BJPsych | The British Journal of Psychiatry (2023) 222, 44–46.

Correspondence

Edited by Kiriakos Xenitidis and Colin Campbell

Contents

RE: Impact of COVID-19 on mental health research: is this the breaking point?

Research and COVID-19: why join the club?

25 July 2022

Despite considerable funding, few psychiatrists could point to genetic or neuroimaging studies that have changed day-to-day clinical practice over the past three decades. UK psychiatric epidemiology is unhealthy and national mental health data-sets are difficult, often impossible, to access. Health service research is either spurned as low impact or endlessly repeated in meta-analyses supporting service interventions which are visibly failing patients in the field. Sparasci and colleagues[1] highlight progressive national closures of research departments, with psychiatry subsumed under other university departments. Failure to deliver hoped-for breakthroughs to lead psychiatry into the 21st century will not be resolved by asking the wrong research questions. Could psychiatric academia have so little political influence in the real world because it increasingly aligns itself with populist ideologies with no evidence base?

COVID caused others to seriously re-evaluate the value of psychiatric research. Psychiatric studies were shut down because money was needed for a pandemic threatening to overwhelm the National Health Service. Government (but not academic psychiatry) soon grasped that it was not so much the virus posing threats to the nation's public mental health but mass unemployment and economic hardship. Yes, there were real neuropsychiatric harms from the virus. But exaggerating them to obtain grant funding failed to benefit psychiatry, and such funding was inevitably awarded to disciplines with relevant skills in population health sciences, public health, neurology and infectious diseases. Lack of new ideas and methods were exposed in a 'position' paper at the start of the COVID pandemic, aimed to set the agenda and capture grants.[2] Where are those recommendations now? None was substantially funded in psychiatry. The ultimate 'give away' that psychiatry was far out of its depth with COVID was rigid insistence that all future studies include full involvement from people with 'lived experience'[2] – for a potentially deadly viral illness.

The editorial[1] is important because it makes us question future research directions and academics' career prospects. Academic psychiatry has become like a steadily declining, formerly exclusive club, not readily admitting new members unless they share the same ideas and values, with old members steadily replaced by more compliant younger ones, controlled by a ruthless management. Why would anyone young want to join the club if it means lifetime earnings disparity compared with clinicians, pressures to achieve the impossible in terms of grants and impact factors and adhering to an exploitative career model of an 'independent researcher', with the myth of becoming self-funding through research grants? Like exclusive clubs, universities are businesses and psychiatrists are expensive commodities, easily replaced by other members of disciplines such as psychologists who are plentiful, better trained in research at undergraduate level and often desperate for jobs. Few will ever become research professors and most will spend majority of their academic time teaching. This brings in greatest earnings for universities where, for some, research is a loss leader to attract undergraduates. And, as committee membership lists increasingly show, it is now easy to obtain a visiting or honorary chair from a university and call yourself 'professor' with no discernible research credentials.

Declaration of interest

None

References

1 Sparasci O, Bhui K, Biswas A, Chamberlain S, Dubicka B, Dudas R, et al. Impact of COVID-19 on mental health research: is this the breaking point? *Br J Psychiatry* 2022; **220**(5): 254–6.

2 Holmes EA, O'Connor R, Perry VH, Tracey I, Wesseley S, Arsenault L, et al. Multidisciplinary research priorities for COVID-19 pandemic: a call for action for mental health science. *Lancet Psychiatry* 2020; **7**: 547–60.

Jeremy Coid, Emeritus Professor of Forensic Psychiatry, Wolfson Institute of Population Health, Queen Mary University of London, UK. Email: j.w.coid@qmul.ac.uk

doi:10.1192/bjp.2022.146

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

No evidence that *NPSR1* is involved in anxiety

15 January 2021

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.[1]

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.

https://doi.org/10.1192/bjp.2022.167 Published online by Cambridge University Press

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.

David Curtis, UCL Genetics Institute, UCL, and Centre for Psychiatry, Queen Mary University of London, UK. Email: d.curtis@ucl.ac.uk

doi:10.1192/bjp.2022.167

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.

References

1 Nugent NR, Tyrka AR, Carpenter LL, Price LH. Gene-environment interactions: early life stress and risk for depressive and anxiety disorders. *Psychopharmacology* 2011; **214**: 175–96.

2 Sharma S, Powers A, Bradley B, Ressler KJ. Gene × environment determinants of stress- and anxiety-related disorders. *Annu Rev Psychol* 2016; **67**: 239–61.