A genome-wide association study of the Neuroticism general factor

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Abstract

We applied structural equation modeling to genome-wide association studies (GWAS) of the items in a Neuroticism questionnaire. 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. Bioinformatic analysis showed that the genetic variants associated with the Neuroticism general factor tend to lie near or within genes expressed in the brain. Enriched gene sets suggest 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

# 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 producing variation in the trait. Unfortunately, GWAS of personality traits often lack sample sizes large enough to detect many significant loci (de Moor et al., 2012; Lo et al., 2017; Luciano et al., 2012; Terracciano et al., 2010).

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., 2016; Smith et al., 2016). Neuroticism is one of the five factors in the Big Five model of personality. Individuals who score highly in Neuroticism tend to experience diverse and relatively more intense negative emotions. In a GWAS meta-analysis of Neuroticism, Nagel et al. (2018) found 136 significant independent loci. Neuroticism was measured using the Eysenck Personality Questionnaire–Revised Short Form (Eysenck, Eysenck, & Barrett, 1985). In the present study, we further investigated the 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 loci act in accordance with the common-factor model, which is an important tool in the psychology of individual differences. Mc-

Donald (2003) suggested that a common factor might be regarded as mental property with a non-physicalist 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 artifiact. That is, if the loadings of certain dependent variables on their common factor were $\lambda_1$, $\lambda_2$, and so forth, then a SNP with effects on those variables of $\beta\lambda_1$, $\beta\lambda_2$, and so forth (Fig. 1) would strongly suggest that the SNP has on effect of $\beta$ on *something* very much like the common factor, in the manner imagined by McDonald (2003).

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. Kievit et al. (2012) and Lee, McGue, Iacono, Michael, and Chabris (2019) previously tested a similar idea with general intelligence ($g$). In the framing of Kievit et al. (2012): does general intelligence exist as a unitary physical property in the brain, or is it merely a reflection of several distinct brain characteristics? 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 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") (Fig. 1). 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 Results

The online supplement contains a detailed description of the Materials and Methods.

## 2.1 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 = 0.969, SRMR = 0.054). We therefore regarded the

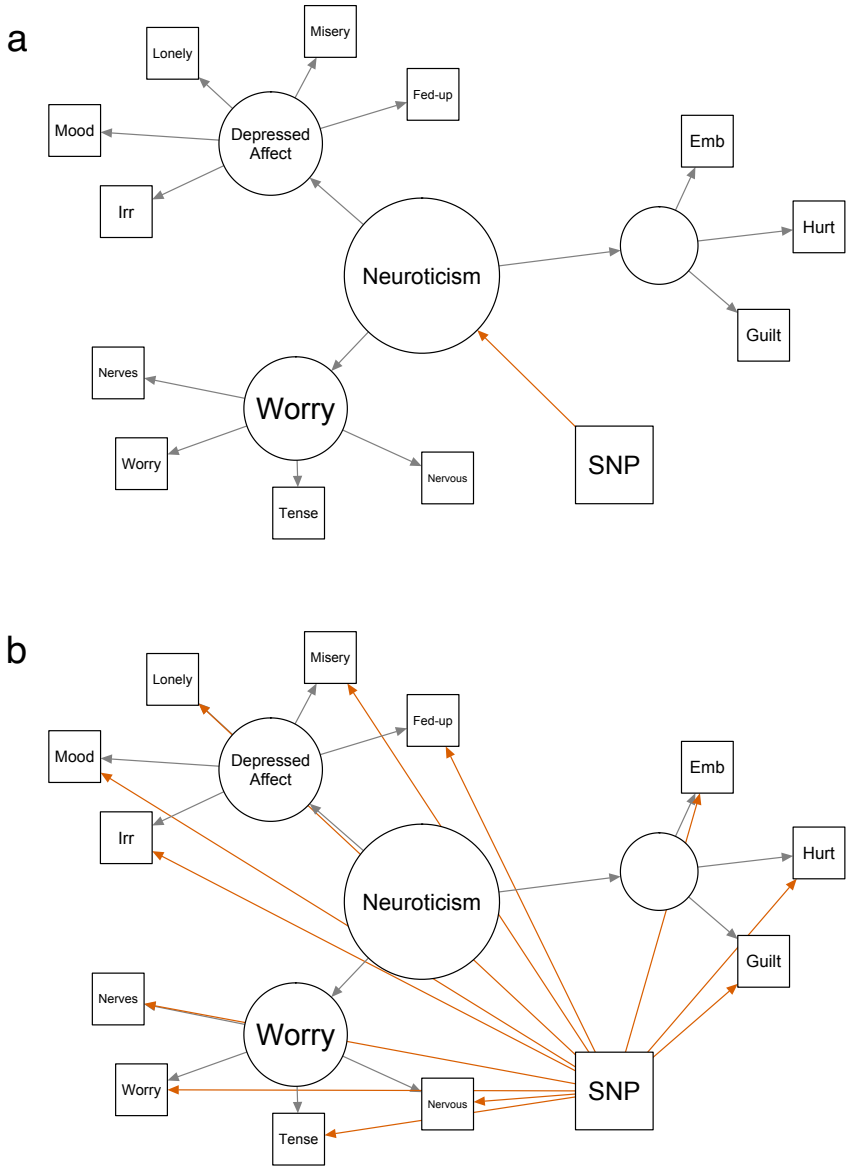


Figure 1: Path diagrams portraying how a single-nucleotide polymorphism (SNP) might be associated with the questionnaire items. (a) The focal SNP (or a nearby highly correlated SNP) acts through the Neuroticism general factor. (b) The focal SNP (or a nearby highly correlated SNP) acts on the 12 items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

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 (0.97) (Supplementary Table 1). 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 conduct a GWAS of this factor when trying to identify SNPs associated with group factors.

## 2.2 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 $Q_{\mathrm{SNP}}$ 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 the current 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 2 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 $Q_{\mathrm{SNP}}$ statistics. Upon treating any SNP with a negative $Q_{\mathrm{SNP}}$ 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 $p > 0.28$ (median $p = 0.68$) with respect to the null hypothesis of the general-factor model fitting better than the group-factor model. If we take the $p < 0.05$ criterion as 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 $Q_{\mathrm{SNP}}$ $p$ values with respect to the null hypothesis of the group-factor model fitting better than the independent-pathway model all met $p < 0.02$ (median $p = 0.001$).

## 2.3 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 Database and defined by fearful and anxious behavior when their member genes are perturbed in mice.

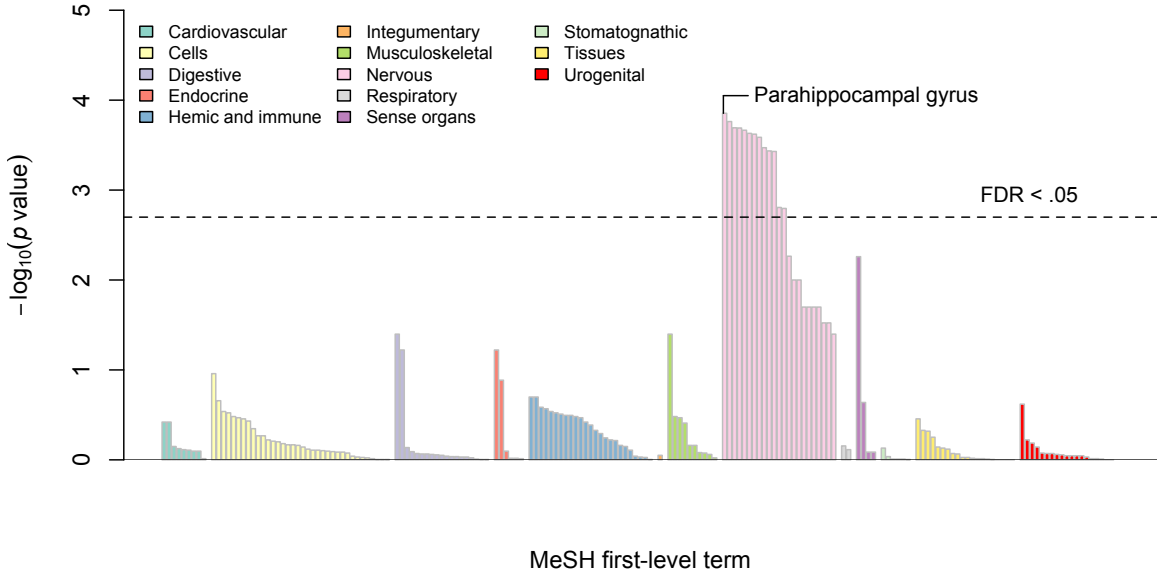


Figure 2: Tissues or cell types with significant expression of genes encompassing or lying near SNPs associated with the Neuroticism items through their general factor (relative to genes in random sets of loci). The tissues are arranged along the $x$-axis by Medical Subject Heading (MeSH) first-level 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 $< 0.05$. See Supplementary Table 3 for complete results.

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 4 for all significant results of the DEPICT gene-set analysis and Supplementary Table 5 for the specific genes in the DEPICT-defined loci. The descriptions of the gene sets are adapted from Gene Ontology and the Mouse Genome Informatics (accessed December 2020).

*Site of polarized growth* ($p = 1.4 \times 10^{-6}$) and *growth cone* ($p = 2.4 \times 10^{-6}$) are defined by the structures involved in the development of axons. *Abnormal neuron physiology* ($p = 8 \times 10^{-5}$) indicates that neuronal function in general is an important component of the biology underlying the Neuroticism general factor.

## 2.4 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, 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 $Q_{\mathrm{SNP}}$ $p$ value less than 0.05.

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 6 lists the 11 total SNPs associated with the residual group

factors. Our experience has shown that 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 conduct biological annotation of these 11 SNPs.

The Supplementary Data contains information about all of the SNPs used in the above analyses.

## 2.5 Independent-pathway SNPs

Our analyses of the common factors assigned a total of 181 lead SNPs to the independent-pathway model, and we proceeded to annotate these. The SNPs were grouped into 112 loci that in turn overlapped 324 genes (Supplementary Table 10). 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 independent-pathway SNPs are mostly independent of those by general-factor SNPs. The significantly enriched tissues/cell types are, as expected, those of the nervous system (Supplementary Table 8). Surprisingly, however, the top two results are *occipital lobe* ($p = 6.4 \times 10^{-6}$) and *visual cortex* ($p = 7.9 \times 10^{-6}$). There are 27 significantly enriched gene sets (Supplementary Table 9). Many are shared with the Neuroticism general factor (*abnormal cued conditioning behavior*, *impaired coordination*, *decreased exploration in new environment*). 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 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 questionnaire items may tend to act through similar biological mechanisms. Sec-

ond, as suggested by the concordance of effect signs observed in the GWAS of the group factors (2.4), 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 contains information about all of the SNPs used in the above analyses.

# 3 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 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 discovery of no genome-wide significant SNPs acting solely through either residual group factor (Supplementary Table 6), 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 statistical significance in a GWAS of the common factor. Future research may attend to this issue of ascertainment bias more carefully. Again, however, it is telling that most of the SNPs ascertained solely for significant association with just one group factor showed evidence of concordant association with the two others as well (2.4). Regardless of what we have failed to ascertain, it is clear that there are a sizable number of polymorphic sites across the genome that bear a striking resemblance to causes of the Neuroticism general factor.

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

We applied DEPICT in order to gain some clues to the biological processes mediating the effects of the general-factor SNPs on Neuroticism. We found that these SNPs disproportionately fall within or near genes designated as high-ranking members of gene sets defined by responses to aversive or novel stimuli (Table 1). This result is remarkably fit-

ting for the personality trait of Neuroticism. Such gene sets became significantly enriched in GWAS of other behavioral traits as their sample sizes grew (e.g., Lee et al., 2018), but it is perhaps meaningful that they are among the first to become significantly enriched in the GWAS of a trait defined by a tendency to experience fear and anxiety. Furthermore, the apparent tendency of these genes to be highly expressed in the parahippocampal gyrus (Fig. 2) is consistent with research and theory linking 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 a previous DEPICT analysis of the questionnaire sum score (Turley et al., 2018) and of a one-factor model implemented in Genomic SEM (Grotzinger et al., 2019). For example, the top two tissues/cell types in the former analysis were the non-specific *brain* and *central nervous system*, but the next most significant result was *parahippocampal gyrus*. The top result in the latter analysis was *parahippocampal gyrus*. Our results are also 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 $\omega_H$ of the EPQ Neuroticism scale to be 0.64 (Revelle & Condon,

2019).

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.

# 4 Conclusions

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.

# Author Contributions

**YK**: Conceptualization, Software, Formal analysis, Writing—original draft. **AG**: Formal analysis, Visualization. **EAW**: Visualization. **CGD**: Writing—reviewing and editing.

**JJL**: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing—reviewing and editing, Visualization, Supervision, Project administration.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix: Supplementary Data

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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