > .28$ (median $p = .68$) with respect to the null hypothesis of the general-factor model fitting better than the group-factor model. If we take the $p < .05$ criterion as

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standard, then our use of Akaike weights to define general-factor SNPs seems conservative. In contrast, for the 63 SNPs qualifying for the independent-pathway model, the Q_{SNP} p values with respect to the null hypothesis of the group-factor model fitting better than the independent-pathway model all met $p < .02$ (median $p = .001$).

Significant tissues/cell types and gene sets

The output of DEPICT provides insight into the biology associated with the SNPs appearing to act through the Neuroticism general factor. Fig. 2 shows that there are 13 tissues/cell types where genes near the general-factor SNPs are significantly expressed. All of these without exception have the MeSH second-level term *central nervous system*. The most significant result is *parahippocampal gyrus* ($p = 1.4 \times 10^{-4}$). The Neuroticism general factor shows the clear signature of a behavioral trait mediated by the brain.

More revealing than these tissue-level results are the significantly enriched gene sets. There are 21 such sets, and Table 1 shows the 6 of these that are not protein-protein interaction (PPI) subnetworks. *Abnormal cued conditioning behavior* ($p = 6 \times 10^{-6}$), *increased anxiety-related response* ($p = 8.9 \times 10^{-5}$), and *decreased exploration in new environment* ($p = 9.1 \times 10^{-5}$) are all taken from the Mouse Genome Informatics database and defined by fearful and anxious behavior when their member genes are perturbed in mice.

3.3 GWAS of the group factors

We now report our attempts to find SNPs associated with the group factor Depressed Affect. Recall that we conducted a GWAS with Genomic SEM, based on a model sending directed edges from the SNP to all three group factors. After discarding SNPs identified as general-factor or independent-pathway SNPs in previous analyses, we ended up with 317 lead SNPs. (Of these 317, 53 reached the strict genome-wide significance threshold $p < 5 \times 10^{-8}$.) Interestingly,

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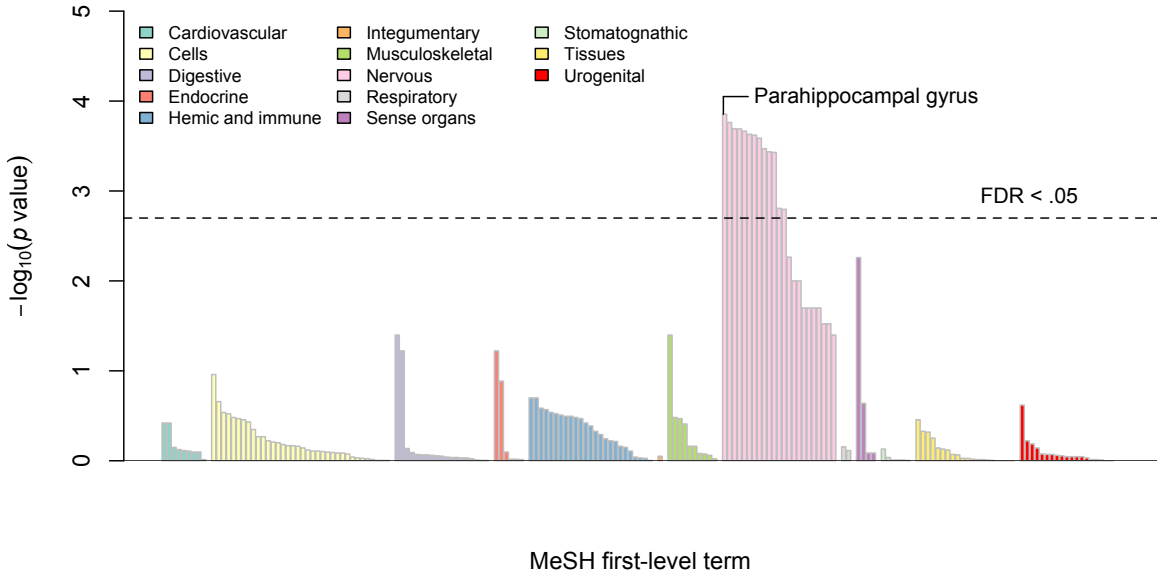

Figure 2: Tissues or cell types with significant expression of genes in the vicinity of SNPs associated with the Neuroticism general factor (relative to genes in random sets of loci). The tissues are arranged along the x-axis by Medical Subject Heading (MeSH) first-level term. The y-axis represents statistical significance on a $-\log_{10}$ scale. The height of the dashed horizontal line corresponds to the p value yielding FDR $< .05$. See Supplementary Table S4 for complete results.

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Table 1: Reconstituted gene sets significantly enriched by lead SNPs for the Neuroticism general factor.

Gene set	Description
Site of polarized growth	Any part of a cell where anisotropic growth occurs.
Growth cone	The migrating tip of a growing neuron projection.
Abnormal cued conditioning behavior	Anomaly in the ability of an animal to learn associations between aversive and neutral stimuli.
Impaired coordination	Reduced ability to execute integrated movements.
Abnormal neuron physiology	Any functional anomaly of the cells that receive, conduct, and transmit nervous impulses.
Increased anxiety-related response	Animals exhibit more responses thought to be indicative of anxiety in behavioral tests.
Decreased exploration in new environment	Animals spend less time investigating a new location.

Non-PPI reconstituted gene sets satisfying FDR < 0.05. See Supplementary Table S5 for all significant results of the DEPICT gene-set analysis and Supplementary Table S6 for the specific genes in the DEPICT-defined loci. The descriptions of the gene sets are adapted from Gene Ontology and Mouse Genome Informatics (accessed December 2020). Gene sets in bold also satisfy FDR $< .05$ for enrichment by lead SNPs categorized as acting through independent pathways.

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only 7 of the 317 lead SNPs were selected by the criterion of an Akaike weight greater than $2/3$ as having no associations with the other two group factors, and none of these 7 reached the stringent genome-wide significance threshold $p < 5 \times 10^{-8}$. It seems there are comparatively few SNPs associated with the residual of Depressed Affect. In contrast, 184 SNPs qualified by virtue of their Akaike weights to the group-factor model (nonzero effects on all three factors), 64 for the independent-pathway model, and 62 for none of the above. Our finding of few SNPs specifically associated with Depressed Affect does not seem to be the result of an overly conservative criterion. With respect to the nested hypotheses of Depressed Affect only and the group-factor model, more than 85 percent of the lead SNPs showed a Q_{SNP} p value less than $.05$.

The 184 SNPs qualifying for the group-factor model showed highly concordant effects on the three factors. In other words, despite being deemed a poor fit to the general-factor model, a SNP's association with one factor was highly predictive of its associations with the two others. The sign concordance between SNP effects on Depressed Affect and Worry was 100 percent. Each sign concordance between a major group factor and the third factor (with little non-Neuroticism variance) was 183/184.

After running the analogous procedure, we identified 286 lead SNPs associated with Worry. (Of these 286, 14 reached $p < 5 \times 10^{-8}$.) Only 4 of the 286 lead SNPs were associated solely with the residual group factor of Worry, none of which attained $p < 5 \times 10^{-8}$. Of the remaining SNPs, 184 qualified by virtue of their Akaike weights for the group-factor model, 54 for the independent-pathway model, and 43 for none of the above. The sign concordances were again either 100 percent or short of perfect by one SNP.

Supplementary Table S7 lists the 11 total SNPs associated with the residual group factors. Such a small number of lead SNPs, particularly when few reach strict genome-wide significance, leads to low statistical power with DEPICT (Turley et al., 2018). Therefore we did not

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conduct biological annotation of these 11 SNPs.

The Supplementary Data contain information about all of the SNPs used in these analyses.

3.4 Independent-pathway SNPs

Our analyses of the common factors assigned a total of 181 lead SNPs to the independent-pathway model (Supplementary Table S8), and we proceeded to annotate these. The significantly enriched tissues/cell types are, as expected, those of the nervous system (Supplementary Table S9).

There are 27 significantly enriched gene sets (Supplementary Table S10). As indicated in Table 1, many are shared with the Neuroticism general factor (*abnormal cued conditioning behavior*, *impaired coordination*, *decreased exploration in new environment*). One of the independent-pathway gene sets, *abnormal contextual conditioning behavior*, is also defined by the learning of fear and caution. The Mouse Genome Informatics database describes the relevant phenotype as an "anomaly in the ability of an animal to learn and remember an association between an aversive experience . . . and the neutral, unchanging environment" (accessed March 2023).

The other significant results point to the early development of the brain (e.g., *central nervous system neuron axonogenesis*) and synaptic activity in the behaving organism (e.g., *glutamatergic synaptic transmission*).

The SNPs were grouped into 112 loci that in turn overlapped 324 genes (Supplementary Table S11). Thirty of these 324 genes were also among the 228 genes overlapping the loci encompassing the lead SNPs for the Neuroticism general factor. This modest intersection suggests that our inferences of enrichment by these two collections of SNPs are mostly independent.

The similarity of the biology implicated by general-factor and independent-pathway SNPs has two possible interpretations. First, the general factor and non-factor influences on the ques-

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tionnaire items may tend to act through similar biological mechanisms. Second, as suggested by the concordance of effect signs observed in the GWAS of the group factors, it may be that the general factor is in fact one of several mechanisms affected by an independent-pathway SNP, the other mechanisms being responsible for the departures from the strict predictions of the general-factor model (Fig. 1a). To investigate the latter possibility, we calculated sign concordances of the SNP effects on the 12 items. Of the 181 SNPs, 117 showed sign-concordant effects on all 12 items, 28 showed a deviant sign with respect to only one item, 15 showed deviant signs with respect to two items, 11 showed deviant signs with respect to three items, and 10 showed deviant signs with respect to four items. The overall impression is that many of these SNPs do not depart too radically from the general-factor model, despite a low Akaike weight for the precise predictions of that model.

The Supplementary Data contain information about all of the SNPs used in these analyses.

4 Discussion

The common-factor model need not be interpreted as a causal account of the correlations between indicators in order to be scientifically and practically useful (Ashton & Lee, 2005; McDonald, 1996, 2003). Nevertheless the extent to which factors do approximate underlying causes is a matter worthy of investigation.

Our results suggest that the factor model of the Neuroticism domain is not just a convenient summary of the correlations between items, but indeed a reasonable approximation to some part of the underlying causal system. For instance, Neuroticism does not appear to be explained entirely by something like the bonds model (Thomson, 1951), which proposes the existence of many distinct causal elements, no single one of which affects all items in the domain. In Thomson's model, items may overlap in what bonds affect them, and a greater overlap produces a greater correlation. A resulting positive correlation between each pair of items then gives the

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appearance of a single causal variable affecting all items when in fact there is no such variable. Bartholomew, Deary, and Lawn (2009) suggested that polymorphic sites in the human genome might turn out to be the substantiation of the abstract bonds in Thomson's model, but our results show that many SNPs identified in a GWAS of a Neuroticism questionnaire are in fact associated with all items as if mediated by the common factors.

Even upon rejecting a simpler model of mediation, we still found evidence for the approximate correctness of such a model. SNPs ascertained through a GWAS of the three group factors were found to show sign-concordant effects on those factors. When combined with our failure to discover any strictly genome-wide significant SNPs acting solely through either residual group factor (Supplementary Table S7), this pattern leads to the hypothesis that the factors present in this questionnaire arise not from dedicated genetic substrates, but rather mainly from variants that happen to act through both the general factor and additional mechanisms that—for whatever reason—cannot be perturbed on their own. In summary, we have genetic evidence supporting the verisimilitude of the Neuroticism general factor at a deep biological level. This evidence weighs against network theories that deny the existence of broad factors influencing many specific traits (Cramer et al., 2012), adding specific neurobiological reasons to other statistical and theoretical reasons to reject such models as sufficient explanations of personality structure (DeYoung & Krueger, 2018).

We concede that our study cannot be absolutely definitive on this point. The lead SNPs account for a small part of the genetic variance in the Neuroticism questionnaire, and generalization from the lead SNPs to the rest of the human genome must wait on further increases in the GWAS sample size. The filtering of SNPs by statistical significance in a GWAS at the latent level may also induce an ascertainment bias that exaggerates the evidence for the approximate validity of the factor model. That is, SNPs departing very markedly from concordance of associations with all of the questionnaire items may be less likely to reach the threshold of

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461 statistical significance in a GWAS of the common factor. Future research may attend to this
462 issue of ascertainment bias more carefully. Again, however, it is telling that most of the SNPs
463 ascertained solely for significant association with just one group factor showed evidence of con-
464 cordant association with the two others as well. Regardless of what we have failed to ascertain,
465 it is clear that there are a sizable number of polymorphic sites across the genome that bear a
466 striking resemblance to causes of the Neuroticism general factor.

467 Previous studies have used multivariate twin modeling to pursue aims similar to our own.
468 For example, Heath, Eaves, and Martin (1989) showed that data from 2,903 pairs of like-sex
469 twins were consistent with some personality scales being influenced by a general heritable fac-
470 tor. In their study this was true of Extraversion and Neuroticism, but not the third EPQ trait of
471 Psychoticism. This work may have contributed to the decline in support for the construct va-
472 lidity of Psychoticism, showing the potential impact of genetic methods on personality theory.
473 Even the fit of genetic correlations to a single factor, however, does not rule out a network or
474 Thomson-like model. The power of the genomic approach lies in subjecting a factor model to
475 an even more precise and hence riskier quantitative test of how directly measurable objects are
476 related to the trait indicators (Meehl, 1978).

477 We applied DEPICT in order to gain some clues to the biological processes mediating the
478 effects of the general-factor SNPs on Neuroticism. We found that these SNPs disproportionately
479 fall within or near genes designated as high-ranking members of gene sets defined by responses
480 to aversive or novel stimuli (Table 1). This result is remarkably fitting for the personality trait of
481 Neuroticism. Such gene sets became significantly enriched in GWAS of other behavioral traits
482 as their sample sizes grew (e.g., Lee et al., 2018), but it is perhaps meaningful that they are
483 among the first to become significantly enriched in the GWAS of a trait defined by a tendency
484 to experience fear and anxiety. Furthermore, the apparent tendency of these genes to be highly
485 expressed in the parahippocampal gyrus (Fig. 2) is consistent with research and theory linking

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Neuroticism to the septo-hippocampal system (Allen & DeYoung, 2017; Gray & McNaughton, 2000; Shackman et al., 2016).

By and large, our biological-annotation results are consistent with previous analyses. For example, the top tissue/cell types in a DEPICT analysis of a one-factor model estimated with Genomic SEM was *parahippocampal gyrus* (Grotzinger et al., 2019). Our results are also broadly consistent with those obtained with a different software tool, MAGMA (de Leeuw, Mooij, Heskes, & Posthuma, 2015), in a GWAS of the questionnaire sum score (Nagel et al., 2018). The three independently significant gene sets in this study were *neurogenesis*, *behavioral response to cocaine*, and *axon part*. Biological annotation apparently tends to yield similar results regardless of whether it is applied to the general factor or to the observed sum score (or a misspecified single factor). Perhaps such consistency is to be expected in light of our evidence for the existence, in some sense other than the psychometric one, of a general factor. A sum score will typically reflect a general factor indicated by all items more than any other source of variance. Indeed, on the basis of the phenotypic correlations between items reported by Nagel, Watanabe, Stringer, Posthuma, and van der Sluis (2018), we calculated McDonald's ω_H (Revelle & Condon, 2019) of the EPQ Neuroticism scale to be 0.64.

We have no explanation for the meager results obtained from the GWAS of the residual group factors. It may be advisable in future studies to try personality models positing group factors other than those emerging from the EPQ (e.g., DeYoung, Quilty, & Peterson, 2007). A diversity of measurement approaches may be difficult to implement in biobank studies where any given research goal is incidental, but psychologists involved in such projects should take advantage of whatever opportunities are offered.

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5 Conclusion

We used structural equation modeling to carry out a GWAS of the Neuroticism general factor and identified 19 lead SNPs satisfying $p < 5 \times 10^{-8}$. Even if deemed not to satisfy the predictions entailed by the hypothesis of acting solely through the general factor, hundreds of other SNPs attaining or approaching statistical significance in various analyses showed mostly sign-concordant effects on the questionnaire items. These findings do not settle the issue of the causal structure underlying the correlations between personality items. All we claim is that when we look for evidence of genetic effects on a causal intermediary very similar to the general factor of Neuroticism, such evidence can be found. The SNPs acting through the general factor are found in or near genes highly expressed in the brain, and their pattern of gene-set enrichment is suggestive of neural development and synaptic function, particularly as these processes affect the learning of fear and caution in response to aversive stimuli.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

The Supplementary Data archive contains `R` code and several files containing limited portions of the Genomic SEM output. The original item-level GWAS summary statistics are available at https://ctg.cncr.nl/software/summary_statistics. The GWAS summary statistics generated for this paper are available at XXX.

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