No evidence that *NPSR1* is involved in anxiety

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A recent report claimed that a variant, rs324981, of the neuropeptide S receptor gene (*NPSR1*) modulated the relationships between childhood trauma, self-efficacy and trait anxiety but the analyses performed were so seriously flawed as to render the conclusions completely invalid (Schiele et al., 2020).

The authors fail to mention in the abstract the main finding, which is that they found no association at all between rs324981 genotype and anxiety. Nor did they find an effect of genotype on anxiety in two-way interaction analyses. They only claimed an effect when genotype was included in a three-way interaction term. It is utterly implausible that a real effect would appear in this situation. The reason these results have appeared is clear from Figure 1, which shows that the apparent relation is driven by a handful of outliers which, purely by chance, have a similar configuration in the discovery and replication samples.

The authors report an unfeasibly small p value of 4×10^{-8} to support their conclusion. This is simply a consequence of treating the values as if they followed a gaussian distribution when they clearly do not. The linear regression analysis implemented in SPSS carries out an analysis of variance to obtain a p value and this analysis of variance assumes that the variables are normally distributed. The departure from normality does not prevent linear regression analysis from producing a least squares fit but it does mean that the statistical significance of the findings cannot be assessed.

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.

I declare I have no conflict of interest.

Schiele, M.A., Herzog, K., Kollert, L., Schartner, C., Leehr, E.J., Böhnlein, J., Repple, J., Rosenkranz, K., Lonsdorf, T.B., Dannlowski, U., Zwanzger, P., Reif, A., Pauli, P., Deckert, J., Domschke, K. (2020) Extending the vulnerability–stress model of mental disorders: three-dimensional NPSR1 × environment × coping interaction study in anxiety . Br. J. Psychiatry 1–6.