The authors have not even attempted to transform the variables to more closely approximate a normal distribution. Given the complexity of the analyses and the erratic distribution of the data points, the correct approach to obtaining a robust *P*-value would be to perform permutation testing, which would be trivial to undertake.

According to the GWAS catalogue (https://www.ebi.ac.uk/gwas/), which includes thousands of publications, rs324981 is not associated with any trait at genome-wide significance. It is a cause for concern that flawed candidate gene studies, such as this one, continue to be published in peer-reviewed journals.

Declaration of interest

None

Reference

1 Schiele MA, Herzog K, Kollert L, Schartner C, Leehr EJ, Böhnlein J, et al. Extending the vulnerability–stress model of mental disorders: three-dimensional NPSR1 × environment × coping interaction study in anxiety. *Br. J. Psychiatry* 2020; **217**(5): 645–50.

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RE: Extending the vulnerability-stress model of mental disorders: three-dimensional NPSR1 × environment × coping interaction study in anxiety

12 October 2022

This is to respond to the letter 'No evidence that *NPSR1* is involved in anxiety' by D. Curtis submitted on 15 January 2021. We have very carefully conceptualised the design of the present study and conducted all analyses *lege artis* as described in detail in the Methods section. Thus, we decisively reject the points raised by the reader, which in no way invalidate any of the results presented in the manuscript.

As evident from the title of the comment, the reader appears to have misunderstood the hypothesis, methodology, results and discussion of the research in question. We would like to direct the reader's attention to the introduction of the paper, where it is clearly stated that the main objective of the paper was the investigation of a moderator effect in an extension of traditional G × E models by additionally accounting for coping ability, rather than a direct effect of genotype. In light of the fact that mental disorders are multifactorial in origin and rest on the complex interplay of genetic and environmental – both detrimental and protective – factors, no such direct association can or should readily be assumed, in candidate gene research or otherwise. Therefore, the fact that no main effect was observed is most certainly not 'the main finding' of the paper as claimed by the reader, nor was it any objective at all. The main finding, if we may reiterate, is – as is obvious from the title, abstract and body of the paper – the observed three-way interaction effect of *NPSR1* genotype, childhood trauma and self-efficacy differentially modulating trait anxiety and by this further qualifying established G × E models of anxiety.[1,2]

To this end, a moderator analysis was conducted as fully appropriate to statistically address this research question of probing the hypothesised interaction effect. Accordingly, and as clearly stated in the Methods section of the paper, variables were centred (i.e. *z*-transformed) to avoid statistical interference errors as is recommended for this type of analysis.[3,4] Furthermore, it is absolutely incorrect to conclude that 'the statistical significance of the findings cannot be assessed' for non-normally distributed data. First, in multiple regression, the normality assumption applies only to the residuals, not to the independent variables. Second, in large samples (>10 observations per variable), which the presently investigated discovery sample of $N = 1403$ certainly constitutes, violations of the normality assumption do not affect the results (cf. 'While [*t*-test and linear regression] are valid even in very small samples if the outcome variable is Normally distributed, their major usefulness comes from the fact that in large samples they are valid for any distribution.'[5]). Third, variable transformations in spite of this may, by contrast, even bias results.[6] Fourth, what the reader refers to as 'outliers' represent natural variation in the data and are not due to measurement error or poor sampling and therefore should not be excluded arbitrarily. Still, even if excluding participants with high psychometric scores (>3 s.d.[7]; $N_{discovery} = 11$, $N_{replication} = 10$), the model remains robustly significant (discovery: $\beta = 0.119$, $P = 5.0513 \times 10^{-7}$; replication: $\beta = 0.112$, $P = 0.010$); hence, the reported results cannot at all be attributed to putative 'outliers'. Finally, we point out that the reported *P*-values for both samples are absolutely accurate. Their value, however, obviously does not equate to effect size, which would be reflected by the reported regression coefficients.

The presently investigated functionally relevant single-nucleotide polymorphism in the *NPSR1* gene was chosen based on a plethora of published evidence for its involvement in anxiety and particularly panic disorder (see references cited in the manuscript, including a review[8]) despite not being reported in presently available anxiety disorder genome-wide association studies (GWAS). GWAS published to date on anxiety disorders and particularly on panic disorder are, however, far from being sufficiently powered to reveal any statistically meaningful results, suffer from high phenotypical heterogeneity and are stricken with poor ancestral diversity.[9] Therefore, a role of *NPSR1* variation in anxiety also at a genome-wide level cannot be excluded at the moment. We are, however, absolutely aware of the fact that the present candidate-gene-based study is to be seen as only paradigmatic for the approach proposed here for the first time of applying an extended G × E × C model preferably in sufficiently large samples allowing for a genome-wide analysis as explicitly stated in the Discussion section ('Finally, on a genetic level, beyond the single candidate-gene approach future research may want to address the G × E × C model under consideration of haplotype or epistatic genetic effects as well as in the context of GWAS in sufficiently powered samples. This is because, in particular, recent genome-wide studies have reported several loci to significantly contribute to coping and resilience phenotypes.'[10]). Finally, whether to appreciate and publish candidate gene studies such as the present one is entirely at the discretion of the respective journal and its editors. Evidently, the *BJPsych* has quite recently not only published the present candidate-gene-based study but also several others focusing on candidate genes including *SIRT1*,[11] *CACNA1C*[12,13] and *MAOA*.[14]

Declaration of interest

K.D. is a member of the Steering Committee Neuroscience, Janssen Inc.

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